NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for CADMIUM

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NTP Report on Carcinogens Listing for Cadmium and Cadmium Compounds

Carcinogenicity

Cadmium and Cadmium Compounds are *known to be human carcinogens* based on findings of increased risk of cancers in exposed worker populations and supporting evidence of malignant tumor formation by multiple routes of exposure at various sites in multiple species of experimental animals.

In several cohort studies of workers exposed to various cadmium compounds, the risk for death from lung cancer is elevated (IARC, 1993). Although confounding factors, such as co-exposure to arsenic, were present in several of these studies, it was concluded that the increase in lung cancer risk was unlikely to be completely explained by exposure to arsenic (IARC, 1993). Follow-up analysis of some of these cohorts has not definitively eliminated arsenic as a possible confounding factor but has confirmed that cadmium exposure is associated with elevated lung cancer risk under some circumstances (Sorahan and Lancashire, 1997; Sorahan et al., 1995). In some early cohort studies, an increased risk of mortality from prostate cancers was found in cadmium-exposed workers but later cohort studies have not confirmed this observation. Additional epidemiological evidence (case-control studies, geographic distribution studies, etc.) suggests an association between cadmium exposure in human populations and prostate (van der Gulden et al., 1995; García Sánchez et al., 1992; Shigematsu et al., 1982; Bako et al., 1982); renal (Mandel et al., 1995; Kolonel, 1976); and bladder (Siemiatycki et al., 1994) cancers.

Inhalation of a variety of cadmium compounds has repeatedly been reported to produce dose-dependent increases in pulmonary adenocarcinomas in rats, and occasionally to produce pulmonary tumors in mice but not in hamsters (IARC, 1993). Intratracheal instillation of cadmium compounds produces malignant lung tumors in rats (IARC, 1993). Oral exposure to cadmium chloride produces dose-related increases in leukemia and benign testicular tumors in rats. In several studies, single or multiple injections (s.c., i.m., or i.p.) of a variety of soluble and insoluble cadmium compounds have caused local sarcomas in rats and mice (IARC, 1993; Waalkes and Rehm, 1994a). Subcutaneously injected cadmium compounds produce a variety of tumors including prostate tumors in rats, testicular tumors in rats and mice, lymphomas in mice, adrenal tumors in hamsters and mice, and lung and liver tumors in mice (IARC, 1993; Waalkes and Rehm, 1994a, b, c; Waalkes et al., 1994). Based on the carcinogenicity of a wide variety of cadmium compounds, it was concluded by IARC that it is ionic cadmium that is the active, carcinogenic species (IARC, 1993).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Many studies have shown in cultured animal cells that cadmium compounds damage genetic material. DNA strand breaks, mutations, chromosomal damage, cell transformations, and disrupted DNA repair have been observed in *in vitro* studies. Cadmium does not bind covalently to cellular components, including DNA. Cadmium can induce chromosomal aberrations in exposed human populations. It has been concluded by IARC that ionic cadmium is the active, genotoxic form of the metal (IARC, 1993).

The sensitivity of cells or tissues to cadmium appears to be related, at least in part, to expression of the metallothionein (*MT*) gene. Activation of the *MT* gene can limit the genotoxic effects of cadmium. Relative expression of the pulmonary *MT* gene appears to be the basis for the sensitivity of rats and the insensitivity of mice to lung tumors induced by inhaled cadmium.

Additionally, other target tissues of cadmium carcinogenesis in rodents show minimal basal expression or poor activation upon stimulation of the *MT* gene (Oberdörster et al., 1994).

No data are available that indicate the mechanisms thought to account for cadmium carcinogenesis in experimental animals would not also operate in humans.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 CHEMICAL PROPERTIES

1.1 Chemical Identification

Cadmium is a silver-white, blue-tinged, malleable metal. It has an atomic weight of 112.41 and belongs to group IIB of the periodic table. Cadmium is a rare element and not found in nature in its pure state. The cadmium minerals do not occur in quantities that support mining. Cadmium is generally the by-product of processing sulfide ores for zinc, lead, and copper (IARC, 1993).

Table 1-1. Cadmium and Cadmium Compounds, Identifiers

Name	CAS Registry No.	Molecular Formula	Molecular Weight	Water Solubility[a]
Cadmium	7440-43-9	Cd	112.41	Insoluble
Cadmium acetate	543-90-8	$Cd(CH_3COO)_2$	230.50	Freely Soluble
Cadmium carbonate	513-78-0	$CdCO_3$	172.42	Practically Insoluble
Cadmium chloride	10108-64-2	$CdCl_2$	183.32	Freely Soluble
Cadmium hydroxide	21041-95-2	$Cd(OH)_2$	146.43	Practically Insoluble
Cadmium nitrate	10325-94-7	$Cd(NO_3)_2$	236.43	Soluble in 0.6 part water
Cadmium oxide	1306-19-0	CdO	128.41	Practically Insoluble
Cadmium stearate	2223-93-0	$Cd(C_{36}H_{72}O_4)$	681.37	n.g.
Cadmium sulfate	10124-36-4	$CdSO_4$	208.47	Freely Soluble
Cadmium sulfide	1306-23-6	CdS	144.47	0.13 mg/100 g
Cadmium-copper alloy	7364-06-0 12685-29-9 132295-56-8 132295-57-9	Cd•Cu	varies with compound alloy	n.g.

n.g.= not given

[a]Solubility taken from *The Merck Index* (Budavari, 1996).

1.2 Physical-Chemical Properties

Cadmium occurs as a soft, blue-white, malleable metal or grayish-white powder. It is soluble in acid, ammonium nitrate, and hot sulfuric acid and insoluble in cold and hot water. Cadmium carbonate occurs as a white amorphous powder that is soluble in acids, potassium cyanate, and ammonium salts and insoluble in ammonia and water, both cold and hot. Cadmium chloride occurs as small, white-to-colorless, hexagonal crystals. It is soluble in water and acetone and insoluble in ethanol. Cadmium fluoborate is extremely hygroscopic and very soluble in water. When heated to decomposition, it emits toxic fumes of cadmium, hydrofluoric acid, and other fluorinated compounds. Cadmium nitrate occurs as white, amorphous pieces or hygroscopic needles. It is very soluble in acids and soluble in ethanol, acetone, water, and ammonia. Cadmium oxide occurs as a colorless amorphous powder or brown-red cubic crystals. It is soluble in acids, ammonium salts, and alkalies, but is insoluble in cold and hot water. When heated to decomposition, it emits toxic fumes of cadmium. Cadmium sulfate occurs as white rhombic crystals. It is soluble in water but insoluble in alcohol, acetate, and ammonia. Cadmium sulfide is a yellow-orange or brown powder. It forms a colloid in hot water; it is soluble in acids and ammonia and insoluble in cold water. When heated to decomposition, cadmium sulfate and cadmium sulfide emit toxic fumes of cadmium and sulfur oxides (SO_x).

Cadmium metal is available in purities ranging from 99.5%-99.999% in the following grades: technical, powder, pure sticks, ingots, slabs, and high-purity crystals with less than 10 ppm impurities. Cadmium carbonate is available in a commercial grade that has a purity of about 98% with lead, zinc, and iron as impurities. Reagent-grade cadmium carbonate, with purities ranging from 99.9%-99.995%, is also available. Commercial cadmium chloride is a mixture of hydrates that is similar to the dihydrate form of cadmium chloride. The commercial grade available in the United States typically contains about 51% cadmium and 0.005% each of iron and copper; higher purity grades (99.9%) are also available. Cadmium fluoborate is available commercially in a 50% aqueous solution. Cadmium nitrate is available in technical and reagent grades (purity > 99%) with typical impurities of chloride, sulfate, copper, iron, lead, zinc, and arsenic. Commercial-grade cadmium oxide is available in the United States with a purity of 99.7%; common contaminants are lead and thallium. Cadmium sulfate is available in technical and C.P. grades. Cadmium sulfide is available in technical, N.D., high-purity (single crystals), and commercial grades. Typically, cadmium sulfide is available in mixtures depending upon its use as either a pigment or a phosphor.

1.3 Packaging and Shipping

Cadmium is available in bars, sheets, wire, or gray, granular powder (HSDB, 1997).

2.0 HUMAN EXPOSURE

Consumption of food, drinking water, incidental ingestion of soil or dust contaminated with cadmium, inhalation of cadmium-containing particles from ambient air, inhalation of cigarette smoke, or working in an occupation involving exposure to cadmium fumes and dusts are all means of human exposure to cadmium (ATSDR, 1997). Food is the major source of cadmium exposure for nonsmokers. Drinking water normally has very low levels of cadmium.

Exposure to cadmium may be monitored in blood or urine by atomic absorption spectrometry and polarography. Cadmium concentrations of 0.1 μg/L can be determined using

graphite furnace atomic absorption spectroscopy. These methods are explained in detail by IARC (Vol. 58, 1993, pp. 124-125). Neutron activation analysis (*in vivo* and *in vitro*) and x-ray fluorescence (*in vivo*) are used as techniques to measure cadmium in tissue (ATSDR, 1997). The *in vivo* techniques are used to measure occupational exposure.

2.1 Use

The principal use of cadmium is the coating and electroplating of metals to prevent corrosion. Relative cadmium usage in 1991 was estimated as 45% for batteries, 20% for coating and plating, 16% for pigments, 12% for plastic and synthetic products, and 7% for alloys and other metal products. From 1988 to 1991, the relative consumption of cadmium increased about 5% per year for batteries, decreased about 10% for coating and plating, remained at approximately 15% for pigments, remained at an average of 12% for plastic and synthetic products, and remained at an average of 9% for alloys (USDOI, 1991).Cadmium sulfide (CdS) and cadmium selenium sulfide (CdSeS) are used in pigments, primarily for plastics, and as stabilizers for poly(vinyl chloride) (PVC). Cadmium is also used in nickel-cadmium (Ni-Cd) batteries (electrode material), fungicides, alloys, and other uses (IARC, 1993; Carson et al., 1986; ATSDR, 1997).

Cadmium carbonate and cadmium chloride have been used as fungicides for golf courses and home lawn turf (ATSDR, 1997). By 1997, all cadmium pesticides had undergone voluntary cancellation (OPP, 1997). Cadmium carbonate is used as a catalyst in organic reactions and as a source of cadmium in other reactions. The intermetallic compounds, including cadmium sulfide (CdS), cadmium selenide (CdSe), and cadmium telluride (CdTe), have been used as semiconductors for photoconductors, photovoltaic cells, and infrared windows (ACGIHa, 1986; Kirk-Othmer V.4, 1978; both cited by IARC, 1993). Cadmium salts, especially the oxide and anthranilate, are used as anthelmintics in treating swine and poultry (Budavari, 1996). Cadmium chloride is used in photocopying, printing, dyeing, electroplating baths, and the manufacture of special mirrors and of cadmium yellow. A cadmium fluoborate bath is used for electrodeposition of cadmium on high-strength steels to avoid the problem of hydrogen embrittlement inherent in cyanide plating (Kirk-Othmer V.4, 1978; cited by IARC, 1993). Cadmium nitrate and cadmium oxide are used in the production of cadmium salts, photographic emulsions, coloring glass and porcelain, and in the laboratory as reagents. Cadmium oxide also finds use in plating baths, in electrodes for storage batteries, in phosphors, as a nematocide, as a starting material for PVC heat stabilizers, and as an additive in nitrite rubbers and plastics such as Teflon®. Cadmium sulfate and cadmium sulfide are used in pigments, fluorescent screens, in photoelectric cells, and in electroplating. Cadmium sulfide is the most widely used cadmium compound and is used primarily as a pigment (Sax, 1987; Kirk-Othmer V.4, 1978; both cited by IARC, 1993).

2.2 Production, Producers, and Import/Export Volume

Cadmium is chiefly recovered as a by-product of smelting domestic and imported zinc concentrates; as such, its production is dependent upon the demand for zinc. TRI95 (1997) listed ASARCO Incorporated, Denver, CO (cadmium refinery); Big River Zinc Corp., Sauget, IL; Jersey Miniere Zinc Co., Clarksville, TN; and Zinc Corp. of America, Bartlesville, OK, as producers in 1995. These producers recovered and produced cadmium as a by-product of smelting domestic and imported zinc concentrates, and one company (ASARCO, Inc.) in Colorado refined cadmium from other sources such as lead smelter baghouse dust (Llewellyn,

1993). In 1997, only two companies produced primary cadmium in the United States—the electrolytic plants in Sauget, IL, and Clarksville, TN (USDOI, 1997).

Production for 1972 through 1977 ranged from 4.1 million to 7.5 million lb (Kirk-Othmer V.4, 1978; cited by IARC, 1993). The 1979 TSCA Inventory reported that in 1977, there were 14 producers of cadmium producing 6.3 million lb and 18 importers importing 2.6 million lb (TSCA, 1979). From 1980 through 1989, U.S. annual cadmium production averaged 3.3 million lb (range 2.2-4.2 million lb), imports averaged 5.6 million lb (4.2-7.0 million lb), and exports averaged 0.45 million lb (0.02-1.4 million lb). In the period 1990-1997, production remained about the same (average 3.3 million lb, range 2.2-4.5 million lb), but imports were lower (average 3.0, range 1.7-4.5 million lb) and exports were higher (average 1.1 million lb, range 0.02-3.2 million lb) (USDOI, 1985, 1987, 1988, 1990, 1991, 1997; Plachy, 1997).

2.3 Types of Exposure

2.3.1 Environmental Exposure

2.3.1.1 Ambient Air

Atmospheric cadmium is generally in the form of particulate matter. Combustion processes produce very fine cadmium-containing particles. The principal species in the air are cadmium oxide and some cadmium salts, which occur as stable forms in the environment. Cadmium compounds in atmospheric emissions are dispersed by winds and deposited by wet or dry processes (ATSDR, 1997).

Cadmium concentrations in ambient air are generally less than 0.005 $\mu g/m^3$, but concentrations up to 0.5 $\mu g/m^3$ have been detected in air near cadmium-emitting facilities (Elinder, 1985a; cited by ATSDR, 1997).

The mean annual airborne concentration of cadmium in an area about 1 km from a zinc smelter was 0.023 $\mu g/m^3$. Concentrations of 0.003-0.023 $\mu g/m^3$ were found in U.S. urban areas (IARC, 1993).

Cadmium intake from ambient air is less than 0.8 μg/day in non-industrial areas (WHO, 1989; cited by WHO, 1993). Annual cadmium levels in industrial areas of Germany, Netherlands, and Belgium ranged from 1 to 3 ng/m^3, 0.7 to 2 ng/m^3, and 10 to 60 ng/m^3, respectively, between the years of 1980 to 1986 (Ros and Slooff, 1987; cited by WHO, 1993).

In 1995, atmospheric releases of "cadmium" totaled 11,939 lb (5.427 Mg). Of 45 facilities surveyed in 1995, 25 reported air emissions of cadmium. Sixteen reported emissions of less than 50 lb (0.023 Mg); 5 reported approximately 250 lb (0.113 Mg); 2 reported approximately 1000 lb (0.454 Mg); 1 reported 1881 lb (0.853 Mg); and one reported 6640 lb (3.012 Mg) (TRI95, 1997). Industries reporting releases of cadmium and cadmium-containing compounds included the following categories: inorganic (SIC 2819) and agricultural chemicals (SIC 2879); plastic materials and resins (SIC 2821); national security (SIC 9711); and hydraulic cement (SIC 3241). Primary metal industries reporting releases were copper (SIC 3331); metal products, nec (SIC 3399); and nonferrous metals, nec (SIC 3339). Industries involved in recycling nonferrous metals (SIC 3341); metalworking (SIC 3351, 3356, 3362, 3369, and 3444); and electroplating (SIC 3353 and 3471) reported releases. The manufacturers of the following products also reported releases of cadmium or cadmium-containing compounds: batteries (SIC 3691 and 3692); rubber and plastic footwear (SIC 3021); and steel pipes and tubes (SIC 3317).

Blast furnaces and steel mills (SIC 3312) are other sources in the iron and steel industry (TRI95, 1997).

The total air release of "cadmium compounds" reported separately in 1995 was 41,113 lb (18.65 Mg). Of 109 facilities reporting releases to air in 1995, 24 reported individual releases greater than 200 lb (0.091 Mg), 6 of which reported releases greater than 1000 lb (0.454 Mg) (TRI95, 1997). The industries reporting releases of cadmium compounds in air were classified in the following categories based on the type of product manufactured: metals (SIC 3331 and 3339), chemicals (including inorganic chemicals, nec) (SIC 2819), and custom compound purchased resins (SIC 3087) (TRI95, 1997).

There is significant inhalation exposure in industrial areas where zinc, lead, or copper smelters are located. Ambient air concentrations in rural areas are usually less than 1 ng/m^3, and in urban areas range from 5-40 ng/m^3. In the United States, about 2 million lb of cadmium are emitted during cadmium production and up to another 2 million lb are emitted from the use of cadmium. Burning of fossil fuels, such as coal or oil, and the incineration of municipal waste materials contributes to the cadmium emitted in the air (ATSDR, 1997).

Industry has increased cadmium recovery at primary smelters so release to the environment from industrial operations is expected to decrease (USDOI, 1991). Reduction of air emissions is evident by atmospheric releases of cadmium (4775 lb) and cadmium compounds (39,889 lb) reported to the U.S. EPA in 1996 (TRI96, 1998).

2.3.1.2 Water

Cadmium can occur in drinking water, which is contaminated by a cadmium impurity in galvanized zinc coatings, or by cadmium in solders used to join copper pipes. A guideline value of 3 μg/L for all cadmium forms in drinking water and a maximum level of 10 μg/L in drinking and bottled water is recommended (WHO, 1984, 1992; 1992 paper cited by IARC, 1993). Cadmium intake from drinking water is usually less than 2 μg/day (WHO, 1989; cited by WHO, 1993).

Cadmium solubility in water depends on the acidity of the water. At lower pHs, suspended particles or sediment-bound cadmium dissolve (Ros and Slooff, 1987; cited by WHO, 1993).

In 1995, the total release of "cadmium" to surface water in the United States was 458 lb (0.208 Mg). Of 9 facilities surveyed, 8 reported a release of less than 100 lb (0.045 Mg) and 1 reported a release of 250 lb (0.113 Mg) (TRI95, 1997). Industries reporting releases of cadmium to water were classified into the following categories based on type of product produced: organic fibers (SIC 2824), petroleum refining (SIC 2911), electronic connectors (SIC 3678), chemicals (SIC 2869), primary metals (3339), secondary metals (SIC 3341), metalworking (SIC 3351, 3356, and 3362), and storage batteries (SIC 3691).

In 1995, the total release of "cadmium compounds" to waters in the United States was 650 lb (0.295 Mg): 21 facilities reported minor releases, and only one reported a release greater than 200 lb (0.091 Mg) (TRI95, 1997). The industries reporting releases of cadmium compounds to water were classified as manufactures of primary metals (SIC 3331 and SIC 3339).

In 1996, a total of 1010 lb of cadmium and a total of 3614 lb of cadmium compounds were released to surface water (TRI96, 1998).

Cadmium can leach into ground water from pipes and solder used on pipes or from chemical/hazardous waste sites. It has been estimated that the ground water in New Jersey has a median level of 1 μg Cd/L with a high level of 405 μg/L. Ground water surrounding waste sites was found to have a concentration of 6,000 μg/L (ATSDR, 1997).

2.3.1.3 Soil and Plants

Cadmium is taken up and retained by aquatic and terrestrial plants and is then transferred to animals, where the cadmium deposits in the liver and kidneys. Cadmium in soil may exist in soluble form in soil water or in insoluble complexes with inorganic and organic soil constituents. Cadmium concentrations in soil tend to be greater when the pH of the soil is low. Increases in cadmium soil levels have resulted from application of municipal sewage sludge and phosphate fertilizers, which increases human exposures from food chain accumulation in plants and animals (ATSDR, 1997).

The total reported U.S. land disposal releases of "cadmium" in 1995 were 19,938 pounds (9.044 Mg) based on reports from nine facilities. Of these facilities, two released less than 100 lb (0.045 Mg); five released 100 to 500 lb (0.045 to 0.227 Mg); one released 8500 lb (3.856 Mg); and one released 9946 lb (4.511Mg) (TRI95, 1997).

In 1995, only five facilities were responsible for the total land releases of 49,119 lb of "cadmium compounds" (TRI95, 1997). In 1996, the total land release of "cadmium compounds" was 10-fold higher (502,027 lb). Five facilities were responsible for 97.3% of total land releases in 1996. An inorganic pigments manufacturer, not among the top five in 1995, was responsible for 67.4% of total releases to land in 1996. Total land release of "cadmium" was also higher in 1996 (51,420 lb) (TRI96, 1998).

The total underground injection of "cadmium compounds" (injected as a disposal method) was 109 lb (0.049 Mg) in 1995 (TRI95, 1997). In 1996, the total underground injection of "cadmium compounds" was 82 lb (TRI96, 1998).

Contaminated topsoil may be indirectly responsible for the greatest human exposure to cadmium due to the uptake of cadmium in soil into edible plants and tobacco. Topsoil may be contaminated by the application of phosphate fertilizers or sewage sludge. It has been found that uncontaminated top soil in the Unites States may contain an average of 0.25 ppm cadmium; levels up to 800 ppm have been found for soils in polluted areas (ATSDR, 1997).

2.3.1.4 Consumer Products

Cadmium pigments have been used in the production of cosmetics. The European Economic Community (EEC) banned this use in 1990. Cadmium pigments have also been used in plastics and printing inks for paper and textiles (IARC, 1993). Other consumer products include nickel-cadmium (nicad) batteries and cadmium-plated fasteners (Budavari, 1996).

The greatest potential for above-average exposure of the general public to cadmium is from smoking, which may double an individual's intake of cadmium; tobacco smokers are exposed to an estimated 1.7 μg Cd/cigarette (ATSDR, 1997).

2.3.1.5 Food

Food is the main source of human exposure for nonsmoking members of the population. In the United States, adult intake is estimated to be about 30 μg/day based on the Total Diet

Study, with the largest contribution from grain cereal products, potatoes, and other vegetables; average cadmium levels in U.S. foods range from 2 to 40 ppb (ATSDR, 1997). Some grains have been found to have a higher natural concentration of cadmium than others because of inherent genetic and physiological characteristics. The sunflower kernel, for example, does so, even when grown in uncontaminated soils, and habitual consumption will lead to an increased average intake of dietary cadmium. There is, therefore, potential for an increased body burden of the element (Reeves and Vanderpool, 1997). Fishermen who consume large amounts of fish from contaminated waters may also be exposed to higher levels of the metal, so much so that the EPA has recommended that it be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs (ATSDR, 1997).

WHO (1989; cited by WHO, 1993) set the provisional tolerable weekly intake (PTWI) of dietary cadmium as 7 μg/kg body weight, which was reconfirmed in 1990 (WHO, 1993).

2.3.1.6 Biomarkers and Biological Exposure Indexes

The metallothionein (MT) gene expression has been developed for use as a biomarker of heavy metal exposure (Ganguly et al., 1996). Reverse transcription-PCR (RT-PCR) was used to determine the level of MT-specific mRNA in blood samples from exposed workers and control subjects. There was a strong correlation between the airborne cadmium that registered on personal monitors and the blood levels of cadmium.

An association has been observed between the increase of the cadmium concentration in the urine, and abnormal values of several renal biomarkers (i.e., functional markers such as β_2-microglobulin in serum, urinary excretion of low and high molecular weight proteins; cytotoxicity markers such as tubular antigens and enzymes in urine; biochemical markers such as eicosanoids, glycosaminoglycans, and sialic acid in urine). Results of three studies support the conclusion that low-molecular-weight proteinuria indicate an exposure to a concentration of cadmium higher than the recommended biological threshold limit value. The authors noted that additional studies on biomarkers other than microproteinuria are needed to assess the validity of the use of biomarkers for identification of occupational exposure to cadmium (Lauwerys et al., 1995).

The American Conference of Governmental Industrial Hygienists biological exposure indexes (BEIs) for cadmium are 5 μg cadmium/g creatinine in the urine and 5 μg cadmium/L in the blood (ACGIH, 1996).

2.3.2 Occupational Exposure

Occupational exposure to cadmium and cadmium compounds varies with the process in which cadmium is being used. IARC (1993) summarized various occupational processes and exposure concentrations. Exposure levels were obtained by ambient air monitoring and biological monitoring (IARC, 1993).

The four major sources of occupational exposure are smelting of zinc and lead ores; producing, processing, and handling of cadmium powders; welding or remelting of cadmium-coated steel; and working with solders that contain cadmium. The major route of occupational exposure to cadmium is inhalation of dust and fumes and incidental ingestion of dust from contaminated hands, cigarettes, or food. In its more recent report, OSHA estimated that in 1990 approximately 512,000 workers were exposed to cadmium (ATSDR, 1997).

The National Occupational Exposure Survey (NOES) conducted in 1981-1983 estimated that 93,681 workers were exposed to cadmium or cadmium-containing substances; of these, 16,450 were female (18% of the surveyed workforce) (NIOSH, 1990). A breakdown of worker exposure by industry is given in **Table 2-1**.

Table 2-1. NIOSH National Occupational Exposure Survey (NOES, 1980-83)[a]: By Industry

Industry	Plants	Total Employees	Female Employees
Cadmium-Pure			
Fabricated Metal Products	22	269	22
Transportation Equipment	3	65	
Total	**25**	**334**	**22**
Cadmium dust-MF unknown			
Rubber and Misc. Plastics Products	3	24	
Fabricated Metal Products	122	1224	
Machinery, Except Electrical	3	44	
Electric and Electronic Equipment	2	7	
Instruments	118	2595	1887
Total	**248**	**3894**	**1887**
Cadmium-MF Unknown			
Heavy construction contractors	39	1334	
Special Trade Contractors	452	13779	
Apparel and other textile products	37	73	
Printing and publishing	154	1172	
Chemicals and allied products	61	1062	797
Petroleum and coal products	7	775	105
Rubber and misc. plastics products	141	2588	121
Stone, clay, and glass products	110	5208	
Primary metal industries	168	7875	
Fabricated metal products	778	15077	4637
Machinery, except electrical	905	9172	1149
Electric and electronic equipment	162	2416	755
Transportation equipment	126	1258	135
Instruments and related products	278	9043	3088
Miscellaneous manufacturing industries	746	7053	2742
Trucking and warehousing	12	1020	
Transportation by air	62	3561	
Electric, gas, and sanitary services	204	3310	
Automotive dealers & service stations	223	223	
Business services	45	2467	705
Health services	101	502	307
Total	**4811**	**88968**	**14541**
Cadmium Powder-MF Unknown			
Primary metal industries	90	360	
Transportation equipment	5	125	
Total	**95**	**485**	

a = (NIOSH, 1990); MF = manufacturer

2.4 Regulations and Criteria

Under the Clean Water Act (CWA), the water quality criteria published by EPA for cadmium and its compounds for the protection of human health are identical to Safe Drinking Water Act (SDWA) standards of 10 μg/L. EPA's Carcinogen Assessment Group includes cadmium oxide, cadmium sulfide, and cadmium sulfate on its list of potential carcinogens. Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), reportable quantities (RQs) have been established for cadmium and cadmium chloride. EPA issued a Rebuttable Presumption Against Registration (RPAR) for cadmium-containing pesticides under FIFRA. Also under FIFRA, there are labeling and reporting requirements. By 1997, all cadmium pesticides had undergone voluntary cancellation (OPP, 1997).

Cadmium and cadmium compounds are also regulated under the Resource Conservation and Recovery Act (RCRA) and Superfund Amendments and Reauthorization Act (SARA). Both RCRA and SARA subject cadmium and its compounds to reporting requirements.

FDA, under FD&CA, has set a maximum concentration level of 0.005 mg Cd/L in bottled water and limits the amount of cadmium in color additives and direct food additives.

In 1984, NIOSH recommended that exposure to cadmium be reduced to the lowest possible level (NIOSH, 1996).

OSHA adopted permissible exposure limits (PELs) for toxic effects other than cancer for cadmium: 0.1 mg/m^3 as an 8-hr time-weighted average (TWA) for fumes, 0.3 mg/m^3 as a ceiling for fumes, 0.2 mg/m^3 as an 8-hr TWA for dust, and 0.6 mg/m^3 as a ceiling for dust; the standards were adopted by OSHA. OSHA regulates cadmium and certain cadmium compounds under the Hazard Communication Standard and as chemical hazards in laboratories.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
CPSC	45 FR 51631. Published 8/4/80. CPSC 10: Commission denied a petition for a rule declaring sewage sludge products banned hazardous substances.	The Commission noted that sludges may contain high levels of cadmium and cadmium compounds, but declined to act based on anticipated EPA action on this matter. (Some municipal sewage sludges have been sold as fertilizers for home use.)
EPA	40 CFR 60—PART 60—STANDARDS OF PERFORMANCE FOR NEW STATIONARY SOURCES. Promulgated: 36 FR 24877, 12/23/71. The provisions of this part apply to cadmium, cadmium chloride, cadmium sulfate, and cadmium sulfide.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 60.740—Subpart VVV—Standards of Performance for Polymeric Coating of Supporting Substrates Facilities. The provisions of this part apply to cadmium, cadmium chloride, cadmium sulfate, and cadmium sulfide.	
	40 CFR 61—PART 61—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS. Promulgated: 38 FR 8826, 04/06/73. U.S. Code: 7401, 7412, 7414, 7416, 7601. The provisions of this part apply to cadmium.	This part lists substances that, pursuant to section 112 of the CAA, have been designated as hazardous air pollutants, and applies to the owner or operator of any stationary source for which a standard is prescribed under this part.
	40 CFR 63—PART 63—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Code: 7401 et seq. The provisions of this part apply to cadmium and cadmium compounds (not otherwise specified).	Standards that regulate specific categories of stationary sources that emit (or have potential to emit) one or more hazardous air pollutants are listed in this part pursuant to section 112(b) of the CAA.
	40 CFR 63.70—Subpart D—Regulations Governing Compliance Extensions for Early Reductions of Hazardous Air Pollutants. The provisions of this part apply to cadmium.	The provisions of this subpart apply to an owner/operator of an existing source wishing to obtain a compliance extension from a standard issued under section 112(d) of the CAA.
	40 CFR 116—PART 116—DESIGNATION OF HAZARDOUS SUBSTANCES. Promulgated: 43 FR 10474, 03/13/78. U.S. Code: 33 U.S.C. 1251 et seq. The provisions of this part apply to cadmium, cadmium chloride, cadmium acetate, and cadmium bromide.	This regulation designates hazardous substances under section 311(b)(2)(a) of the FWPCA. The regulation applies to discharge of the substances identified in table 116.4 to surface waters.
	40 CFR 116.4—Sec. 116.4 Designation of hazardous substances. U.S. Code: FWPCA 311(b)(2)(A) and 501(a) as amended by the CWA of 1977.	RQs apply to discharges of substances listed, including isomers and hydrates and any solutions or mixtures containing the substances.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 117—PART 117—DETERMINATION OF REPORTABLE QUANTITIES FOR HAZARDOUS SUBSTANCES. U.S. Code: FWPCA 311(b)(2)(A) and 501(a) as amended by the CWA of 1977. The provisions of this part apply to cadmium chloride, cadmium acetate, cadmium bromide.	Discharges to water of amounts equal to or greater than the reportable quantities (RQ) must be reported to EPA.
	40 CFR 117.3—Sec. 117.3 Determination of Reportable Quantities.	**Compound** **RQ (lb)** Cadmium acetate 10 Cadmium bromide 10 Cadmium chloride 10
	40 CFR 122—PART 122—EPA ADMINISTERED PERMIT PROGRAMS: THE NATIONAL POLLUTANT DISCHARGE ELIMINATION SYSTEM. Promulgated: 48 FR 14153, 04/01/83. U.S. Code: 33 U.S.C. 1251 et seq., the CWA. The provisions of this part apply to cadmium.	Regulations cover basic EPA permitting requirements for effluent discharges from point sources to waters of the United States. Appendix D lists pollutants that must be identified by dischargers if expected to be present.
	40 CFR 122.21 ff.—Subpart B—Permit Application and Special NPDES Program Requirements. Promulgated: 48 FR 14153, 04/01/83, as amended through 55 FR 48062, 11/16/90. The provisions of this part apply to cadmium.	Specific requirements pertaining to application for a NPDES permit (applicability, time to apply).
	40 CFR 131—PART 131—WATER QUALITY STANDARDS. Promulgated: 48 FR 51405, 11/08/83. U.S. Code: 33 U.S.C. 1251 et seq. (CWA). The provisions of this part apply to cadmium.	A water quality standard defines the water quality goals of a water body, or portion thereof, by designating the use or uses to be made of the water, and setting criteria necessary to protect the uses. This part describes the requirements and procedures for developing, reviewing, revising, and approving water quality standards by the States as authorized by section 303(c) of the CWA.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 132—PART 132—WATER QUALITY GUIDANCE FOR THE GREAT LAKES SYSTEM. The provisions of this part apply to cadmium.	
	40 CFR 136—PART 136—GUIDELINES ESTABLISHING TEST PROCEDURES FOR THE ANALYSIS OF POLLUTANTS. U.S. Code: 33 U.S.C. 1251, et seq. The provisions of this part apply to cadmium and cadmium nitrate.	The procedures described in this part shall be used whenever the waste constituent specified is required to be measured for section 402 of the CWA and/or reports required to be submitted under NPDES permits.
	40 CFR 141—PART 141—NATIONAL PRIMARY DRINKING WATER REGULATIONS. Promulgated: 40 FR 59570, 12/24/75. U.S. Code: Public Health Service Act sections 1413-1416, 1445, and 1450 as amended by 1974 SDWA; U.S.C. 300. The provisions of this part apply to cadmium.	To protect a safe drinking water supply, community and non-transient, non-community water systems must monitor for certain compounds listed.
	40 CFR 141.31 ff.—Subpart D—Reporting, Public Notification and Recordkeeping. The provisions of this subpart apply to cadmium.	A supplier of water shall report to the State the results of any test measurement or analysis required by this part. This part gives background information on several compounds with health concerns at certain levels of exposure.
	40 CFR 141.50 ff.—Subpart F—Maximum Contaminant Level Goals. Promulgated: 50 FR 46901, 11/13/85, and others.	The maximum contaminant level goal (MCLG) for cadmium is 0.005 mg/L.
	40 CFR 141.60 ff.—Subpart G—National Revised Primary Drinking Water. Regulations: Maximum Contaminant Levels. The provisions of this subpart apply to cadmium. Promulgated: 52 FR 25716, 07/08/87.	Maximum contaminant levels apply to community water systems and non-transient, non-community water systems based on the best available technology treatment techniques. The maximum contaminant level for cadmium in community water systems and non-transient, non-community water systems is 0.005 mg/L.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 148—PART 148—HAZARDOUS WASTE INJECTION RESTRICTIONS. Promulgated: 53 FR 28154, 07/26/88. The provisions of this part apply to cadmium.	Hazardous wastes to be restricted from EPA Class I hazardous waste injection wells are identified.
	40 CFR 165—PART 165—REGULATIONS FOR THE ACCEPTANCE OF CERTAIN PESTICIDES AND RECOMMENDED PROCEDURES FOR THE DISPOSAL AND STORAGE OF PESTICIDES AND PESTICIDE CONTAINERS. The provisions of this part apply to cadmium.	All cadmium pesticides have undergone voluntary cancellation (OPP, 1997)
	40 CFR 192—PART 192—HEALTH AND ENVIRONMENTAL PROTECTION STANDARDS FOR URANIUM AND THORIUM MILL TAILINGS. Promulgated: 48 FR 602, 01/05/83. U.S. Code: 42 U.S.C. 2022, as added by the Uranium Mill Tailings Radiation Control Act of 1978. The provisions of this part apply to cadmium.	The provisions of this part control the residual radioactive material at designated processing or depository sites under section 108 of the Uranium Mill Tailings Radiation Control Act of 1978, and apply to the restoration of such sites following any use of the subsurface minerals under section 104(h) of the Uranium Mill Tailings Radiation Control Act of 1978.
	40 CFR 227—PART 227—CRITERIA FOR THE EVALUATION OF PERMIT APPLICATIONS FOR OCEAN DUMPING OF MATERIALS. Promulgated: 42 FR 2476, 01/11/77. U.S. Code: 33 U.S.C. 1412 and 1418. The provisions of this part apply to cadmium compounds.	Ocean dumping permits will be based on an evaluation of the permit application pursuant to the criteria set forth in this part and upon the requirements set for disposal site management pursuant to the criteria set forth in part 228 of this subchapter H.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 228—PART 228—CRITERIA FOR THE MANAGEMENT OF DISPOSAL SITES FOR OCEAN DUMPING. Promulgated: 42 FR 2482, 01/11/77. U.S. Code: 33 U.S.C. 1412 and 1418. The provisions of this part apply to cadmium.	The criteria of this part apply to the evaluation of proposed ocean dumping under Title I of the Act, and effective management of ocean disposal sites to prevent unreasonable degradation of the marine environment from all wastes being dumped in the ocean.
	40 CFR 257—PART 257—CRITERIA FOR CLASSIFICATION OF SOLID WASTE DISPOSAL FACILITIES AND PRACTICES. Promulgated: 44 FR 53460, 09/13/79. U.S. Code: 42 U.S.C. 6907(a)(3) and 6944(a); 33 U.S.C. 1345(d). The provisions of this part apply to cadmium.	Appendix I gives max. contaminant levels to determine whether waste disposal activities comply with the ground-water criteria of 40 CFR 257.3-4.
	40 CFR 258—PART 258—CRITERIA FOR MUNICIPAL SOLID WASTE LANDFILLS. Promulgated: 56 FR 51016, 10/09/91. U.S. Code: 33 U.S.C. 1345(d) and (e); 42 U.S.C. 6907(a)(3), 6912(a), 6944(a) and 6949a(c). The provisions of this part apply to cadmium.	The provisions of this part establish minimum national criteria under RCRA, as amended, for all MSWLF units and under the CWA, as amended, for MSWLF that are used to dispose of sewage sludge. The criteria ensure the protection of human health and the environment.
	40 CFR 279—PART 279—STANDARDS FOR THE MANAGEMENT OF USED OIL. Promulgated: 57 FR 41612, 09/10/92. When burned for energy, used oil exceeding any "Allowable Level" (AL) in Table 1 is subject to this part. Limits: AL for cadmium is 2 ppm (maximum concentration).	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTE, Appendix VIII—Hazardous Constituents. Promulgated: 45 FR 33119, 05/19/80; 53 FR 13388, 04/22/88. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, 6922, and 6938. Cadmium and cadmium compounds are listed in Appendix VIII as hazardous constituents of waste; however, hazardous waste numbers (HWN) are not given for either listing.	Appendix VIII is a consolidated list of hazardous constituents identified in this part. Solid wastes containing these constituents are subject to notification requirements of RCRA section 3010 and must be disposed of in RCRA-permitted facilities.
	40 CFR 261—Subpart D—Lists of Hazardous Wastes. The provisions of this part apply to cadmium compounds.	
	40 CFR 264.90 ff.—Subpart F—Releases From Solid Waste Management Units. The provisions of this part apply to cadmium.	All solid waste management units must comply with the requirements in CFR 264.101.
	40 CFR 264.272 ff.—Subpart M—Land Treatment. Promulgated: 47 FR 32361, 07/26/82. The provisions of this subpart apply to cadmium.	Owner/operator subject to this subpart must establish a land treatment program that is designed to ensure that hazardous constituents placed in or on the treatment zone are degraded, transformed, or immobilized within the treatment zone.
	40 CFR 266—Subpart H—Hazardous Waste Burned in Boilers and Industrial Furnaces. The provisions of this part apply to cadmium.	Appendix V to Part 266 lists a risk specific dose (for carcinogenicity; 10^{-5}) of 5.6×10^{-3} $\mu g/m^3$ for cadmium: The sum for all compounds of the ratios of the actual ground level concentration to the level established in Appendix V cannot exceed 1.0 $\mu g/m^3$.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 268—PART 268—LAND DISPOSAL RESTRICTIONS. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, and 6924. The provisions of this part apply to cadmium.	If a generator's waste is listed in 40 CFR part 261, subpart D, the generator must test his waste. This part identifies hazardous wastes that are restricted from land disposal and defines those limited circumstances under which an otherwise prohibited waste may continue to be disposed.
	40 CFR 268.40 ff.—Subpart D—Treatment Standards. Promulgated: 56 FR 3879, 01/31/91. The provisions of this part apply to cadmium.	Restricted wasted identified in sec. 268.41 may be land disposed only if an extract of the waste or of the treatment residue of the waste developed using the test method in Appendix II of part 261 does not exceed the value shown in Table CCWE of sec.268.41 for any hazardous constituent listed in CCWE for that waste; exceptions do apply.
	40 CFR 300—PART 300—NATIONAL OIL AND HAZARDOUS SUBSTANCES POLLUTION CONTINGENCY PLAN. Promulgated: 55 FR 8813, 03/08/90. U.S. Code: 42 U.S.C. 9605; 42 U.S.C. 9620; 33 U.S.C. 1321(c)(2). The provisions of this part apply to cadmium.	This part provides the organizational structure and procedures for preparing for and responding to discharges of oil and releases of hazardous substances, pollutants, and contaminants which may present an imminent and substantial danger to public health or welfare.
	40 CFR 300—Subpart J—Use of Dispersants and Other Chemicals. The provisions of this part apply to cadmium.	
	40 CFR 302—PART 302—DESIGNATIION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 5 0 FR 13474, 04/04/85. U.S. Code: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361. The provisions of this part apply to cadmium, cadmium acetate, cadmium bromide, cadmium chloride, and cadmium compounds.	40 CFR Part 302 designates under section 102(a) of CERCLA 1980 those substances in the statutes referred to in section 101(14) of CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of the substances. This part also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 302.4—Sec. 302.4 Designation of hazardous substances.	EPA designated as hazardous those substances that when released into the environment may present substantial danger to the public health or welfare or the environment. Notification of EPA is required if the RQ is released to the environment.
	40 CFR 302.6—Sec. 302.6 Notification requirements.	**Compound** — **Final RQ (lb)** Cadmium — 10 Cadmium acetate — 10 Cadmium bromide — 10 Cadmium chloride — 10 Cadmium compounds — not given
	40 CFR 355—PART 355—EMERGENCY PLANNING AND NOTIFICATION. Promulgated: 52 FR 13395, 04/22/87. U.S. Code: 42 U.S.C. 11002, 11004, and 11048. The provisions of this part apply to cadmium oxide and cadmium stearate. The threshold planning quantities for cadmium oxide and cadmium stearate are 100/10,000 lb. and 1000/10,000 lb., respectively.	The provisions of this part establish the list of extremely hazardous substances, threshold planning quantities, and facility notification responsibilities necessary for the development and implementation of State and local emergency response plans.
	40 CFR 355.50—Sec. 355.50 Penalties.	
	40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Code: 42 U.S.C. 11013, 11028. This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of SARA (1986). The provisions of this part apply to cadmium.	Information collected under this part is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, to aid in the development of regulations, guidelines, and standards. See section 372.65 for chemicals and chemical categories to which this part applies.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 372—Subpart D—Specific Toxic Chemical Listings. The provisions of this part apply to cadmium.	
	40 CFR 372.65—Sec. 372.65 Chemicals and chemical categories to which this part applies. The provisions of this part apply to cadmium.	
	40 CFR 401—PART 401—GENERAL PROVISIONS. Promulgated: 39 FR 4532, 02/01/74, as amended at 47 FR 24537, 06/04/82. U.S. Code: 33 U.S.C. 1251 et seq. The provisions of this part apply to cadmium.	The provisions of this part set forth the legal authority and general definitions which will apply to all regulations issued concerning specific classes and categories of point sources of industrial effluents under parts 402 through 699.
	40 CFR 403—PART 403—GENERAL PRETREATMENT REGULATIONS FOR EXISTING AND NEW SOURCES OF POLLUTION. Promulgated: 46 FR 9439, 01/28/81. U.S. Code: Several sections of the FWPCA and the CWA of 1977 (Public Law 95-217). The provisions of this part apply to cadmium.	Establishes responsibilities of federal, state, and local government; industry; and the public to implement National Pretreatment Standards to control pollutants that pass through POTWs and contaminate sewage sludge or interfere with treatment processes.
	40 CFR 413—PART 413—ELECTROPLATING POINT SOURCE CATEGORY. Promulgated: 46 FR 9467, 01/28/81. U.S. Code: 33 U.S.C. 1251 et seq. as amended by the CWA of 1977 (Public Law 95-217). The provisions of this part apply to cadmium.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 415—PART 415—INORGANIC CHEMICALS MANUFACTURING POINT SOURCE CATEGORY. Promulgated: 47 FR 28278, 06/29/82. U.S. Code: 33 U.S.C. 1311; 1314(b), (c), (e), and (g); 1317(b) and (c); and 1361. The provisions of this part apply to cadmium, cadmium chloride, cadmium sulfate, cadmium sulfide, and cadmium nitrate.	Limitations depend on the specific compound and specific industry category. Pretreatment standards for existing sources (PSES) and new sources (NSPS) are given for effluents from specific industries achievable by appropriate pretreatment.
	40 CFR 421—PART 421—NONFERROUS METALS MANUFACTURING POINT SOURCE CATEGORY. The provisions of this part apply to cadmium. Promulgated: 49 FR 8790, 03/08/84. U.S. Code: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), 1318, and 1361.	The provisions of this part apply to facilities producing primary metals from ore concentrates and recovering secondary metals from recycle wastes which discharge pollutants to waters of the U.S. or which introduce or may introduce pollutants into a POTW.
	40 CFR 421.50 ff.—Subpart E—Primary Electrolytic Copper Refining Sub-category. The provisions of this subpart apply to cadmium.	
	40 CFR 421.80 ff.—Subpart H—Primary Zinc Subcategory. The provisions of this subpart apply to cadmium.	
	40 CFR 421.90 ff.—Subpart I—Metallurgical Acid Plants Subcategory. The provisions of this subpart apply to cadmium.	
	40 CFR 421.190 ff.—Subpart Q—Secondary Indium Subcategory. The provisions of this subpart apply to cadmium.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 423—PART 423—STEAM ELECTRIC POWER GENERATING POINT SOURCE CATEGORY. Promulgated: 47 FR 52304, 11/19/82. U.S. Code: 33 U.S.C. 1311; 1314(b), (c), (e), and (g); 1316(b) and (c); 1317 (b) and (c); 1361.	The provisions of this part apply to discharges resulting from the operation of a generating unit by an establishment generating electricity for distribution and sale which results from a process utilizing fossil-type or nuclear fuel in conjunction with a thermal cycle that uses the steam water system as the thermodynamic medium.
	40 CFR 440—PART 440—ORE MINING AND DRESSING POINT SOURCE CATEGORY. Promulgated: 47 FR 54609, 12/03/82. U.S. Code: 33 U.S.C. 1311, 1314(b), (c), and (e), 1316, 1317, and 1361. The provisions of this part apply to cadmium.	The provisions of subparts A through M are applicable to discharges from mines operated to obtain iron, aluminum, uranium, radium, vanadium, mercury, titanium, tungsten, nickel, antimony, copper, lead, zinc, gold, silver, molybdenum, and platinum ore.
	40 CFR 455—PART 455—PESTICIDE CHEMICALS. Promulgated: 43 FR 17776, 04/25/78. U.S. Code: 33 U.S.C. 1311, 1314, 1316, 1317, and 1361. The provisions of this part apply to cadmium.	
	40 CFR 461—PART 461—BATTERY MANUFACTURING POINT SOURCE CATEGORY. Promulgated: 49 FR 9134, 03/09/84. U.S. Code: U.S.C. 1311, 1314(b). The provisions of this part apply to cadmium.	The provisions of A through G apply to battery manufacturing plants that discharge or may discharge a pollutant to waters of the U.S. or that introduce pollutants to a POTW.
	40 CFR 469—Subpart A—Semiconductor Subcategory. The provisions of this subpart apply to cadmium.	Numerous chromium and cadmium effluent limitations.
	40 CFR 471—PART 471—NONFERROUS METALS FORMING AND METAL POWDERS POINT SOURCE CATEGORY. Promulgated: 50 FR 34270, 08/23/85. U.S. Code: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), and 1361.	The provisions of this part apply to discharges of pollutants to waters of the U.S. and into POTWs from the forming of nonferrous metals (including nonferrous metal alloys), except beryllium, copper, and aluminum and their alloys.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
EPA	40 CFR 471—Subpart D—Precious Metals Forming Subcategory. The provisions of this subpart apply to cadmium.	
	40 CFR 471—Subpart G—Uranium Forming Subcategory. The provisions of this subpart apply to cadmium.	
	40 CFR 503—PART 503—STANDARDS FOR THE USE OR DISPOSAL OF SEWAGE SLUDGE. The provisions of this part apply to cadmium.	
	40 CFR 795—PART 795—PROVISIONAL TEST GUIDELINES. The provisions of this part apply to cadmium.	
FDA	21 CFR 73—PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION. Promulgated: 42 FR 15643, 03/22/77. U.S. Code: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.	This part lists color additives that are exempt from certification in foods, drugs, cosmetics, and medical devices.
	21 CFR 73.1001ff.—Subpart B—Drugs.	The color additives listed may be safely used in amounts consistent with good manufacturing practice to color externally applied drugs, including those for use around eyes.
	21 CFR 73.1646—Sec. 73.1646 Bronze powder.	The color additive bronze powder shall not contain more than 15 ppm cadmium.
	21 CFR 73.1647—Sec. 73.1647 Copper powder.	The color additive copper powder shall not contain more than 15 ppm cadmium.
	21 CFR 73.1991—Sec. 73.1991 Zinc oxide.	The color additive zinc oxide shall not contain more than 15 ppm cadmium.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 165—PART 165—BEVERAGES. Promulgated: 60 FR 57124, 11/13/95 effective 5/13/96. U.S. Code: 21 U.S.C. 321, 341, 343, 343A, 348, 349, 371, 379e.	The regulations in subparts A and B govern the labeling and effective chemical substance limits for specific standardized beverages.
	21 CFR 165.110 ff.—Subpart B—Requirements for Specific Standardized Beverages—Bottled Water.	Allowable concentration of cadmium in bottled water is 0.005 mg/L.
	21 CFR 172—PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION. Promulgated: 42 FR 14491, 03/15/77. U.S. Code: 21 U.S.C. 321, 341, 342, 348, 371, 379e.	The regulations in subparts A through I govern the amount of food additives allowed for human consumption.
	21 CFR 172.310 ff.—Subpart D—Special Dietary and Nutritional Additives.	Allowable concentrations of cadmium in various special dietary and nutritional additives are 0.05-0.1 ppm.
	21 CFR 172.800 ff.—Subpart I—Multipurpose Additives.	Allowable concentration of cadmium in baker's yeast glycan (based on dry weight) is 0.13 ppm.
	21 CFR 184—PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE. Promulgated: 42 FR 14653, 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348, 371.	Substances, directly added to human food, that are generally recognized as safe (GRAS) are listed.
	21 CFR 184.1005 ff.—Subpart B—Listing of Specific Substances Affirmed as GRAS.	
	21 CFR 184.1983—Sec. 184.1983 Baker's yeast extract.	Baker's yeast extract cannot contain (on a dry weight basis) more than 0.13 ppm cadmium.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
NIOSH	8/76. Criteria for a Recommended Standard: Occupational Exposure to Cadmium.	Summary of current NIOSH recommendation: exposure limit—Ca, lowest feasible concentration.
	8/23/76. Recommended that exposure to cadmium be limited to a 10-hr TWA of 40 $\mu g/m^3$ and a ceiling limit of 200 $\mu g/m^3$ (as sampled over 15 min).	This recommendation was based on observed adverse lung and kidney effects.
	9/84. Recommended that exposure to cadmium be reduced to the lowest feasible level.	Based upon lung cancer, prostatic cancer, and renal system effects.
	9/27/84. Current intelligence bulletin #42—Cadmium.	
	5/7/90. Comments to the Department of Labor, proposed rule on occupational exposure to cadmium	
	7/17/90. Testimony to the Department of Labor, proposed rule on occupational exposure to cadmium.	
	9/4/90. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure.	
OSHA	29 CFR 1910.1000—Sec. 1910.1000 Air Contaminants. Promulgated: 58 FR 40191, 07/27/93. OSH Act: Air Contaminants.	PEL (fumes) $\leq$ 0.1 mg/m^3 (as Cd) 8-hr TWA, 0.3 mg/m^3 ceiling; PEL (dust) $\leq$ 0.2 mg/m^3 (as Cd) 8-hr TWA, 0.6 mg/m^3 ceiling.
	29 CFR 1910.1200, 1915, 1917, 1918, 1926, 1928. Promulgated 11/25/83. OSH Act: Hazard Communication.	Requires chemical manufacturers and importers and all employers to assess chemical hazards and to provide information to employees. Hazard Communication Program to include labels, material safety data sheets, and worker training.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
OSHA	29 CFR 1910.1450—Sec. 1910.1450 Occupational Exposure to Hazardous Chemicals in Laboratories. Promulgated: 61 FR 5508, 02/13/96. OSH Act: Final rule for occupational exposure to hazardous chemicals in laboratories.	As a select carcinogen (IARC Group 2A), cadmium and certain cadmium compounds are listed as chemical hazards in laboratories. Employers are required to provide employee information and training and a Chemical Hygiene Plan.

[a] The regulations in this table have been updated through 62 FR 41162, July 31, 1997.

3.0 HUMAN STUDIES

3.1 Review of Cadmium Epidemiology (IARC, 1993)

The IARC Working Group for consideration of metallic cadmium, cadmium alloys, and some cadmium compounds concluded that there is sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds (IARC, 1993, pp. 148-161; see Appendix A). The majority of reviewed studies evaluated the risk from occupational cadmium exposure. These studies provided strong, consistent evidence that the risk for lung cancer is increased among workers exposed to cadmium.

In general, earlier studies indicated that there was an increased risk of prostate cancer among cadmium workers, but later studies did not confirm the increase risk. A review of epidemiologic studies on cadmium and prostate cancer (Waalkes and Rehm, 1994a) noted several problems. The studies almost exclusively examined European populations; most studies were limited to fatal cancers; and possible risk factors (confounders) in prostate carcinogenesis (e.g., zinc, androgens, and estrogens) have never been incorporated in the occupational analyses. Stayner et al. (1995), using data from the NIOSH cadmium study (Lemen et al., 1976), performed a statistical evaluation of several statistical and biological models for quantitative risk assessment and found that the selection of a particular model may greatly influence risk estimation.

3.2 Human Studies Published Post-IARC (1993)

Full design details and results for the studies described in this section are presented in **Table 3-1**. All standardized mortality ratios (SMRs) have been converted to base 1, to facilitate comparison with risk and odds ratios (RRs and ORs).

3.2.1 Occupational Exposure

3.2.1.1 Case-Control Studies

Rooney et al. (1993) conducted a nested case-control study of prostate cancer among workers of the United Kingdom Atomic Energy Authority. The cases (n = 136) were men who worked for the United Kingdom Atomic Energy Authority and either died from prostate cancer or were diagnosed with prostate cancer before 1987. Confirmation of the diagnosis was obtained

for 70% of cases. The controls (n = 404) were men who worked for the Authority and did not have prostate cancer. The cases were matched with the controls by year and age of starting work, last place of work, ever having been monitored for ionizing radiation, and survival. Based on the work of the subject and his/her exposure history obtained from records, health physicists classified exposure level as none (or unlikely), probable but relatively low, or probable and relatively high. No information on potential confounding factors was used in the study. Twelve cases (9%) and 35 controls (9%) were considered exposed. No association was found between potential occupational exposure to cadmium and prostate cancer (OR = 1.06; CI = 0.46-2.30).

In a population-based study conducted by Siemiatycki et al. (1994), 484 male residents of Montreal with bladder cancer diagnosed between 1979 and 1986 were compared with 533 population-based controls identified from voter lists and random digit dialing, and with 1879 controls with cancer at other sites (excluding lung and kidney). Potential exposure to a variety of substances was determined using job histories, and a detailed review was conducted by a team of industrial hygienists and chemists. Occupational exposure to cadmium compounds was classified as either nonsubstantial or substantial based on rater confidence, latency, duration, and concentration and frequency. The risk of bladder cancer was increased at the substantial exposure level for cadmium (OR = 4.0 [CI = 1.0-16.3]), adjusting for age, ethnicity, socioeconomic status, smoking, coffee consumption, and status (self/proxy) of the respondent. After adjustment for these factors and exposure to other occupational exposures, the odds ratio was 3.2 (CI = 0.7- 13.6).

A follow-up to the Siemiatycki et al. (1994) study was conducted by Aronson et al. (1996), in which occupational risk factors for prostate cancer were analyzed. The results from a case-control study in Montreal, Quebec, were used: cases included 449 males with prostate cancer diagnosed between 1979 and 1985, controls included 533 population-based controls and 1,550 cancer controls. Cancer controls were cancer patients excluding those with lung cancer. Lifetime exposure to cadmium compounds based on occupation was determined by personal interview or proxy. Occupational exposure (substantial or non-substantial) was defined as in the Siemmiatycki et al. (1994) study. No substantial exposure cases were found. The odds ratio of prostate cancer from cadmium for the non-substantial exposure group was not statistically significant (partially-adjusted OR = 1.01, CI = 0.36-2.82; fully-adjusted OR = 0.83, CI 0.28-2.48).

Mandel et al. (1995) evaluated occupational exposure to cadmium in an international multicenter case-control study of renal cell carcinoma. The 1732 incident cases (1050 men, 682 women) included patients aged 20-79 years diagnosed with renal-cell adenocarcinoma between 1989 and 1991 in six geographic regions in five countries. Population-based controls (1429 men, 880 women) were selected using a variety of methods and were frequency matched by sex and age. Potential exposure to cadmium was based on self-report. An association was found for the entire cadmium group before stratification for duration (OR = 2.0 [CI = 1.0-3.9]). When exposure was further analyzed by duration, it was determined that the risk of renal-cell adenocarcinoma in men actually decreased with increasing length of exposure (1-11 yr, OR = 4.3 [CI = 1.5-12.2]; 12-30 yr, OR = 1.0 [CI = 0.3-3.6]; 31-44 yr, OR = 1.0 [CI = 0.3-3.7]). Therefore, the authors stated that these findings would "argue against a causal interpretation" of the association between exposure to cadmium and the increased risk of renal-cell carcinoma. Data for women was not given, but were described as not significant.

van der Gulden et al. (1995) conducted a case-control study of prostate cancer in the Netherlands. The cases were men (mean age 72 years) diagnosed with prostate cancer between January 1988 and April 1990, selected from a Netherlands regional cancer registry. The controls were male patients (mean age 69 years) treated for prostate hyperplasia and with no signs of malignancy in one hospital from the same region during the same period. Self-administered mail questionnaires with supplemental items for metal workers were used to obtained exposure data. The questionnaire also obtained data on potential confounding factors. Eighteen cases and 73 controls were either sometimes exposed or frequently exposed (definition of sometimes exposed and frequently exposed were not given) to cadmium (age-adjusted OR = 1.10; CI = 0.64-1.89). An association was found for frequent exposure to cadmium (7 cases and 11 controls; OR = 2.76; CI = 1.05-7.27). It can be argued that the choice of a single hospital, among 17 in the region, for selecting controls was not justified, nor was there enough detail provided on the selection of potential confounders.

3.2.1.2 Cohort Studies

Sorahan et al. (1995) conducted an updated analysis of a cohort evaluated previously by Bonnell (1959; cited by Sorahan et al., 1995) and Holden (1980a,b; cited by Sorahan et al., 1995). The analysis included data from an additional 13 years of follow-up. A total of 347 male copper-cadmium alloy workers were included in the study. The workers had begun employment in one of two factories (factory A or factory B) between 1922 and 1978 and were employed for a minimum of 1 year. They had been exposed to a mean level of 69.6 μg Cd/m^3 from 1926 to 1980 and were followed up through December 1992. Sorahan et al. (1995) also included 624 vicinity workers (workers employed in a workshop in which copper-cadmium alloy was made, but were never employed directly in the production of copper-cadmium alloys) from factory B and 521 iron and brass foundry workers in their follow-up study. Vicinity workers had a mean cadmium exposure level of 6.16 μg/m^3 from 1926-1980. All groups of workers were followed up through December 1992.

Compared to the general population of England and Wales, the lung cancer mortality experience of the copper-cadmium alloy workers was close to the expected value (observed 18, expected 17.84, SMR 1.01 [0.60-1.59]). When the mortality of copper-cadmium alloy workers, vicinity workers, and foundry workers was evaluated by time from start of employment, the SMR for nonmalignant diseases of the respiratory system was increased in all groups (alloy workers: observed 54, expected 23.5, SMR 2.30; vicinity workers: observed 71, expected 43.0, SMR 1.65; foundry workers: observed 34, expected 17.1, SMR 1.99). The SMR for lung cancer was also increased in vicinity workers, but not iron and brass foundry workers (observed 55, expected 34.3, SMR 1.60).

Work histories of the copper-cadmium alloy workers and assessment by an industrial hygienist, health physicist, and others were used to develop individual estimates of cumulative cadmium exposure. A Poisson regression was used to evaluate differences in mortality between exposure categories with adjustments for age, year of starting alloy work, factory, and duration alloy work. The relative risk of developing nonmalignant chronic respiratory diseases for these workers increased with increasing cumulative exposure to cadmium (a comparison was made to a group of copper-cadmium alloy workers with low exposure, < 1600 μg Cd/m^3). The relative risk was calculated as unlagged, or was lagged by 10 years. Under unlagged conditions, RRs were as

follows: < 1600 μg/m^3 (1.0); 1600-4800 μg/m^3 (4.54 [1.96-10.51]); ≥ 4800 μg/m^3 (4.74 [1.81-12.43]). With a lag of 10 years, RRs were as follows: < 1600 μg/m^3 (1.0); 1600-4800 μg/m^3 (2.57 [1.20-5.49]); ≥ 4800 μg/m^3 (4.21 [1.67- 10.58]). Both trends were statistically significant (unlagged, 1.96 [1.27-3.02]; lagged, 2.02 [1.29-3.17]). There was no increased risk for lung cancer in the workers at any level of cadmium exposure (relative to lowest exposure level, middle exposure category RR = 0.85; CI = 0.27-2.68; highest exposure category RR = 0.81; CI = 0.18-3.73). Lagged analyses did not show elevated RRs. The study results indicate an association between cadmium exposure and an increased risk of nonmalignant chronic respiratory diseases, but not lung cancer. The potential confounding effects of other occupational exposures and the small number of exposed workers in the lung cancer analyses limit interpretation.

Sorahan and Lancashire (1997) reanalyzed the mortality data of 571 male production workers from a cadmium recovery facility in the United States. Newly abstracted and detailed job history data for 1926-1976 were used to derive estimates of individual cumulative cadmium exposure. In addition, an exposure assessment was performed for arsenic compounds. A Poisson regression was used to estimate the relative risk of lung cancer in relation to four cumulative cadmium exposure categories (< 400, 400-999, 1000-1999, > 2000 mg/m^3·days). Adjustments were made for age, year of hire, and Hispanic ethnicity. A significant trend for increasing relative risk with higher cadmium exposure level was found [relative to the lowest category, RR = 2.30 (CI = 0.72-7.36) for the second level; RR = 2.83 (CI = 0.75-10.72) for the third level; RR = 3.88 (CI = 1.04-14.46) for the fourth level]. Lagging the exposure by 10 and 20 years appeared to strengthen the trend. An additional analysis was conducted as an attempt to evaluate the joint effects of cadmium and arsenic exposure. The estimated cumulative cadmium exposure was stratified by departments with either high or minimal arsenic exposure. The dose-response relationship between cadmium exposure and risk of lung cancer was significant for the departments with high arsenic exposure (cumulative cadmium exposure ≥ 1000, RR = 4.02, CI = 1.34-12.03), but not significant for departments with minimal or no arsenic exposure, although the highest cadmium level RR was elevated (≥ 1000 RR = 2.68, CI = 0.80- 2.00). The suggested association between cadmium and risk of lung cancer is uncertain because of the results with arsenic.

3.2.2 Nonoccupational Exposure

3.2.2.1 Exposure from Accidental Cadmium Releases

A follow-up study to the 1974-1975 survey by Ishikawa Prefectural Health Authority on the inhabitants of the cadmium-polluted Kakehashi River basin in Ishikawa Prefecture, Japan, was conducted by Nishijo et al. (1995). In the study, the residents were classified as either urinary retinol binding protein (RBP)-negative or positive (< 4 or 4 mg/L). Cadmium exposure is related to renal tubular dysfunction and urinary RBP is an indicator of renal dysfunction. The study included 2408 residents (1079 men, 1329 women) who were exposed to cadmium from an upstream copper mine. An SMR analysis was conducted using mortality data for the general Japanese population (number not given). Adjusted for age, death from the following conditions was increased in RBP-positive subjects, as compared to RBP-negative subjects: diabetes mellitus (women only, 5/113 vs. 4/1216, SMR 7.31 vs. 0.60), cardiovascular diseases (men, 14/65 vs. 76/1014, SMR 1.82 vs. 0.83; women, 28/113 vs. 96/1216, SMR 1.97 vs. 1.04), respiratory diseases (men only, 8/65 vs. 43/1014, SMR 2.06 vs. 0.96), and kidney and urinary

diseases (men, 4/65 vs. 11/1014, SMR 6.28 vs. 1.32; women, 5/113 vs. 12/1216, SMR 4.32 vs. 1.35). When all exposed subjects (RBP-negative and -positive) were compared to general population controls, death from malignant neoplasms of the respiratory system (men only, observed 16/1079, SMR 0.609), ischaemic heart disease (men only, observed 24/1079, SMR 0.632), heart failure (women only, observed 86/1329, SMR 1.79), digestive diseases (women only, observed 24/1329, SMR 1.66), kidney and urinary diseases (men, observed 15/1079, SMR 1.67; women, observed 17/1329, SMR 1.63), and senility (men, observed 26/1079, SMR 1.78; women, observed 67/1329, SMR 2.49) was increased. Incidences in the general population were not given.

Nakagawa et al. (1996) conducted a follow up study of a 1981-1982 survey of inhabitants (aged ≥ 50 years) of cadmium polluted areas in the Ishikawa Prefecture, Japan. The 3178 subjects were classified as either urinary β_2-microglobulin-negative or -positive (urinary β_2-microglobulin is an indicator of renal tubular dysfunction) and were observed until the end of March 1991. The mortality rate in the general Japanese population (number not given) during the study period was used as a control.

SMR values were significantly higher in urinary β_2-microglobulin-positive subjects than in urinary β_2-microglobulin-negative subjects for cardiovascular disease (women only, 39/329 vs. 37/1425; SMR 1.58 vs. 0.86), heart failure (men, 19/205 vs. 19/1219, SMR 2.08 vs. 0.77; women, 32/329 vs. 24/1425, SMR 2.40 vs. 1.09), cerebral infarction (men, 17/205 vs. 22/1219, SMR 2.09 vs. 1.02; women, 21/329 vs. 14/1425, SMR 1.85 vs. 0.77), kidney disease (men only, 5/205 vs. 4/1219, SMR 2.57 vs. 0.73), and malignant neoplasms (women only, 18/329 vs. 25/1425, SMR 1.17 vs. 0.55). Evaluation of mortality from malignant neoplasms by site revealed that the SMRs for esophageal cancer and breast cancer were significantly higher in urinary β_2-microglobulin-positive women than in urinary β_2-microglobulin-negative women (esophagus, 3/329 vs. 0/1425, SMR 10.29 vs. 0; breast, 2/329 vs. 1/1425, SMR 4.30 vs. 0.43).

3.2.2.2 Exposure from Cigarettes

Hertz-Picciotto and Hu (1994) modeled the risk of lung cancer incurred from the inhalation of cadmium in cigarette smoke, basing the potency extrapolations of the models on two sets of data: epidemiologic data from a study conducted by Stayner et al. (1992) and rodent bioassay data by Takenaka et al. (1983). From the epidemiological study, dose-response data from 625 cadmium production workers employed for at least 6 months between 1940 and 1969 were used to calculate potency. Extrapolation to cigarette smoke was accomplished by converting cumulative exposure in units of mg/m^3 to μg cadmium inhaled. Using male Wistar rat bioassay data from a cadmium carcinogenicity study, experimental concentrations of cadmium chloride were converted to μg/day of inhaled cadmium. Exposure doses were assumed to be equivalent to the daily concentration per unit of body surface area in humans and potency was assumed to be equivalent to that in humans.

The potency data which was converted to μg inhaled Cd was then used to estimate the quantity of cadmium inhaled by a smoker. Both the quantity of cadmium in mainstream smoke and a portion of cadmium in inhaled sidestream cigarette smoke (some sidestream smoke is inevitably inhaled by the smoker) were incorporated into the calculation. Using this technique, the amount of cadmium inhaled by a light smoker (1 pack/day as defined by the model) was estimated between 2 μg/day (minimum from mainstream smoke and no sidestream smoke) and

5.2 μg/day (maximum for mainstream smoke and 6% for sidestream). This estimate was doubled for heavy (2 packs/day) smokers. Nonsmokers were assumed to have no exposure to cadmium from cigarettes.

Lung cancer death rates and all-cause death rates for light and heavy smokers and controls were calculated by partitioning lung cancer and all-cause mortality rates taken from U.S. Vital Statistics. The excess lifetime risk of lung cancer from inhalation of cadmium from cigarettes was the difference between the cumulative risk of lung cancer with and without the contribution from cadmium.

Based on the epidemiological data and on estimates of the concentration of cadmium in cigarettes, Hertz-Picciotto and Hu (1994) calculated that 1 to 18 lung cancer deaths (CI = 7-95) per 10,000 smokers may be attributed to inhaled cadmium in cigarette smoke. This value is equivalent to approximately 0.2-1.6% (CI = 1.6-8.8%) of lung cancer deaths caused by smoking. Using rat bioassay potency data, the authors estimated that 80-416 lung cancer deaths (CI = 136-707) per 10,000 smokers, or 13-47% (CI = 23-81%) of smoking-induced lung cancer mortality, may be attributed to inhaled cadmium in cigarette smoke.

The authors noted that the human-based risk assessment results were within the plausible range, but that the substantial estimated lifetime risk determined in the animal-based assessment was probably implausible (Hertz-Piccioto and Hu, 1994).

3.2.2.3 Multiple Exposure Routes

Antila et al. (1996) conducted a case-control study of cadmium levels in breast fat. Cases (all women) were permanent residents of Helsinki, Finland, who were diagnosed with breast cancer; their mean age was 56 years. Controls (all women and permanent residents of Helsinki) had died from accidents or nonmalignant illness and were free of any malignancy. The mean age of controls was 53 years. Sources and methods for identifying cases and controls were not given. Data on lifestyle and other potential confounding factors were collected, but there was no discussion of their direct use in the analysis. Breast adipose tissue was obtained from October 1985 to February 1986. No difference was found between the mean concentration of cadmium in breast fat from 43 breast cancer patients and from 32 controls (20.4 ± 17.5 μg/g for cases vs. 31.7 ± 39.4 μg/g for controls). Cadmium levels ranged from 3.2-86.9 μg/g in cases and from 0.1-160.4 μg/g in controls. Cadmium concentration did not correlate significantly with age, stage of cancer, zinc, copper, or selenium concentration. A suggestive correlation between cadmium levels and smoking was reported (Spearman's rank correlation R = 0.505 between level of smoking and cadmium among cases). The study was based on a small number of subjects, the study base from which case and control subjects were derived was not described, adjustment for potential confounders was not clearly discussed, and there was no mention of the possible effect of disease (breast cancer) on measured cadmium levels.

Table 3-1. Summary of Epidemiology Studies Published Post-IARC (1993)

Study Design	Study Participants			Nature of Exposure			Results[a]		Description of Model	Study Method	Reference
	Source	Number	Response Rate (%)	Substance	Duration	Level					
3.2.1 Occupational Exposure											
Case-control	cases: men who worked for U.K. Atomic Energy Authority and died from prostate cancer or registered as having it before 1987 controls: men who worked for the Authority and did not have prostate cancer; matched by year/age of starting work, last place of work, monitoring for ionizing radiation, survival	cases: 136 controls: 404	not specified	cadmium	not specified	exposure level was classified as none (or unlikely), probable but relatively low, or probable and relatively high	OR (CI) for prostate cancer: 1.06 (0.46-2.30)		risk was determined by means of conditional maximum likelihood methods	informatio n on workers was obtained from records	Rooney et al. (1993)
case-control	cases: male residents of Montreal with bladder cancer diagnosed between 1979 and 1986 controls: population-based and cancer controls (cancer patients excluding those with bladder, lung, or kidney cancer)	cases: 484 controls: 533 (population-based); 1879 (cancer controls)	cases: 84 controls: 72 for popu-lation controls; not specified for cancer controls	cadmium compounds	lifetime	substantial[b] non-substantial[c]	partially adjusted OR: 4.0 (1.0-16.3) partially adjusted OR: 0.6 (0.1-2.8)	fully adjusted OR: 3.2 (0.7-13.6) fully adjusted OR: 0.5 (0.1-2.4)	partially adjusted model: exposure, age, ethnicity, socio-economic status, smoking, coffee consumption, self/proxy of respondent; fully adjusted model: above and titanium dioxide, acrylic fibers, polyethylene, chlorine, cutting fluids, cadmium, aromatic amines	personal interview or proxy	Siemiatycki et al. (1994)

Table 3-1. Summary of Epidemiology Studies Published Post-IARC (1993) (Continued)

Study Design	Study Participants			Nature of Exposure			Results[a]	Description of Model	Study Method	Reference
	Source	Number	Response Rate	Substance	Duration	Level				
case-control	cases: male residents of Montreal with prostate cancer diagnosed between 1979 and 1986 controls: population-based and cancer controls (cancer patients excluding those with lung cancer)	cases: 449 controls: 533 (population-based); 1550 (cancer controls)	cases: 81 controls: 72 (population-based); not specified for cancer controls	cadmium compounds	lifetime	substantial[b] non-substantial[c]	No exposed cases partially adjusted OR: 1.01 (0.36-2.82) fully adjusted OR: 0.83 (0.28-2.48)	partially adjusted model included: exposure, age, ethnicity, socio-economic status, Quetelet index and self/proxy; fully adjusted model included: above, metallic, aluminum alloy, and chromium dusts, acrylic fiber, soot, formaldehyde, other pyrolysis fumes, diesel engine emissions, liquid fuel combustion products, propane engine emissions, nitric acid, chloroform, perchloroethylene, mineral spirits, and lubricating oils and greases	personal interview or proxy	Aronson et al. (1996)
Case control	cases: men and women diagnosed with renal-cell adenocarcinoma between 1989 and 1991 in 6 geographic regions in 5 countries; aged 20-79 yr controls: population-based, matched to cases by sex and age	cases: 1732 (1050 men, 682 women) controls: 2309 (1429 men, 880 women)	cases: 72.3 controls: 74.7	cadmium	≥ 1 yr	not specified	OR data for men (duration of exposure in parentheses): 2.0 (1.0-3.9) (≥ 1 yr) 4.3 (1.5-12.2) (1-11 yr) 1.0 (0.3-3.6) (12-30 yr) 1.0 (0.3-3.7) (31-44 yr) data for women not given, but described as not significant	adjusted for age, smoking status, body-mass index, education, and study center	personal interview	Mandel et al. (1995)

Table 3-1. Summary of Epidemiology Studies Published Post-IARC (1993) (Continued)

Study Design	Study Participants			Nature of Exposure			Results[a]	Description of Model	Study Method	Reference
	Source	Number	Response Rate	Substance	Duration	Level				
case-control	cases: men from the Netherlands diagnosed with prostate cancer between January 1988 and April 1990; mean age 72 yr controls: male patients from the Netherlands treated in same period for prostate hyperplasia and with no signs of malignancy; mean age 69 yr	cases: 18 sometimes or frequently exposed to cadmium; 7 frequently exposed controls: 73 sometimes or frequently exposed to cadmium; 11 frequently exposed	not specified	cadmium	not specified	sometimes or frequently exposed frequently exposed	OR for prostate cancer: 1.10 (0.64-1.89) 2.76 (1.05-7.27) There was no relationship between socioeconomic status or urbanization grade and prostate cancer risk. The definitions of "sometimes" and "frequently" exposed were not given. In addition, the choice of a single hospital, among 17 in the region, for selecting controls was not justified, nor was there detail provided on the selection of potential confounders.	adjusted for age	mailed question-naire	van der Gulden et al. (1995)
	cases: male copper-cadmium alloy workers, vicinity workers (employed where copper-cadmium alloy was made, but never employed directly in production of alloy), and iron and brass foundry workers who started employment between 1922 and 1978 and worked for ≥ 1 yr; controls: internal comparison based on exposure level	cases: 347 copper-cadmium alloy workers; 624 vicinity workers; 521 iron and brass foundry workers controls: same as cases	not specified	cadmium	≥ 1 yr	(µg Cd/ m^3·yr) < 1600 1600-4800 ≥ 4800 trend	RR for non-malignant respiratory diseases: unlagged / lagged by 10 yr 1.0 / 1.0 4.54 (1.96-10.51) / 2.57 (1.20-5.49) 4.74 (1.81-12.43) / 4.21 (1.67-10.58) 1.96 (1.27-3.02) / 2.02 (1.29-3.17) There was no increased risk for lung cancer with any level of exposure. The potential confounding effects of other occupational exposures and the small number of exposed workers in the lung cancer analyses limit interpretation.	adjusted for age, year of start of alloy work, factory, and time since starting alloy work	follow-up of studies by Bonnell (1959) and Holden (1980a,b); closing date of this study was Dec. 1992	Sorahan et al. (1995)

Table 3-1. Summary of Epidemiology Studies Published Post-IARC (1993) (Continued)

Study Design	Study Participants			Nature of Exposure			Results[a]	Description of Model	Study Method	Reference
	Source	Number	Response Rate	Substance	Duration	Level				
Cohort	subjects: male copper-cadmium alloy workers, vicinity workers (employed where alloy was made, but never employed directly in production of alloy), and iron and brass foundry workers who started employment 1922- 1978 controls: general population of England and Wales	cases: 347 copper-cadmium alloy workers; 624 vicinity workers; 521 iron and brass foundry workers controls: not specified	not specified	cadmium	≥ 1 yr	mean exposure from 1926-1980: alloy workers, 69.6 µg Cd/m^3; vicinity workers, 6.16 µg/m^3; foundry workers not given	Lung cancer mortality in alloy workers close to expected value (observed 18, expected 17.84, SMR 1.01 [0.60-1.59]). When mortality of alloy, vicinity, and foundry workers was evaluated by time from start of employment, SMR for nonmalignant diseases of respiratory system increased in all groups (alloy: observed 54, expected 23.5, SMR 2.30; vicinity: observed 71, expected 43.0, SMR 1.65; foundry: observed 34, expected 17.1, SMR 1.99). SMR for lung cancer also increased in vicinity workers (observed 55, expected 34.3, SMR 1.60), but not foundry workers.	adjusted for age, year of start of alloy work, factory, and time since starting alloy work	follow-up of studies by Bonnell (1959) and Holden (1980a,b); closing date of this study was Dec. 1992	Sorahan et al. (1995)
Case-control	cases: male production workers from a U.S. cadmium recovery facility, employed 1926-1969 controls: internal comparison based on exposure level	cases: 571 controls: same as cases	not applicable	cadmium or cadmium and arsenic	≥ 6 mo	mg/m^3·days < 400 400-999 1000-1999 > 2000	unlagged RR for lung cancer: 1.0 2.30 (0.72-7.36) 2.83 (0.75-10.72) 3.88 (1.04-14.46) Lagging exposure by 10 or 20 yr strengthened trend. Dose-response relationship between cadmium and lung cancer risk significant for departments with high arsenic exposure (cumulative cadmium exposure ≥ 1000, RR 4.02 [1.34-12.03]), but not significant for departments with minimal or no arsenic exposure, although highest cadmium level RR elevated (≥ 1000, RR 2.68 [0.80- 2.00]).	adjusted for age, year of hire, and Hispanic ethnicity	A Poisson regression used to estimate lung cancer risk using existing job history data from 1926 to 1976	Sorahan and Lancashire (1997)

Table 3-1. Summary of Epidemiology Studies Published Post-IARC (1993) (Continued)

Study Design	Study Participants			Nature of Exposure			Results[a]	Description of Model	Study Method	Reference
	Source	Number	Response Rate	Substance	Duration	Level				
3.2.2.1 Exposure from Accidental Releases										
Cohort	subjects: inhabitants, aged ≥ 50 yr, of Kakehashi River basin in Ishikawa Prefecture, Japan, an area polluted by cadmium controls: population-based, from rest of Japan	subjects: 2408 (1079 men, 1329 women) controls: not specified	95%	cadmium released from an upstream copper mine	not specified	level of exposure measured by urinary RBP[e]-negative or positive (< 4 mg/L or ≥ 4 mg/L)	Death increased in RBP-positive subjects, compared to RBP-negative subjects from: diabetes mellitus (women only, 5/113 vs. 4/1216, SMR 7.31 vs. 0.60), cardiovascular diseases (men, 14/65 vs. 76/1014, SMR 1.82 vs. 0.83; women, 28/113 vs. 96/1216, SMR 1.97 vs. 1.04), respiratory diseases (men only, 8/65 vs. 43/1014, SMR 2.06 vs. 0.96), kidney and urinary diseases (men, 4/65 vs. 11/1014, SMR 6.28 vs. 1.32; women, 5/113 vs. 12/1216, SMR 4.32 vs. 1.35). Death increased in all subjects, compared to population controls from: malignant respiratory neoplasms (men only, 16/1079, SMR 0.609), ischemic heart disease (men only, 24/1079, SMR 0.632), heart failure (women only, 86/1329, SMR 1.79), digestive diseases (women only, 24/1329, SMR 1.66), kidney and urinary diseases (men, 15/1079, SMR 1.67; women, 17/1329, SMR 1.63), senility (men, 26/1079, SMR 1.78; women, 67/1329, SMR 2.49) increased. Control incidences not given.	model included urinary RBP concentration and age	follow-up until 1991 of 1974-75 survey conducted by Ishikawa Prefectural Health Authority	Nishijo et al. (1995)

Table 3-1. Summary of Epidemiology Studies Published Post-IARC (1993) (Continued)

Study Design	Study Participants			Nature of Exposure			Results[a]	Description of Model	Study Method	Reference
	Source	Number	Response Rate	Substance	Duration	Level				
Cohort	subjects: inhabitants of cadmium polluted areas of Ishikawa Prefecture, Japan controls: not specified (probably population-based, from rest of Japan)	subjects: 3178 controls: not specified	not specified	cadmium	not specified	level of exposure measured by urinary β_2-microglobulin-negative or positive[e]	SMR values higher in urinary β_2-microglobulin-positive subjects than in urinary β_2-microglobulin-negative subjects for cardiovascular disease (women only, 39/329 vs. 37/1425; SMR 1.58 vs. 0.86), heart failure (men, 19/205 vs. 19/1219, SMR 2.08 vs. 0.77; women, 32/329 vs. 24/1425, SMR 2.40 vs. 1.09), cerebral infarction (men, 17/205 vs. 22/1219, SMR 2.09 vs. 1.02; women, 21/329 vs. 14/1425, SMR 1.85 vs. 0.77), kidney disease (men only, 5/205 vs. 4/1219, SMR 2.57 vs. 0.73), malignant neoplasms (women only, 18/329 vs. 25/1425, SMR 1.17 vs. 0.55). Evaluation of malignant neoplasms by site revealed SMRs for esophageal cancer and breast cancer higher in urinary β_2-microglobulin-positive women than in urinary β_2-microglobulin-negative women (esophagus, 3/329 vs. 0/1425, SMR 10.29 vs. 0; breast, 2/329 vs. 1/1425, SMR 4.30 vs. 0.43).	not specified	follow-up of 1981-82 survey	Nakagawa et al. (1996)

Table 3-1. Summary of Epidemiology Studies Published Post-IARC (1993) (Continued)

Study Design	Study Participants			Nature of Exposure			Results[a]	Description of Model	Study Method	Reference
	Source	Number	Response Rate	Substance	Duration	Level				
3.2.2.2 Exposure from Cigarettes										
Modeling based on epidemiological data and rodent bioassay data	cases: former, light, and heavy smokers controls: nonsmokers	not applicable	not applicable	cadmium in mainstream and a portion of sidestream cigarette smoke (since some sidestream smoke is inevitably inhaled by the smoker)	not specified	not specified	Based on epidemiologic data (Stayner et al., 1992): 1 to 18 lung cancer deaths (CI = 7-95) per 10,000 smokers may be attributed to cadmium in cigarette smoke. This is equivalent to ~ 0.2-1.6% (CI = 1.6-8.8%) of lung cancer deaths caused by smoking. Based on data from a rodent bioassay (Takenaka et al., 1983): 80-416 lung cancer deaths (CI = 136-707) per 10,000 smokers, or 13-47% (CI = 23-81%) of smoking-induced lung cancer mortality, may be attributed to cadmium in cigarette smoke.	Potency data was extrapolated by: converting both dose-response data from exposed workers and cadmium chloride aerosol exposure of rodents to µg Cd inhaled. µg Cd inhaled from smoking was calculated by estimating exposures for two groups: light smokers (1 pack/day) inhaling between 2 and 5.2 µg/day Cd and heavy smokers (2 pack/day) inhaling twice that amount. Lung cancer death rates and all-cause death rates for light and heavy smoking and controls were calculated by partitioning lung cancer and all-cause mortality rates from U.S. Vital Statistics. Excess lifetime risk of lung cancer from inhalation of cadmium from cigarettes was the difference between the cumulative risk of lung cancer with and without the contribution from cadmium.	quantitative risk assessment based on epidemiological data and rodent bioassay data	Hertz-Picciotto and Hu (1994)

Table 3-1. Summary of Epidemiology Studies Published Post-IARC (1993) (Continued)

Study Design	Study Participants			Nature of Exposure			Results[a]	Description of Model	Study Method	Reference
	Source	Number	Response Rate	Substance	Duration	Level				
Case-control	cases: women diagnosed with breast cancer; mean age 56 yr, permanent residents of Helsinki, Finland controls: deceased women who died from accidents or nonmalignant illness and had no malignancy, mean age 53 yr, permanent residents of Helsinki, Finland	cases: 43 controls: 32	not specified	cadmium	lifetime	not specified	Cadmium concentrations in breast fat of cases did not differ from controls (20.4 ± 17.5 μg/g vs. 31.7 ± 39.4 μg/g in controls). Concentrations ranged from 3.2-86.9 μg/g in cases and from 0.1-160.4 μg/g in controls. Cadmium concentration did not correlate significantly with age, stage of cancer, zinc, copper, or selenium concentration. The association between cadmium levels and smoking was only suggestive.	a stepwise logistic regression model was used that included age, concentration of cadmium, selenium, copper, and zinc in breast tissue, smoking status, smoking rate, and stage of cancer	samples taken of breast fat from October 1985 to February 1986 and analyzed for cadmium content	Antila et al. (1996)

CI = confidence interval; OR = odds ratio; RBP = retinol-binding protein RR = relative risk; SMR = standardized mortality ratio

[a] All standardized mortality ratios (SMRs) have been converted to base 1, to facilitate comparison with risk and odds ratios (RRs and ORs).
[b] Substantial exposure: > 5 yr since first exposure, > 5 yr duration, and concentration x frequency ≥ 4 (scores 1, 2, 3 correspond to low, medium, high)
[c] Nonsubstantial exposure: > 5 yr since first exposure, < 5 yr duration, and concentration x frequency = any score, or
> 5 yr since first exposure, > 5 yr duration, and concentration x frequency < 4
[d] urinary RBP, retinol binding protein, is an indicator of renal dysfunction
[e] urinary β_2-microglobulin is an indicator of renal tubule dysfunction

4.0 EXPERIMENTAL CARCINOGENICITY

4.1 Review of Cadmium Animal Carcinogenicity (IARC, 1993)

Studies of cadmium salts given by several routes to laboratory animals show that cadmium induces tumors. The tumor induction is influenced by cadmium dose and zinc. Dose-related increases in tumors were seen in rats given cadmium with controlled dietary zinc. Malignant lung tumors were induced in rats by low levels of cadmium for short exposure durations. Local tumors were observed in rats and mice given subcutaneous injections of cadmium. Based on a review and evaluation of these studies, IARC (1993, pp. 208-210; see Appendix A) concluded that there is sufficient evidence for the carcinogenicity of cadmium in experimental animals.

4.2 Animal Carcinogenicity Studies Post-IARC (1993)

Some recent studies with several strains of mice indicate that while all strains are susceptible to cadmium-induced tumors, the site of tumor development is dependent on the strain. These studies also found that chronic nonneoplastic testicular lesions corresponded to parameters of acute testicular toxicity. A rat study indicated that cadmium-induced cancer is influenced by testosterone. A study on the effect of cadmium level on tumor development and oncogene expression provided evidence of the carcinogenic and anticarcinogenic effects of cadmium.

A study of rat myoblast cells (L6) chronically exposed *in vitro* to cadmium showed that cell transformation, to a malignant phenotype or to a phenotype that is protective against tumor development, was dependent on the level of cadmium in the cell culture medium (Abshire et al., 1996a). The cells were exposed *in vitro* for 9 weeks to 0.5 M and 1.0 M cadmium chloride. The cells were then injected subcutaneously into athymic nude mice. Mice were examined for tumors 60 days after the inoculation. Compared to control groups, mice inoculated with the low-dose cells developed highly malignant sarcomas, while mice given the high-dose cells had decreased tumor growth. RNA analysis of cells treated with 0.5 M cadmium chloride revealed increased expression of the proto-oncogenes c-*myc* and c-*jun* after a 2-week exposure, but a decreased expression after 8 weeks of exposure. The results of this study are consistent with *in vivo* studies that indicate cadmium has both carcinogenic and anti-carcinogenic effects.

One study examined the effects of androgen replacement on the testicular carcinogenicity and toxicity of cadmium ($CdCl_2$) in rats (Waalkes et al., 1997). Four treatment groups were defined: control, only testosterone, testosterone + cadmium, and only cadmium. Testosterone implants, approximating normal levels in castrated rats, were made in groups of 10-week-old rats (F344/NCr); other groups were not given implants. Following 2 weeks to allow for stabilization, groups were administered $CdCl_2$ subcutaneously (s.c.) (20 μmol/kg) or saline weekly for 5 weeks. Endocrine function was assessed 10 weeks after initial cadmium exposure, and testicular neoplastic lesions were examined in rats sacrificed within the following two years. The group treated with only cadmium showed a >84% incidence of Leydig cell neoplasia and >97% incidence of chronic degeneration over two years. Testosterone-implanted rats did not develop cadmium-induced or spontaneous Leydig cell cancer, but did show testicular degeneration. Nonimplanted rats given cadmium showed a marked reduction in circulating testosterone (80% reduction compared to controls), a significant testes weight loss (>70%), and a weight loss in sex accessory glands (50% reduction of prostate mass).

Waalkes and Rehm (1994b) investigated the strain-dependent carcinogenic and toxic effects of $CdCl_2$ in mice. Male DBA/2NCr (DBA) and NFS/NCr (NFS) mice were administered $CdCl_2$ (40 μmol/kg) s.c. as a single dose or as weekly doses for 16 weeks beginning at age 8 weeks; the control groups were given only saline. Animals were observed for the following 2 years. A dose-related increased in lymphoma incidence was observed in the DBA but not in the NFS mice. In contrast, sarcoma at the injection site was seen in the NFS mice that received repeated injections of $CdCl_2$ but not in the DBA mice or controls. The $CdCl_2$-treated NFS mice also showed more hepatocellular adenomas and carcinomas than the treated DBA mice or controls, but only at the high dose. At the low dose, the NFS mice developed pulmonary tumors.

The carcinogenic and toxic effects of $CdCl_2$ were studied in another strain of mice (Waalkes and Rehm, 1994c). Groups of male mice (BALB/c) were given 20 μmol/kg $CdCl_2$ s.c. in the dorsal thoracic midline as a single dose or as weekly doses for 16 weeks starting at age 8 weeks. Controls received only saline, and groups were examined for the following 2 years. A dose-related increase in hematopoietic tumors was observed, but not in testicular interstitial-cell tumors. The multiplicity of pulmonary tumors was reduced by the treatment, but the incidence of lung tumors was unaffected. Nephropathy occurred only at the high dose and testicular degeneration was not observed.

A study was performed to determine the carcinogenic and chronic toxic effects of $CdCl_2$ in a strain of mice (Swiss [CR:NIH(S)] resistant to the acute toxicity of cadmium (Waalkes and Rehm, 1995). Groups of male mice at age 8 weeks were given one or repeated s.c. $CdCl_2$ doses (40 μmol/kg) and observed over the next 2 years. Repeated doses were given over 16 weeks and controls received only saline. Survival was significantly reduced only in the group given multiple doses. The incidence of adrenal tumors was significantly increased in the group that received the single dose but not in the group given multiple doses. A few injection-site sarcomas were observed in groups that received the single or multiple doses of cadmium chloride. A dose-related decrease in both the incidence and multiplicity of pulmonary tumors was observed in both treatment groups compared to controls.

The potential carcinogenic effects of a single s.c. dose of $CdCl_2$ (20 μmol $CdCl_2$/kg) were examined in two strains of mice and one strain of hamsters (Waalkes et al., 1994). Groups of male mice (NFS and C57) and male hamsters (Syrian) were given a single s.c. dose of cadmium chloride in the dorsal thoracic midline. The control groups were given only saline, and animals were observed for 2 years. The incidence of hematopoietic system tumors (lymphoma) was significantly increased in the NFS mice but significantly decreased in the hamsters. Adrenal cortical tumors were increased in the hamsters. Testicular interstitial cell tumors were not increased in any group treated with cadmium. Chronic testicular toxicity in the hamsters and the NFS mice was indicated by interstitial cell hyperplasia.

Table 4-1. Post-IARC (1993) Experimental Carcinogenicity Studies of Cadmium

Species, Strain, and Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments	References
athymic nude mice (Ncr-nu) groups of 10 male	10 males inoculated with in vitro cells from growth medium without cadmium chloride	cadmium chloride	1) rat myoblast cells exposed *in vitro* to two levels of cadmium chloride (0.5 M or 1.0 M) for 9 wk 2) cells s.c. injected into mice	mice examined for tumors 60 days after inoculation with treated cells	mice inoculated with low-dose cells had highly malignant sarcomas mice inoculated with high-dose cells had decreased tumor growth	Abshire et al. (1996a)
F344/NCr male rats	group given only saline	cadmium chloride testosterone	treatment groups: 1) testosterone only 2) testosterone plus 20 µmol/kg cadmium 3) 20 µmol/kg cadmium only testosterone implants made in groups of 10-wk-old rats, s.c. injection of cadmium chloride or saline after 2 wk	5 wk, examined over 2 yr	The group treated with only cadmium over 2 years showed a >84% incidence of Leydig cell neoplasia and >97% incidence of chronic degeneration. Testosterone-implanted rats did not develop cadmium-induced or spontaneous Leydig cell cancer, but did show testicular degeneration. Nonimplanted rats given cadmium showed a marked reduction in circulating testosterone (80% reduction compared to controls), a significant testes weight loss (>70%), and a weight loss in sex accessory glands (50% reduction of prostate mass).	Waalkes et al. (1997)
male mice: 1) DBA/2NCr (DBA) 2) NFS/NCr (NFS)	groups given only saline	cadmium chloride	groups given cadmium chloride s.c. as single dose of 40 µmol/kg or weekly doses	16 wk, examined over 2 yr	Dose-related increase in lymphoma incidence was observed in DBA but not NFS mice. In contrast, sarcoma at the injection site was seen in NFS mice that received repeated injections but not in DBA mice or controls. NFS mice also showed more hepatocellular adenomas and carcinomas than DBA mice or controls, but only at the high dose. At the low dose, NFS mice developed pulmonary tumors.	Waalkes and Rehm (1994b)

Table 4-1. Post-IARC (1993) Experimental Carcinogenicity Studies of Cadmium (Continued)

Species, Strain, and Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments	Reference
male mice BALB/c	group given only saline	cadmium chloride	20 µmol/kg s.c. as single or weekly doses	16 wk; examined over 2 yr	A dose-related increase in hematopoietic tumors was observed, but not testicular interstitial-cell tumors. The multiplicity of pulmonary tumors was reduced by the treatment, but the incidence of lung tumors was unaffected. Nephropathy occurred only at the high dose and testicular degeneration was not observed.	Waalkes and Rehm (1994c)
male mice Swiss [CR:NIH(S)]; 8 wk	group given only saline	cadmium chloride	40 µmol/kg as single or repeated s.c. doses;	repeated doses given over 16 wk; examined over 2 yr	Survival was significantly reduced only in the group given multiple doses. The incidence of adrenal tumors was significantly increased, compared to controls, in the group that received the single dose but not in the group given multiple doses. A few injection-site sarcomas were observed in groups that received the single or multiple doses of cadmium chloride. A dose-related decrease in both the incidence and multiplicity of pulmonary tumors was observed in both treatment groups compared to controls.	Waalkes and Rehm (1995)
two strains of male mice: NFS;C57 one strain of male hamsters: Syrian	group treated with only saline	cadmium chloride	20 µmol/kg	single dose, examined over 2 yr	The incidence of hematopoietic system tumors (lymphoma) was significantly increased in NFS mice but significantly decreased in hamsters. Adrenal cortical tumors were increased in hamsters. Testicular interstitial cell tumors were not increased in any group treated with cadmium. Chronic testicular toxicity in hamsters and NFS mice was indicated by interstitial cell hyperplasia.	Waalkes et al. (1994)

5.0 GENOTOXICITY

Studies on the genotoxic effects of cadmium as reviewed by IARC (1993) are summarized in Appendix A (pp. 188-206). Summaries of cadmium genotoxicity studies that were not published by IARC or that were published after IARC (1993) are summarized below and in **Table 5-1**. In prokaryotic systems, cadmium did not induce *his* gene mutations in *Salmonella typhimurium* without S9 activation. In mammalian systems *in vitro*, cadmium did induce DNA damage in human AHH-1 cells, human MRC5CV1 cells, and human leukocytes; and for gene mutations in mouse lymphoma and Chinese hamster ovary cells. Cadmium did not induce *in vitro* DNA damage in human U937 cells or rat splenocytes. *In vivo*, cadmium did induce chromosomal aberrations in mouse spermatocytes. In humans, cadmium induced chromosome-type aberrations, but not micronuclei, in the lymphocytes of exposed workers at cadmium factories.

5.1 Prokaryotic Systems

Cadmium did induce *his* gene mutations in *Salmonella typhimurium* (strains and dose levels not provided) in the absence but not the presence of S9 metabolic activation (Wong, 1988; cited by ATSDR, 1993).

5.2 Mammalian Systems *In Vitro*

Littlefield et al. (1994) reported that cadmium chloride exposure at 50 μM for 4 hours induced DNA damage (measured by fluorescence spectrophotometry) in human lymphoblastoid AHH-1 cells but not in male F344 rat splenocytes. The presence of magnesium ions (Mg^{++}) in the media exerted a protective effect, and significantly reduced the level of DNA damage in AHH-1 cells but not splenocytes. Minisini et al. (1994) found that a 20 μM-cadmium (salt not specified) exposure for 3 hours did not induce DNA damage in human U937 premonocytic cells. Coogan et al. (1994) reported that prior exposure of TL-1215 rat liver cells to low concentrations of cadmium chloride (10 μM for 24 hours) protected against the subsequent DNA damage induced by 500 μM $CdCl_2$ for 2 hours. Metallothioneins were produced by the cells in a time dependent manner during pretreatment offering protection against exposure at a high concentration. Hartmann and Speit (1996) reported that cadmium sulfate induced DNA damage in both human MRC5CV1 cells and human peripheral blood leukocytes in the single cell gel electrophoresis assay.

In Chinese hamster ovary (CHO) cells, 0.75 to 1.25 μM cadmium acetate induced gene mutations at the *hprt* locus (Yang et al. 1996). PCR followed by DNA sequencing of the mutants revealed base substitutions, splice mutations, and large genomic deletions. Gene mutations were also reported in mouse lymphoma cells treated with 0.9 to 36 μM cadmium sulfate for 3 hours both in the presence and absence of S9 activation (Sofuni et al., 1996).

5.3 Mammalian Systems *In Vivo*

Chromosomal aberrations were reported to be induced in CFLP mice spermatocytes after a single intraperitoneal (i.p.) injection of cadmium chloride (Selypes et al., 1992). A significant increase was found only in the number of numerical chromosomal aberrations, most frequently hypo- and hyper-haploid meioses.

5.4 Human Studies *In Vivo*

Chromosomal aberrations found in the lymphocytes of 83 men and 22 women employed at a cadmium alloy factory in Italy (Alessio et al., 1993). An increase in chromosome-type aberrations occurred only in workers with a high body burden (greater than1000 μg-yr/m^3 air). Forni (1994) later reported that chromosome aberrations but not micronuclei could be detected in the lymphocytes of 40 male cadmium workers with a cumulative exposure index ranging from greater than100 to less than1000 μg-yr/m^3 air.

Table 5-1. Summary of Cadmium Genotoxicity Studies

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Doses Used	Endpoint Response +/- Activation	Comments	Reference
Prokaryotic Systems							
Salmonella typhimurium (strains not provided in source used)	*his* gene mutations (plate incorporation)	+/-	NG	NG	positive/ negative	No other experimental details were given.	Wong (1988; cited by ATSDR, 1993)
Mammalian Systems *in vitro*							
U937 human premonocytic cells	DNA damage (alkaline unwinding assay)	-	Salt not specified	20 μM for 3 hr	negative	No detectable DNA strand breaks were observed.	Minisini et al. (1994)
male Fischer 344 rat splenocytes	DNA damage (as measured by fluorescence spectrophotometry)	-	$CdCl_2$	50 μM for 4 hr +/- 0.4 mM Mg	negative	Cadmium did not induce DNA damage. The presence or absence of magnesium in the media had no effect.	Littlefield et al. (1993)
Human lymphoblastiod AHH-1 cells	DNA damage (as measured by fluorescence spectrophotometry)	-	$CdCl_2$	50 μM for 4 hr +/- 0.4 mM Mg	positive	The presence of cadmium-induced DNA damage was reduced significantly by the protective effect of magnesium in the media.	Littlefield et al. (1993)
MRC5CV1 human fibroblast cells	DNA damage (single cell gel assay)	-	$CdSO_4$	10 to 200 μM for 2 hr	positive	When cells were treated with benzo[*a*]pyrene (BaP) and post treated with a non-damaging dose of $CdSO_4$, repair of the BaP-induced DNA lesions was inhibited by $CdSO_4$.	Hartmann and Speit (1996)
Human leukocytes	DNA damage (single cell gel assay)	-	$CdSO_4$	10 to 2000 μM for 2 hr	positive	When cells were treated with BaP and post treated with a non-damaging dose of $CdSO_4$, repair of the BaP-induced DNA lesions was inhibited by $CdS0_4$.	Hartmann and Speit (1996)
TRL-1215 rat liver epithelial cells	DNA damage (alkaline elution)		$CdCl_2$	10 μM for 24 hr followed by 500 μM for 2 hr	positive	Prior exposure to low conc. protected against the damage induced by 500 μM . Metallothioneins were produced during pretreatment offering protection against the high concentration exposure.	Coogan et al. (1994)

Table 5-1. Summary of Cadmium Genotoxicity Studies (Continued)

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Doses Used	Endpoint Response +/- Activation	Comments	Reference
Chinese hamster ovary (CHO) cells	*hprt* gene mutations	-	Cd acetate	0.75 , 1.0, & 1.25 μM for 24 hr	positive	PCR followed by DNA sequencing revealed base substitutions (transversions > transitions), splice mutations, and large genomic deletions.	Yang et al. (1996)
mouse lymphoma L5178Y cells	*tk* gene mutations (microwell method)	+/-.	$CdSO_4$	0.1 to 4.0 μg/mL (0.9 to 36 μM) for 3 hr	positive/ positive	Top doses tested were 1.0 μg/mL without S9 and 4.0 μg/mL with S9.	Sofuni et al. (1996)
Mammalian Systems *in vivo*							
male CFLP mice	chromosome aberrations in spermatocytes	n.a.	$CdCl_2$	single 1 mg/kg i.p. dose for 3 days or 6 months	positive after 3 days, negative after 6 months	A significant increase was found only in the number of numerical chromosomal aberrations, most frequently hypo- and hyperhaploid meioses.	Selypes et al. (1992)
Human Studies *in vivo*							
83 men and 22 women employed at cadmium alloy factory	chromosome aberrations	n.a.	NG	time weighted average over 15 years was 50 $\mu g/m^3/yr$	positive	An increase in chromosome-type aberrations in cultured lymphocytes occurred only in workers with a high body burden of cadmium (>1000 μg-yr/m^3).	Alessio et al. (1993)
40 male cadmium workers	chromosome-type aberrations	n.a.	NG	cumulative exposure index of <100 to >1000 μg-yr/m^3 air	positive	The mean level of chromosome-type aberrations in lymphocytes was 1.15% in the exposed workers compared to 0.45% in the control population.	Forni et al. (1994)
40 male cadmium workers	micronuclei induction	n.a.	NG	cumulative exposure index of <100 to >1000 μg-yr/m^3 air	negative	The mean level of micronucleated lymphocytes was 2.03% in the exposed workers compared to 2.30% in the control population.	Forni et al. (1994)

Abbreviations: n.a. = not available; NG = not given; HID = highest ineffective dose; LED = lowest effective dose

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, Metabolism and Excretion

6.1.1 Absorption

Humans are primarily exposed to cadmium through the respiratory and gastrointestinal tracts (Mennear, 1979), though limited penetration through the skin can occur (section 6.1.1.3).

6.1.1.1 Inhalation

Inhalation of cadmium by animals in various acute and chronic experiments showed 5 to 20% of the cadmium as being deposited in the lungs (Friberg et al., 1986; cited by IPCS, 1992). Between 50 and 100% of the deposited cadmium may be absorbed over the weeks following a single dose (Friberg et al., 1985; cited by IPCS, 1992). An absorption efficiency of 40% via the lungs in dogs was calculated (Friberg et al. 1974; cited by Mennear, 1979). Elinder (1976; cited by IPCS, 1992) calculated that 50% of the cadmium inhaled via cigarette smoke could be absorbed, based on data on organ burdens of cadmium and smoking history.

6.1.1.2 Intestinal Tract

Gaston rats receiving a single oral dose of cadmium by intubation retained only 1% of the dose in the liver and 1% in the kidney, while 96% was excreted in the feces within 2 weeks of exposure (Decker et al., 1957; cited by Mennear, 1979). Mice absorbed 0.5 to 8% of an oral dose by intubation within 4 hours (Cotzias et al., 1961; cited by Mennear, 1979). The average absorption of ingested radioactive cadmium in humans was 5% based on limited observation (Kitamura, 1972; Rahola et al., 1972; Yamagata et al., 1974; Flanagan et al., 1978; all cited by IPCS, 1992). Gastrointestinal absorption of cadmium chloride in hamsters was very slow, with only 1% of a 3-μg dose absorbed 24 hours after oral administration in an aqueous solution (DFG, 1993). Ingested inorganic cadmium compounds are absorbed and distributed differently than metallothionein-bound cadmium. Mice have lower levels of cadmium in blood and liver and higher levels in the kidneys following exposure to cadmium-thionein compared to cadmium chloride (Cherian et al., 1978; cited by IPCS, 1992). Absorption of cadmium through the intestinal tract increased up to 3-fold in animals on diets low in cadmium and protein (Friberg et al., 1974, 1975; both cited by IPCS, 1992). A deficiency in iron caused increased absorption of cadmium in animals (Hamilton and Valberg, 1974; cited by IPCS, 1992) as well as in humans (Flanagan et al., 1978; cited by IPCS, 1992).

6.1.1.3 Skin

Application of a solution of soluble cadmium compounds led to a 1.8% penetration through the skin over 5 hours (Skog and Wahlberg, 1964; cited by IPCS, 1992).

6.1.2 Distribution

The liver and renal cortex of exposed animals have the highest concentration of cadmium, although distribution does vary with the mode of administration (IPCS, 1992). Concentrations of cadmium in the liver increase first in animals exposed to either a single or repeated dose, followed by a slow increase in the concentration in the kidneys (Gunn and Gould, 1957; Friberg et al., 1985; both cited by IPCS, 1992). A subcutanous injection leads to an 11-fold preference for deposition in the liver, whereas an oral administration is partitioned equally between the liver

and the kidneys (Nomiyama et al., 1976; cited by IPCS, 1992). Humans have a similar distribution pattern, with cadmium being stored primarily in the liver and the kidneys, especially in the renal cortex of previously unexposed people (Friberg et al., 1974; cited by IPCS, 1992). Brain, bone, and fat have the lowest concentrations (Sumino et al., 1975; Cherry, 1981; both cited by IPCS, 1992). High concentrations of cadmium are seen in the liver and kidneys of humans who work with cadmium or are exposed to high levels. The relative liver or kidney concentrations are determined by the individual duration and magnitude of exposure, and by the efficiency of the renal function (Friberg et al., 1974, 1985; both cited by IPCS, 1992).

6.1.3 Metabolism

Immediately after parenteral administration to dogs, cadmium is found mostly in the plasma (Walsh and Burch, 1959; cited by IPCS, 1992). In the first hours after injection, plasma levels decrease rapidly. After 24 hours, less than 1% of the initial level of cadmium remains, and this value continues to decrease very slowly (IPCS, 1992). During the rapid initial decrease, cadmium in mice is bound to plasma proteins with molecular weights of 40,000 to 60,000. During the slower decrease, cadmium binds to a low molecular weight (LMW) protein. The 40,000- to 60,000- da protein is probably albumin, whereas the LMW protein is the same size as metallothionein (Nordberg, 1978; cited by IPCS, 1992). The metallothionein plasma concentration increased in rats given cadmium chloride in saline as 40 injections (five injections per day) containing 0.12 mg/day (0.65 μmol/day) (Vander Mallie and Garvey, 1979; cited by IPCS, 1992), suggesting that the LMW protein that binds cadmium is likely to be metallothionein. Measurable levels of metallothionein have been found in human plasma (Nordberg et al.,1982; cited by IPCS, 1992).

Divalent metals such as cadmium and zinc induce metallothionein (MT). In all mouse strains studied, the MT-I isoform represented over 88% of the MT found in liver 24 hours after ingestion of zinc or cadmium. MT-I and MT-II are the two major isoforms of MT found in mammalian liver (Kloth et al., 1995) and MT-II is the major isoform in most species except for dog and mouse (Chan and Cherian, 1993; cited by Kloth et al., 1995).

Nordberg (1972; cited by Mennear, 1979) and Tanaka et al. (1975; cited by Mennear, 1979) both hypothesized that metallothionein mediates the transport of cadmium from the liver to the kidneys. The theory was supported by the observations that metallothionein appeared in blood (Nordberg et al., 1971b; cited by Mennear, 1979), and that intravenous (i.v.) administration led to accumulation of metallothionein in the kidneys of mice (Nordberg et al., 1975; cited by Mennear, 1979) and rats (Tanaka et al., 1975; Cherian and Shaikh, 1975; both cited by Mennear, 1979).

Glomerular filtration rapidly clears metallothionein-bound cadmium in the plasma, which can then be reabsorbed in the renal tubules or excreted in the urine (Cherian and Shaikh, 1975; Nordberg et al., 1975; Webb and Etienne, 1977; Fowler and Nordberg, 1978; all cited by IPCS, 1992). Metallothionein has a protective role in cadmium toxicity as demonstrated in animal and *in vitro* studies (Cherian and Nordberg, 1983; cited by IPCS, 1992). Subcutaneous injection of mice with metallothionein isolated from rabbit and mouse liver resulted in acute renal tubular cell toxicity (Nordberg et al., 1975; cited by IPCS, 1992). Templeton and Cherian (1991; cited by Müller et al., 1994) interpreted these apparently disparate results as meaning that intracellular MT protects against cadmium exposure while toxicity results from extracellular MT.

Metallothionein with different ratios of cadmium and zinc produces renal tubular cell toxicity proportional to the cadmium content (Suzuki, 1982; cited by IPCS, 1992). Parenterally administered cadmium-metallothionein is thought to enter the proximal renal tubular cell linings and to be degraded in the lysosomes, releasing cadmium into the cytosol. This results in cellular degradation and necrosis (Cherian et al., 1976; Fowler and Nordberg, 1978; Squibb et al., 1982, 1984; all cited by IPCS, 1992).

Cadmium stimulates release of calcium in a manner that is very specific for divalent metals. Like calcium-mobilizing hormones, cadmium and other active metals cause an immediate and marked production of inositol triphosphate and other second messengers in a cell-specific manner. The action of these metals appears to occur at an external site via a sialoprotein (Smith et al., 1989a, b, 1992; Dwyer et al., 1991; Chen and Smith, 1992; all cited by Smith et al., 1994). These observations suggest that cadmium interacts with an orphan receptor to stimulate calcium mobilization (Smith et al., 1994).

6.1.4 Excretion

Mice given s.c. injections of cadmium for 24-25 weeks had a daily urinary excretion of cadmium representing 0.01-0.02% of the total body burden (Nordberg, 1972; cited by IPCS, 1992). After oral administration to rabbits and monkeys (Nomiyama and Nomiyama, 1976a, b; Nomiyama et al., 1979, 1982a; all cited by IPCS, 1992) similarly low urinary excretion rates were observed. Urinary excretion in humans increases with age in a manner that coincides with increasing body burden (Katagari et al., 1971; Tsuchiya et al., 1976; Elinder et al., 1978; Kowal et al., 1979; all cited by IPCS, 1992). Higher urinary excretion is seen in smokers (Elinder et al., 1978; Kowal et al., 1979; both cited by IPCS, 1992). Fecal excretion accounts for a few percent of the dose in the first few days following injection (Friberg et al., 1974; cited by IPCS, 1992), and is initially higher than urinary excretion following administration of a single or repeated dose (Nomiyama, 1978; cited by IPCS, 1992). Gastrointestinal excretion is higher than urinary excretion during and after parenteral exposure to cadmium (Nordberg, 1972; Elinder and Pannone, 1979; both cited by IPCS, 1992). Cadmium is also found in hair and breast milk (Anke et al., 1976; Schroeder and Balassa, 1961; cited by IPCS, 1992), although these excretion routes represent a minimal amount when compared with total excretion.

In order to assess the effect of exposure withdrawal in correcting elevated proteinuria, a reinvestigation of a study of male alkaline battery workers was completed by Dewell (1996). Starting in 1968, workers with elevated proteinuria were removed from exposure to cadmium. Cadmium levels in urine (CdU) were reported for workers at two stages: prior to their withdrawal from cadmium exposure, and after re-employment elsewhere in the company (Adams, 1979; cited by Dewell, 1996). A two-year decrease in CdU levels was found when workers were removed from cadmium exposure. But the initial decrease was followed by a leveling off at a steady rate of decrease. In the reinvestigation, Dewell (1996) concluded that the decline in CdU levels in workers removed from cadmium exposure does not differ (except in the initial two-year period) from that of workers still exposed to cadmium.

6.2 Pharmacokinetics

The biological half-times in various animal species range from weeks to two years (IPCS, 1992). When one human received radioactive cadmium and was examined for the stable and radioactive isotopes after administration, a half-time of 26 years was reported (Shaikh and

Smith, 1980; cited by IPCS, 1992). Half-times of 93 to 202 days were reported in three similar studies that followed subjects for approximately 100 days (Rahola et al., 1972; Flanagan et al., 1978; McLellan et al., 1978; all cited by IPCS, 1992).

Half-times in various organs were calculated based on data from Japan on the accumulation of cadmium with increasing age and a series of one-compartment mathematical models (Tsuchiya et al., 1976; cited by IPCS, 1992). Cadmium in the kidneys had an estimated half-time of 17 years, while the half-time of cadmium in the liver was 7 years. When an 8-compartment model was used, the half-times were reported to be 12 years in the kidney and 7.5 years in the liver (Kjellström and Nordberg, 1978; cited by IPCS, 1992). An autopsy study found the longest half-time in the muscle tissue (Kjellström, 1977; cited by IPCS, 1992). The biological half-time may be different following high cadmium exposure compared to normal environmental exposure (IPCS, 1992). Cadmium workers were examined by *in vivo* neutron activation analysis during a 3- to 4-year period following exposure. The half-time for cadmium in the liver was 2 years in three workers showing proteinuria, while nine workers with no proteinuria had an average liver half-time of 13.5 years. The biological half-time for cadmium is always shorter when there is renal tubular dysfunction (Fletcher et al., 1982; cited by IPCS, 1992). The half-time of cadmium in the blood of five smelter workers who were exposed to high levels of cadmium was determined by repeated analysis carried out over a 10- to 13- year period. The half-time of cadmium in blood had short-term (75-128 days) and long-term (7.4-16 years) components (Järup et al., 1983; cited by IPCS, 1992).

6.3 Dietary Cadmium

One study (Sell and Ilic, 1994) suggests that dietary cadmium may affect the progression of liver tumors in mice. Groups of hepatitis B transgenic mice were administered a diet with high (5 μg/g) or low (<0.05 μg/g) levels of cadmium for up to 20 months. The liver tumor incidence was similar in groups given both levels of cadmium, but male mice fed the high cadmium diet had more poorly differentiated liver tumors than the group given the low cadmium diet. This result indicates that dietary cadmium may influence the progression of liver tumors.

7.0 MECHANISMS OF CARCINOGENESIS

7.1 Metallothionein

7.1.1 Metallothionein and Cadmium Sensitivity

Metallothionein (MT) protects against carcinogenesis by sequestering cadmium. The species differences in the carcinogenicity of cadmium may be attributable to differences in the baseline levels and inducibility of MT. An interspecies comparison of MT in the lung of animals that inhaled cadmium chloride aerosols indicates that the MT level may help account for observed species differences in lung cancer induction by cadmium. Rats and mice were exposed to cadmium chloride aerosols of 100 $\mu g/m^3$ for 4 weeks. MT was then analyzed in the lung and free lung cell homogenates, and analyzed in the lung by immunocytochemistry. Cadmium retained in the lung after 4 weeks was also determined. The retained cadmium was greater in mice than in rats. The MT levels were significantly greater in the mouse lung than in the rat lung; the mouse lung showed a greater MT induction after cadmium exposure, and displayed a greater baseline MT level than the rat lung (Oberdörster et al., 1994).

A later study also examined MT induction in rats and mice after inhalation of cadmium (Kenaga et al., 1996). Fischer 344 rats and $B6C3F_1$ mice were exposed to cadmium chloride aerosols of 0, 30, 50, and 150 $\mu g/m^3$ air (rats) or 0, 10, 30, and 100 $\mu g/m^3$ air (mice) for 4 weeks. At increasing times after exposure (1, 30, 133 days), MT, cadmium, and immune cells were analyzed in lung lavagate and lung tissue. A dose-dependent inflammatory response was observed in both species. This response persisted in mice exposed to the highest concentration, but did not persist in rats throughout the observation period. Cadmium retention in the lung was also significantly greater in mice than rats. Mice were found to have a greater pulmonary baseline of MT than rats, and mice maintained induced MT levels for a longer period than rats.

The sensitivity to cadmium-induced necrosis seems to be due to a reduced capacity to produce MT. Human hepatocellular carcinomas also have low levels of MT expression, which suggests that the tumors might be sensitive to cadmium (Waalkes et al., 1996).

7.1.2 Gene Activation

Tissue specific metallothionein gene activation could correspond to susceptibility to carcinogenesis following cadmium exposure. Prostate tumors observed in rats chronically-exposed to cadmium occurred exclusively within the ventral lobe; no tumors were detected in the dorsolateral lobe (Waalkes et al., 1988, 1989; Waalkes and Rehm, 1992; Hoffmann et al., 1985a, b, 1988; Shirai et al., 1993; all cited by Coogan et al., 1995). MT gene activation was quiescent in the ventral prostate of the rat, while the MT gene was active in the dorsal prostate (Coogan et al., 1994). Neither MT-I nor MT-II expression increased in response to cadmium treatments in the rat ventral prostate. High basal levels of expression of MT-I and MT-II in the rat dorsolateral prostate were not further increased by cadmium exposure (Coogan et al., 1995). Cadmium in rodents also targets the testes, where interstitial cell tumors can occur at high incidence following a single injection. Metal induction stimuli have no effect on the MT gene in testes. Inhalation of cadmium results in carcinogenicity in a species-specific manner, with less pulmonary MT expressed in susceptible rats than in resistant mice (Cherian et al., 1994).

7.1.3 DNA Damage

A concentration-dependent increase in DNA strand breaks was observed when cadmium/zinc-metallothionein (Cd/Zn-MT) was incubated with supercoiled DNA, but not when Cd or Zn ions alone were added to the DNA (Müller et al., 1994). Since both agents that alkylate the thiol group and the divalent cation-scavenger EDTA could inhibit DNA fragmentation, it seems likely that the Cd/Zn-MT complex itself is involved in the induction of DNA breaks (Müller et al., 1994). A known hydroxy radical scavenger, benzoate, and an unspecific radical scavenger, α-tocopherol, were able to inhibit MT-dependent DNA strand breaks. When Cd/Zn-MT was mixed with a spin-trapping agent, typical electron spin resonance (ESR) signals were detected. These results suggest the generation of a radical by Cd/Zn-MT (Müller et al., 1994).

7.1.4 Proto-oncogenes

The activities of c-*myc* and c-*jun*, the proto-oncogenes, are induced by cadmium (Jin and Ringertz, 1990; cited by Abshire et al., 1996a). These inductions are prevented by pre-incubation with zinc ions (Abshire et al., 1996b). Zinc pre-incubation increased MT protein levels 5-fold and this is thought to be the mechanism. The induction of proto-oncogenes by

cadmium was blocked, presumably by the 5-fold increase in MT protein levels caused by zinc pre-incubation (Abshire et al., 1996b). Cadmium-treated cells injected in nude mice induced large, rapidly growing tumors, but the transformation was not associated with increased expression of proto-oncogenes and the MT levels were not reported (details in section 4) (Abshire et al, 1996a).

7.2 Cell Signaling

Cadmium stimulation through the putative orphan receptor (section 6.1.3) leads to activation of protein kinases, which may be the means by which cadmium induces proto-oncogenes as described above. The estrogen receptor can be specifically activated by cadmium through its hormone binding domain, which suggests that cadmium exposure could result in an increased risk of breast cancer (Stoica et al., 1996).

7.3 Free Radical Formation

Cadmium can restore DNA binding in the zinc finger of the human estrogen receptor after the zinc has been removed. Zinc fingers are DNA-binding proteins that can act as ligand-induced transcription factors. The estrogen receptor zinc finger has a similar affinity for its specific DNA oligonucleotide whether zinc or cadmium is used to restore DNA binding. When a redox metal such as iron is used to replace the zinc, free radicals are formed. This would be a mechanism for DNA damage, especially considering the proximity of the zinc finger to DNA (Sarkar, 1995).

Shen and Sangiah (1995) found that the indices of hydroxyl free radicals, 2,5-dihydroxybenzoic acid and 2,3-dihydroxybenzoic acid, were significantly increased in mouse testes following 5 days of cadmium chloride exposure. Pretreatment with vitamin E significantly reduced the induction of free radicals. The testicular GSH content and the ratio of reduced glutathione to oxidized glutathione (GSH/GSSG) were decreased following cadmium chloride treatment of mice (Shen and Sangiah, 1995).

Oxidative stress was observed in testicular Leydig cells twelve hours after exposure to cadmium chloride. Lipid peroxidation levels, iron content, and cellular production of hydrogen peroxide were all found to be elevated (Koizumi and Li, 1992). The Leydig cells in the testis are the target for cadmium carcinogenesis. As oxidative stress was induced in Leydig cells, the cellular defense mechanisms were compromised as glutathione reductase and catalase activities were reduced and glutathione peroxidase activity was increased. The superoxide dismutase activity in Leydig cells did not change, but the xanthine oxidase activity was found to be increased 6 to 9 hours after the exposure (Koizumi and Li, 1992). These observations suggest that cadmium carcinogenesis in target cell populations such as testicular Leydig cells could be initiated in part by active oxygen species such as H_2O_2 (Koizumi and Li, 1992).

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APPENDIX A

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 58 (Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry), 1993, pp. 119-237

CADMIUM AND CADMIUM COMPOUNDS

Cadmium and cadmium compounds were considered by previous working groups, in 1972, 1975 and 1987 (IARC, 1973, 1976, 1987a). New data have since become available, and these are included in the present monograph and have been taken into consideration in the evaluation. The agents considered are metallic cadmium, cadmium alloys and some cadmium 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 cadmium, cadmium–copper alloy and some cadmium compounds are presented in Table 1. The cadmium compounds shown are those for which data on carcinogenicity or mutagenicity were available or which are commercially important compounds. It is not an exhaustive list and does not necessarily include all of the most commercially important cadmium-containing substances.

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

Chemical name	CAS Reg. No.[a]	Synonyms and trade names	Formula
Cadmium	7440-43-9	Cadmium metal; CI 77180	Cd
Cadmium acetate	543-90-8 (24558-49-4; 29398-76-3)	*Acetic acid, cadmium salt*; bis(acetoxy)-cadmium; cadmium(II) acetate; cadmium diacetate; cadmium ethanoate; CI 77185	$Cd(CH_3COO)_2$
Cadmium carbonate	513-78-0 [93820-02-1]	*Carbonic acid, cadmium salt*; cadmium carbonate ($CdCO_3$); cadmium monocarbonate; chemcarb; kalcit; mikrokalcit; supermikrokalcit	$CdCO_3$
Cadmium chloride	10108-64-2	Cadmium dichloride; dichlorocadmium	$CdCl_2$
Cadmium hydroxide	21041-95-2 (1306-13-4; 13589-17-8)	*Cadmium hydroxide ($Cd(OH)_2$)*; cadmium dihydroxide	$Cd(OH)_2$
Cadmium nitrate	10325-94-7 (14177-24-3)	*Nitric acid, cadmium salt*; cadmium dinitrate; cadmium(II) nitrate; cadmium nitrate ($Cd(NO_3)_2$)	$Cd(NO_3)_2$
Cadmium stearate	2223-93-0	Alaixol II; cadmium distearate; cadmium octadecanoate; cadmium(II) stearate; octadecanoic acid; cadmium salt; SCD; stabilisator SCD; stabilizer SCD; stearic acid, cadmium salt	$Cd(C_{36}H_{72}O_4)$

Table 1 (contd)

Chemical name	CAS Reg. No.[a]	Synonyms and trade names	Formula
Cadmium sulfate	10124-36-4 (62642-07-3) [31119-53-6]	Cadmium monosulfate; cadmium sulfate; *sulfuric acid, cadmium salt (1:1)*	$CdSO_4$
Cadmium sulfide	1306-23-6 (106496-20-2)	Cadmium monosulfide; cadmium orange; cadmium yellow; CI 77199	CdS
Cadmium oxide	1306-19-0	Cadmium monoxide	CdO
Cadmium–copper alloy[b]	37364-06-0	*Copper base, Cu,Cd*	Cd.Cu
	12685-29-9 (52863-93-1)	*Cadmium nonbase, Cd,Cu*	Cd.Cu
	132295-56-8	*Copper alloy, base, Cu 99.75-100, Cd 0.05–0.15*; IMI 143; UNS C14300	Cd.Cu
	132295-57-9	*Copper alloy, base, Cu 99.60-100, Cd 0.1–0.3*; UNS C14310	Cd.Cu

[a]Replaced CAS Registry numbers are shown in parentheses; alternative CAS Registry numbers are shown in brackets.
[b]116 cadmium-copper alloys are registered with the Chemical Abstracts Service.

1.1.2 *Chemical and physical properties of the pure substances*

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

Cadmium (atomic number, 48; relative atomic mass, 112.41) is a metal, which belongs, together with zinc and mercury, to group IIB of the periodic table. The oxidation state of almost all cadmium compounds is +2, although a few compounds have been reported in which it is +1. There are eight naturally occurring isotopes (abundance is given in parentheses): 106 (1.22%), 108 (0.88%), 110 (12.39%), 111 (12.75%), 112 (24.07%), 113 (12.26%), 114 (28.86%) and 116 (7.58%). Although cadmium is slowly oxidized in moist air at ambient temperature, it forms a fume of brown-coloured cadmium oxide when heated in air. Other elements that react readily with cadmium metal upon heating include halogens, phosphorus, selenium, sulfur and tellurium (Hollander & Carapella, 1978; Schulte-Schrepping & Piscator, 1985).

There is no evidence that organocadmium compounds (in which the metal is bound covalently to carbon) occur in nature, although cadmium may bind to proteins and other organic molecules and form salts with organic acids (e.g. cadmium stearate) (WHO, 1992a).

Cadmium has a relatively high vapour pressure (0.001 mm Hg [0.133 Pa] at 218 °C; 1.0 mm Hg [133.3 Pa] at 392 °C; 100 mm Hg [13.3 kPa] at 611 °C). When reactive gases or vapours, such as oxygen, carbon dioxide, water vapour, sulfur dioxide, sulfur trioxide or hydrogen chloride, are present, cadmium vapour reacts to produce cadmium oxide, carbonate, hydroxide, sulfite, sulfate or chloride, respectively. These compounds may be formed in stacks and emitted into the environment (Schulte-Schrepping & Piscator, 1985; WHO, 1992a).

Table 2. Physical and chemical properties of cadmium and cadmium compounds

Chemical name	Relative atomic/ molecular mass	Melting-point (°C)	Typical physical description	Density (g/cm^3)	Solubility
Cadmium metal	112.41	320.9	Silver-white, blue-tinged malleable metal	8.642	Soluble in ammonium nitrate, dilute nitric acid, hot sulfuric acid; insoluble in water
Cadmium acetate	230.50	256	Colourless crystal with slight acetic acid odour	2.341	Soluble in water, ethanol, methanol
Cadmium carbonate	172.42	321 (dec.)	White trigonal solid	4.26 (4 °C)	Practically insoluble in water (28 μg/L) and ammonia; soluble in dilute acids; insoluble in organic solvents
Cadmium chloride	183.32	568	Colourless to white, hygroscopic, rhombohedral or hexagonal crystals	4.047	Soluble in water (1400 g/L) and acetone; slightly soluble in methanol, ethanol; insoluble in diethyl ether
Cadmium hydroxide	146.43	130 (dec.)	White trigonal crystal or amorphous solid	4.79 (15 °C)	Almost insoluble in water (2.6 mg/L); soluble in dilute acids and ammonium salts; insoluble in alkaline solutions
Cadmium nitrate	236.43	350	Colourless solid	NR	Soluble in water (1 kg/L at 0 °C, 3.3 kg/L at 60 °C); soluble in diethyl ether, ethyl acetate, acetone, ethanol; very soluble in dilute acids
Cadmium sulfate	208.47	1000	Colourless to white orthorhombic crystals	4.691	Soluble in water (755 g/L); insoluble in acetone, ammonia, ethanol
Cadmium sulfide	144.47	1750 (at 100 atm [101 × 10^2 kPa])	Yellow–orange hexagonal (α) or cubic (β) dimorphic, semi-transparent crystals; yellow–brown powder	4.82 (α); 4.50 (β)	Soluble in concentrated or warm dilute mineral acids with evolution of hydrogen sulfide; very slightly soluble in ammonium hydroxide; almost insoluble in water (1.3 mg/L); forms a colloid in hot water
Cadmium oxide	128.41	> 1500	Dark-brown cubic crystals or amorphous powder	8.15 (crystal); 6.95 (amorphous)	Soluble in dilute acids and ammonium salts; almost insoluble in water (9.6 mg/L); insoluble in alkali

From Hollander & Carapella (1978); Parker (1978); Sax & Lewis (1987); Budavari (1989); Cadmium Association/Cadmium Council (1991); Lide (1991); WHO (1992a); Agency for Toxic Substances and Disease Registry (1989). NR, not reported; dec., decomposes

Some cadmium compounds, such as cadmium sulfide, carbonate and oxide, are practically insoluble in water. Few data are available, however, on the solubility of these compounds in biological fluids, e.g. in the gastrointestinal tract and lung. The water-insoluble compounds can be changed to water-soluble salts by acids or light and oxygen; e.g. aqueous suspensions of cadmium sulfide gradually photooxidize to soluble (ionic) cadmium. Cadmium sulfate, nitrate and halides are water-soluble (Ulicny, 1992; WHO, 1992a).

1.1.3 *Technical products and impurities*

Cadmium metal—produced in a wide range of forms and purities for various uses. Purities range from 99.0% (reagent grade) to 99.9999% (zone-refined), and forms include powder, foils, wires, ingots and others. Typical impurities (%, max.) include: Zn, 0.02–0.1; Cu, 0.0001–0.015; Pb, 0.0001–0.025; Fe, 0.0001–0.001; Bi, 0.0005; Sn, 0.01; Ag, 0.01; Sb, 0.001; and As, 0.003 (J.T. Baker, 1989; Alfa Products, 1990; Spectrum Chemical Mfg Corp., 1991; Aldrich Chemical Co., 1992; Strem Chemicals, 1992; Atomergic Chemetals Corp., undated; D.F. Goldsmith Chemical & Metal Corp., undated)

Cadmium acetate—reagent grade; 99.999% (Alfa Products, 1990)

Cadmium chloride—purities: 99.0–> 99.99%; American Chemical Society reagent grade, 95–> 99%; anhydrous, 99.99–99.999%; impurities (%): NO_3, 0.003; SO_4, 0.005–0.01; NH_4, 0.002–0.01; Cu, 0.001; Fe, 0.001; Pb, 0.005; and Zn, 0.1 (J.T. Baker, 1989; Alfa Products, 1990; CERAC, Inc., 1991; Spectrum Chemical Mfg Corp., 1991; Aldrich Chemical Co., 1992; Strem Chemicals, 1992)

Cadmium sulfate (as $3CdSO_4.8H_2O$)—purities: 98–99.999%; American Chemical Society reagent grade, 98–99.0%; impurities (%): Cl, 0.001; NO_3, 0.003; Cu, 0.002; Fe, 0.001; Pb, 0.003; Zn, 0.1; and As, 1–2 ppm (J.T. Baker, 1989; Alfa Products, 1990; Aldrich Chemical Co., 1992)

Cadmium sulfide—purities: > 98–99.999%; phosphor (luminescent) grade, 99.99–99.999% (Alfa Products, 1990; CERAC, Inc., 1991; Aldrich Chemical Co., 1992; Strem Chemicals, 1992; D.F. Goldsmith Chemical & Metal Corp., undated). Some of the trade names associated with cadmium sulfide include: Cadmium Golden; Cadmium Golden 366; Cadmium Lemon Yellow; Cadmium Lemon Yellow 527; Cadmium Orange; Cadmium Primrose 819; Cadmium Sulfide Yellow; Cadmium Yellow; Cadmium Yellow 000; Cadmium Yellow 892; Cadmium Yellow Conc. Deep; Cadmium Yellow Conc. Golden; Cadmium Yellow Conc. Lemon; Cadmium Yellow Conc. Primrose; Cadmium Yellow 10G Conc.; Cadmium Yellow OZ Dark; Cadmium Yellow Primrose 47-4100; Cadmopur Golden Yellow N; Cadmopur Yellow; Capsebon; C.P. Golden Yellow 55; Ferro Lemon Yellow; Ferro Orange Yellow; Ferro Yellow; GSK; PC 108; Primrose 1466.

Cadmium oxide—purities: 99.0–99.9999%; reagent grade, 99.0%; commercial grade, 99.7%; impurities (%): Cl, 0.002; NO_3, 0.01; SO_4, 0.20; Cu, 0.005; Fe, 0.002; and Pb, 0.01 (J.T. Baker, 1989; Alfa Products, 1990; CERAC, Inc., 1991; Aldrich Chemical Co., 1992; Strem Chemicals, 1992; D.F. Goldsmith Chemical & Metal Corp., undated).

Impurities that occur in cadmium compounds that have been the subjects of previous monographs are lead (IARC, 1987b) and arsenic (IARC, 1987c).

1.1.4 *Analysis*

Selected methods for the determination of cadmium and cadmium compounds in various media are presented in Table 3.

Table 3. Methods for the analysis of cadmium and cadmium compounds (as Cd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Collect on membrane filter; dissolve with nitric acid	FLAA	0.03 μg/m^3; 0.002 μg/ml	Kleinman *et al.* (1989a)
	Collect on cellulose ester membrane filter; add nitric and hydrochloric acids; heat, then cool	FLAA	0.05 μg/sample	Eller (1987)
	Collect on cellulose ester membrane filter; ash with nitric:perchloric acid solution (4:1); heat; repeat; heat to dryness; dilute with nitric:perchloric acid solution (4:1)	ICP	1 μg/sample	Eller (1984a)
Water, ground- and surface	Acidify with nitric and hydrochloric acids (Method 3005)	FLAA; ICP at 226.5 nm	0.005 mg/L; 4 μg/L	US Environmental Protection Agency (1986a,b) (Methods 6010 & 7130)
Aqueous samples, extracts, wastes	Acidify with nitric acid; heat and evaporate to low volume; cool; add nitric acid; reheat and reflux with hydrochloric acid (Method 3010)			
Oils, greases, waxes	Dissolve in xylene or methyl isobutyl ketone (Method 3040)			
Sediments, sludges, soils	Digest with nitric acid and hydrogen peroxide; reflux with hydrochloric acid (Method 3050)			
Aqueous samples, extracts, wastes	Acidify with nitric acid; evaporate to low volume; cool; add nitric acid; heat to complete digestion (Method 3020)	GFAA	0.1 μg/L	US Environmental Protection Agency (1986c) (Method 7131)
Sediments, sludges, soils	Digest with nitric acid and hydrogen peroxide; reflux with nitric acid (Method 3050)	GFAA	0.1 μg/L	US Environmental Protection Agency (1986c) (Method 7131)
Tissue samples	Ash in hot concentrated nitric acid	AA	0.0006 μg/ml	Kleinman *et al.* (1989b)
Urine	Adjust pH to 2.0 and add polydithiocarbamate resin; filter through cellulose ester membrane filter; ash in low-temperature oxygen plasma or with nitric:perchloric acid solution (4:1)	ICP	0.1 μg/sample	Eller (1984b)

Table 3 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Urine (contd)	Complex with hexamethylene ammonium/hexamethylene dithiocarbamate; extract with diisopropyl ketone/xylene	GFAA	0.2 µg/L	Angerer & Schaller (1988)
Blood	Solubilize with Triton-X-100; deproteinate with 1 M nitric acid (Recommended reference method of the Commission of Toxicology of IUPAC)	GFAA	0.2 µg/L	Stoeppler & Brandt (1980); Angerer & Schaller (1985)

Abbreviations: FLAA, flame atomic absorption spectrometry; ICP, inductively coupled argon plasma atomic emission spectrometry; GFAA, graphite furnace atomic absorption spectrometry; AA, atomic absorption spectrometry

The cadmium concentrations in environmental and biological specimens vary widely: only a few nanograms of cadmium may be present in specimens of air, water and biological fluids, whereas hundreds of micrograms or more may be present in kidney, sewage sludge and plastics. Different techniques are therefore required for sample collection and preparation and for analysis. Atomic absorption spectrometry, electrochemical methods such as anodic stripping voltammetry and pulse polarography, neutron activation, X-ray microanalysis and spark source emission spectroscopy are used for the determination of cadmium in various media.

In general, the techniques available for measuring cadmium in the environment and in biological materials cannot differentiate between different compounds. With special separation techniques, cadmium-containing proteins can be isolated and identified. In most studies to date, the concentration or amount of cadmium in water, air, soil, plants and other environmental or biological material has been determined as the element.

The most commonly used methods, atomic absorption spectrometry and polarography, were discussed in detail in WHO (1992b). Atomic absorption spectrometry is the most reliable and practicable method, especially for the biological monitoring of exposure to cadmium. The sensitivity of flame atomic absorption spectrometry is about 10 µg/L; with graphite furnace atomic absorption spectroscopy, cadmium concentrations of about 0.1 µg/L can be determined in urine and blood. Standardized methods for the determination of cadmium in blood and urine have been published (Stoeppler & Brandt, 1980; Angerer & Schaller, 1985, 1988).

The precision and accuracy of the results are strongly influenced by the pre-analytical phase, so that special care must be taken to avoid contamination during sampling, transport and storage of specimens, particularly liquid samples. Contamination of biological samples by sampling devices, containers and sample preparations has been reported (WHO, 1992b). It is strongly recommended that analysis of cadmium be accompanied by an adequate internal and external quality assurance programme. Quality control materials are available for daily use in intralaboratory control and in national and international intercomparison

programmes for the determination of cadmium in blood and urine (Herber *et al.*, 1990a,b; Schaller *et al.*, 1991; Brown, 1992; WHO, 1992b).

A noninvasive technique for determination of cadmium in liver and kidney *in vivo* has been developed, which is based on the principle of neutron activation analysis and takes advantage of the very large cross-sectional area for capture of thermal neutrons of one of the naturally occurring stable isotopes of cadmium, ^{113}Cd (Ellis *et al.*, 1981; Roels *et al.*, 1981). The lowest detection limits for 'field work' techniques currently in use are about 1.5 mg/kg in liver and 2.2 mg/kg in kidney (Ellis *et al.*, 1981). An alternative method for determination of cadmium concentrations in kidney cortex *in vivo* involves X-ray-generated atomic fluorescence (Ahlgren & Mattsson, 1981; Christoffersson & Mattsson, 1983). Skerfving *et al.* (1987) found the limit of detection of this method to be 17 mg/kg in kidney cortex. The analytical validity of these in-vivo techniques has not been studied sufficiently (WHO, 1992b; see also section 4.1).

1.2 Production and use

1.2.1 *Production*

(*a*) *Cadmium metal*

Cadmium is often considered to be a metal of the twentieth century: Unlike some other heavy metals, such as lead and mercury which have been used since ancient times, cadmium has been refined and used only relatively recently, and over 65% of the cumulative world production has taken place in the last few decades. After its discovery by Strohmeyer in 1817 as an impurity in zinc carbonate, more than a century elapsed before the metal or its compounds were used to any significant extent, and only in the last 40–50 years have production and consumption risen (Hollander & Carapella, 1978; Schulte-Schrepping & Piscator, 1985). Cadmium is a relatively rare element and is not found in the pure state in nature. Cadmium minerals do not occur in concentrations or quantities sufficient to justify mining them in their own right, and cadmium is almost invariably recovered as a by-product from the processing of sulfide ores of zinc, lead (see IARC, 1987b) and copper (Cadmium Association/Cadmium Council, 1991; WHO, 1992b).

Because cadmium is primarily a by-product of zinc processing, the level of cadmium output has closely followed the pattern of zinc production, little being produced prior to the early 1920s. The subsequent rapid increase corresponded to the commercial development of cadmium electroplating. Worldwide production reached a plateau in the 1970s, but appeared to be increasing again in the 1980s (Table 4). Canada is the largest source of cadmium concentrate; other major suppliers are Australia, Europe, Japan, Mexico, Peru and the USA. Outside of the former USSR (for which only estimates of production are available), Japan is the largest producer of primary refined cadmium, as it treats concentrates from South America and Australia as well as from its own mines. Australia, Belgium, Canada, China, Germany, Italy, Mexico and the USA are also major producers of refined cadmium. An important source of cadmium is the recycling of secondary raw materials, including cadmium-containing products which have become unusable, such as nickel–cadmium batteries (for the monograph on nickel, see IARC, 1990a); cadmium-containing by-products,

such as steel industry dust and electroplating sludges; and other types of materials the reprocessing of which has become economically feasible or required by law (Förstner, 1984; Cadmium Association/Cadmium Council, 1991; WHO, 1992b).

Table 4. World production of refined cadmium (tonnes)

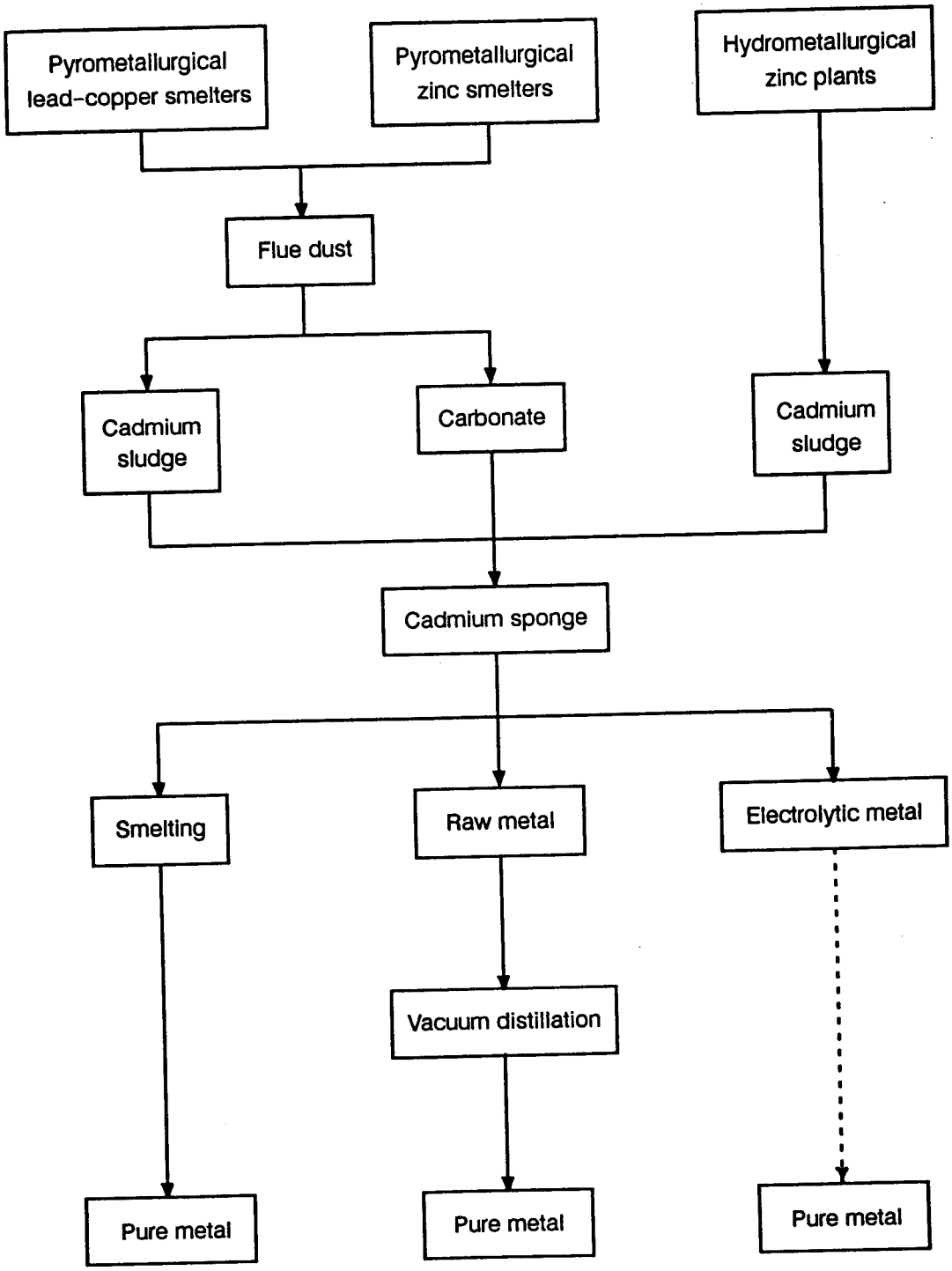
Country or region	1980	1981	1982	1983	1984	1987	1988	1989	1990	1991
Algeria	60	65	65	50	50	102	55	46	65	65
Argentina	18	NR	21	19	20	46	46	54	48	50
Australia	1 012	1 031	1 010	1 100	1 200	944	855	696	638	800
Austria	36	55	48	46	45	26	26	49	44	22
Belgium	1 524	1 176	996	800	850	1 308	1 836	1 761	1 956	1 800
Brazil	41	45	73	189	180	214	161	197	200	200
Bulgaria	210	210	200	200	200	250	300	350	309	300
Canada	1 303	1 298	809	1 107	1 200	1 571	1 694	1 620	1 437	1 400
China	250	270	300	300	300	680	750	800	1 000	1 200
Democratic People's Republic of Korea	140	140	100	100	100	100	100	100	100	100
Finland	581	621	566	616	600	690	703	612	568	593
France	789	663	793	540	500	457	558	790	780	700
Germany	1 210	1 208	1 046	1 111	1 116	1 143	1 189	1 234	990	1 105
India	89	113	131	131	120	214	237	275	277	280
Italy	568	489	475	450	400	320	705	770	665	734
Japan	2 173	1 977	2 034	2 214	2 400	2 450	2 614	2 694	2 451	2 889
Mexico	778	590	607	642	650	935	1 117	976	882	900
Namibia	69	NR	110	25	25	51	106	88	75	75
Netherlands	455	518	497	521	525	517	563	505	590	549
Norway	130	117	104	117	110	147	169	206	286	236
Peru	172	307	421	451	460	351	303	352	265	350
Poland	698	580	570	570	570	620	642	485	373	350
Republic of Korea	365	300	320	320	300	NR	490	500	500	450
Romania	85	85	80	80	80	75	75	70	62	60
Spain	309	303	286	278	250	297	438	361	355	350
United Kingdom	375	278	354	340	340	498	399	395	438	449
USA	1 578	1 603	1 007	1 052	1 686	1 515	1 885	1 550	1 678	1 676
Former USSR	2 850	2 900	2 900	3 000	3 000	3 000	3 000	3 000	2 800	2 500
Former Yugoslavia	201	208	174	48	100	305	405	471	362	280
Zaire	168	230	281	308	310	299	281	224	213	120
Total[a]	18 238	17 381	16 378	16 725	17 687	19 169	21 761	21 325	20 493	20 673

From Plunkert (1985) for 1980–84; Llewellyn (1992) for 1987–91; some figures are estimates. NR, not reported
[a]Totals do not add up because they have been revised.

Figure 1 summarizes the individual steps in the process and their combination for the production of cadmium metal. The flue dust on which volatile cadmium collects when zinc, copper and lead ores are heated in air is the primary starting material for cadmium recovery and refining. This dust must usually be recirculated in order to obtain high concentrations of cadmium. If the primary flue dust is reduced in a rotary oven, lead and zinc remain, while the

cadmium is volatilized and enriched in the secondary flue dust (Schulte-Schrepping & Piscator, 1985).

Fig. 1. Processes for the production of cadmium metal



From Schulte-Schrepping & Piscator (1985)

Zinc metal can be produced by either pyrometallurgical or electrolytic processes, and cadmium is recovered and refined at a number of stages. In one type of pyrometallurgical process, complex lead–zinc ores are refined by the Imperial smelting process. When the concentrate is roasted at 700–1200 °C in sintering furnaces, cadmium-containing flue dust and fume are produced. This is leached in a sulfuric acid solution, and the cadmium is subsequently precipitated as cadmium carbonate, which is dried and refined by distillation to cadmium metal. The cadmium in secondary raw materials, after enrichment in a special furnace, can be added to the concentrate and processed at the same time (Schulte-Schrepping & Piscator, 1985; Cadmium Association/Cadmium Council, 1991).

In hydrometallurgical zinc refining, cadmium-containing zinc concentrate is leached with sulfuric acid, and cadmium is removed from the solution together with copper by reduction with zinc dust, to give a metallic sludge. These cadmium sludges are the most important starting materials for cadmium refining today (Schulte-Schrepping & Piscator, 1985).

In electrolytic processes, the zinc concentrate is also roasted under oxidizing conditions to remove the sulfur, usually in fluidized bed roasters which produce a fine calcine suitable for acid leaching. The calcine is dissolved in sulfuric acid in a leaching plant, then neutralized to precipitate any iron. The bulk of the cadmium is precipitated from the sulfate solution during the second zinc dust stage and the remainder in the third stage. The cadmium precipitate is filtered and forms a cake containing about 25% cadmium, 50% zinc and small amounts of copper and lead; the cake is redissolved in sulfuric acid. A reasonably pure cadmium sponge is produced after two additional acid solution/zinc dust precipitation stages. The sponge is again dissolved in sulfuric acid, and the solution is passed into electrolytic cells where the cadmium is deposited on cathodes. The cathodes are then removed and stripped, and the cadmium is melted and cast into required shapes; it is typically 99.99% pure (Cadmium Association/Cadmium Council, 1991).

(*b*) *Cadmium alloys*

Cadmium can be combined with a number of other nonferrous metals to form alloys with useful commercial properties. Typically, metallic cadmium is added to the molten metal(s) with which it is to be alloyed and, after thorough mixing, the resultant alloy is cast into the desired form (ingot, wire, rod). Depending on the alloy and its application, the cadmium content ranges from < 0.1 to 15%. To facilitate mixing, a master alloy containing much higher levels of cadmium may be prepared first and added to the molten alloying metal (Hollander & Carapella, 1978; Holden, 1982).

(*c*) *Cadmium acetate*

Cadmium acetate is produced by the reaction of acetic acid with cadmium metal or oxide, or by treating cadmium nitrate with acetic anhydride. The dihydrate is obtained by dissolving cadmium metal or oxide in acetic acid, followed by crystallization. Calcination of the dihydrate can be controlled to yield cadmium acetate monohydrate and the anhydrous acetate (Parker, 1978; Budavari, 1989).

(*d*) *Cadmium chloride*

Cadmium chloride is produced by reacting molten cadmium with chlorine gas at 600 °C or by dissolving cadmium metal or the oxide, carbonate, sulfide or hydroxide in hydrochloric acid (see IARC, 1992), and subsequently vaporizing the solution to produce a hydrated crystal. In order to prepare the anhydrous salt, the hydrate is refluxed with thionyl chloride or calcined in a hydrogen chloride atmosphere. It may also be obtained by the addition of dry cadmium acetate to a mixture of glacial acetic acid and acetyl chloride or by distillation from a mixture of cadmium nitrate tetrahydrate in hot concentrated hydrochloric acid (Parker, 1978; Schulte-Schrepping & Piscator, 1985; Sax & Lewis, 1987).

(*e*) *Cadmium hydroxide*

Cadmium hydroxide has been prepared by the addition of a solution of cadmium nitrate to boiling sodium or potassium hydroxide (Parker, 1978). It has also been produced by the action of sodium hydroxide on a cadmium salt solution (Sax & Lewis, 1987).

(*f*) *Cadmium nitrate*

Cadmium nitrate has been produced by the action of nitric acid on cadmium metal or cadmium oxide, hydroxide or carbonate (Parker, 1978; Schulte-Schrepping & Piscator, 1985; Sax & Lewis, 1987).

(*g*) *Cadmium oxide*

Cadmium oxide is produced by the reaction of cadmium metal vapour with air. Pure cadmium metal is melted in a cast-iron or steel kettle and pumped to a heated chamber, where it is vaporized. The vapour is conducted to a reactor, and air is blown through, oxidizing the cadmium and carrying the reaction product into a 'baghouse'. Finer or coarser particles are produced, depending on the ratio of air to cadmium vapour. Cadmium oxide can also be obtained by thermal decomposition of cadmium nitrate or carbonate or by oxidation of molten cadmium by an oxidizing agent (Parker, 1978; Schulte-Schrepping & Piscator, 1985). Cadmium oxide is generated as either a dust or fume, depending on how it is produced.

(*h*) *Cadmium stearate*

Cadmium stearate, one of the cadmium alkanoate salts used as polyvinyl chloride stabilizers, is prepared by the addition of sodium stearate to a solution of cadmium chloride. The cadmium salt precipitates from solution and is filtered, washed and dried. Other salts (laurate, myristate, palmitate) are prepared in analogous reactions (Parker, 1978).

(*i*) *Cadmium sulfate*

The principal cadmium sulfates are $CdSO_4$, $CdSO_4.H_2O$ [13477-20-8] and $3CdSO_4.8H_2O$ [7790-84-3]. They are crystallized from cadmium sulfate solutions or can be precipitated by addition of ethanol. Anhydrous cadmium sulfate is prepared by oxidation of the sulfide or sulfite at elevated temperatures, or by the action of dimethyl sulfate on finely powdered cadmium nitrate, halides, oxide or carbonate. Solutions are prepared by dissolving cadmium metal, oxide, sulfide, hydroxide or carbonate in sulfuric acid. Anhydrous cadmium

sulfate is also produced by melting cadmium with ammonium or sodium peroxodisulfate. Cadmium sulfate monohydrate, which is the form usually marketed, is produced by evaporating a cadmium sulfate solution above 41.5 °C (Parker, 1978; Schulte-Schrepping & Piscator, 1985).

(*j*) *Cadmium sulfide*

Cadmium sulfide can be prepared by the reaction between hydrogen sulfide and cadmium vapour at 800 °C, or by heating a mixture of cadmium or cadmium oxide with sulfur. Usually, the sulfides are precipitated from aqueous solutions of cadmium salts by adding hydrogen sulfide or a soluble sulfide such as sodium sulfide. Cadmium sulfide can also be prepared by passing hydrogen sulfide gas into a solution of a cadmium salt acidified with hydrochloric acid; the precipitate is filtered and dried. It also occurs naturally as the mineral greenockite. The dimorphic sulfide, CdS, is the most widely used cadmium compound. The β form can be transformed to the α form by heating at 750 °C in a sulfur atmosphere. Both forms can be prepared in colours ranging from lemon-yellow through orange and red, depending on the method of preparation and particle size (Parker, 1978; Sax & Lewis, 1987).

1.2.2 *Use*

Typical use patterns for cadmium and its compounds and alloys in several industrialized countries are presented in Table 5.

Table 5. Patterns of use of cadmium in several industrialized countries (%)

Use category	1970[a]	1973[a]	1976[a]	1979[a]	1982[a]	1990[b]
Coating and plating	37	30	36.5	34	29	8
Batteries	8	15	21.5	23	28.5	55
Pigments	24	30	25	27	24	20
Stabilizers for PVC	23	17	12	12	12	10
Alloys and other uses	8	8	5	4	6.5	7

[a]From Schulte-Schrepping & Piscator (1985); figures are based on totals of published statistics for Germany, Japan, the United Kingdom and the USA.
[b]From Cadmium Association/Cadmium Council (1991); figures are for Belgium, France, Germany, Japan, the United Kingdom and the USA.

(*a*) *Cadmium*

Cadmium has a limited number of principal applications, but within the range the metal, its alloys and compounds are used in a large variety of consumer and industrial materials. The principal applications of cadmium fall into five categories: active electrode material in nickel–cadmium batteries; pigments used mainly in plastics, ceramics and glasses; to stabilize polyvinyl chloride (PVC) against heat and light; engineering coatings on steel and some nonferrous metals; and as a component of various specialized alloys. Detailed statistics on use are available for only a limited number of countries, but these indicate that the pattern of

use varies considerably from country to country (Cadmium Association/Cadmium Council, 1991; WHO, 1992a).

Japan is by far the largest user of cadmium, followed by the USA, Belgium, the United Kingdom, France and Germany. Worldwide consumption of cadmium for all uses in 1990 was estimated to have been 18 500 tonnes. The cadmium compounds of greatest commercial importance are cadmium oxide and cadmium sulfide; other important compounds are the hydroxide, chloride, nitrate, sulfate and stearate (adapted from Cadmium Association/-Cadmium Council, 1991).

Examination of the reported trends in cadmium consumption over the last 25 years reveals considerable change in the relative importance of the major applications. The use of cadmium for engineering coatings and electroplating represents the most striking decrease; in 1960, this sector accounted for over half the cadmium consumed worldwide, but in 1985 its share was less than 25%. The decline is usually linked to the widespread introduction of progressively more stringent limits on effluents from plating works and, more recently, to the introduction of restrictions on certain cadmium products in some European countries. In contrast, the use of cadmium in batteries has shown considerable growth in recent years, from only 8% of the total market in 1970 to 37% by 1985. The use of cadmium in batteries is particularly important in Japan, where it represented over 75% of total consumption in 1985 (WHO, 1992b).

Of the remaining applications of cadmium, pigments and stabilizers are the most important, accounting for 22 and 12%, respectively, of total world consumption in 1985. The share of the market represented by cadmium pigments remained relatively stable between 1970 and 1985, but use of the metal in stabilizers during the period showed a considerable decline, largely as a result of economic factors. The use of cadmium as a constituent of alloys is relatively small and has also declined in importance in recent years: it accounted for about 4% of total cadmium use in 1985 (WHO, 1992b).

(*b*) *Cadmium alloys* (from Cadmium Association/Cadmium Council, 1991, unless otherwise specified)

Cadmium forms many binary and more complex alloys, which have useful properties for many commercial applications. Most commercial alloys containing cadmium fall into two major groups, where:

(i) the presence of cadmium improves some feature of the alloy. Small amounts of cadmium can improve hardness and wear resistance, mechanical strength, fatigue strength, castability and electrochemical properties. Cadmium is added principally to alloys based on copper, tin, lead and zinc, although several others benefit from its presence.

(ii) lower melting-points are obtained. Such alloys range from low-melting-point eutectic ('fusible') alloys to high-melting-point non-eutectic alloys used in metal joining.

Cadmium–copper alloys, which have almost twice the mechanical strength and wear resistance of pure copper yet still retain 90% of its conductivity, contain 0.8–1.2% cadmium. The major uses of such alloys are in telephone wires, wiring for railway overhead electrification, conductors for flexible telephone cords, special cables for military and aerospace

uses and electrical components such as contact strips and electric blanket and heating-pad elements (Ricksecker, 1979).

Zinc alloys containing 0.1% cadmium improve the mechanical properties of rolled, drawn or extruded zinc. Zinc alloys containing cadmium in the range of 0.025 to 0.15% are used in anodes to protect structural steelwork immersed in seawater against corrosion.

Lead alloys with up to 0.075% cadmium are sometimes used as sheaths for cables subject to cyclic stress.

Tin-based white metal-bearing alloys with up to 1% cadmium have adequate tensile and fatigue strength for use in marine engines and gearboxes.

Precious metal alloys for jewellery incorporate cadmium for improved hardness and strength. Levels of up to 5% cadmium in gold–silver–copper alloys make Greek gold, a greenish-tinged gold.

Silver electric contacts incorporating 10–15% cadmium or cadmium oxide are useful in many heavy duty electrical applications, such as relays, switches and thermostats.

A *tin–lead–bismuth–cadmium alloy*, which melts at 70 °C, is more commonly known as Woods metal and is used in the bonding of metallized ceramic and glass components to metal frames and chassis, where higher soldering temperatures are not possible. The presence of Woods metal in water sprinkler valves automatically activates the water supply when the local temperature exceeds 70 °C, when it melts.

Cadmium alloyed with silver, zinc or tin makes excellent solders, with tensile strengths two to three times greater than most common solders in the same temperature range. Cadmium is an important component in quaternary alloys with silver, copper and zinc in the lower temperature range of brazing alloys.

The low melting-points and rapid fusing or solidifying characteristics of *low-temperature fusible alloys* containing cadmium lead to a variety of uses. Heat-sensitive fusible links in fire safety devices or kilns and ovens can activate control mechanisms when they melt at specific temperatures. The alloys are used to mount glass lenses firmly during grinding operations.

(c) *Cadmium acetate*

Cadmium acetate is the starting material for cadmium halides and is a colourant in glass, ceramics (iridescent glazes) and textiles. It is also used in electroplating baths, as a laboratory reagent and in the separation of mercaptans from crude oils and gasolines (Greene, 1974; Parker, 1978; Sax & Lewis, 1987).

(d) *Cadmium chloride*

Cadmium chloride is used in electroplating. The significance of cadmium chloride as a commercial product is declining; however, it occurs as an intermediate in the production of cadmium-containing stabilizers and pigments, which are often obtained from cadmium chloride solutions, themselves obtained from cadmium metal, oxide, hydroxide or carbonate. It is also used in the preparation of cadmium sulfide, in analytical chemistry, in photography, in dyeing and calico printing, in the manufacture of special mirrors and of cadmium yellow, in the vacuum tube industry and as a lubricant (Schulte-Schrepping & Piscator, 1985; Sax & Lewis, 1987; Budavari, 1989).

(*e*) *Cadmium hydroxide*

Cadmium hydroxide is a component of cadmium–nickel and silver–cadmium batteries. It often replaces the oxide as the starting material for other cadmium compounds (Parker, 1978; Schulte-Schrepping & Piscator, 1985; Cadmium Association/Cadmium Council, 1991).

(*f*) *Cadmium nitrate*

Cadmium nitrate is the preferred starting material for cadmium hydroxide; it is also used in photographic emulsions (Budavari, 1989; Parker, 1978) and in colouring glass and porcelain (Schulte-Schrepping & Piscator, 1985; Sax & Lewis, 1987).

(*g*) *Cadmium stearate*

Cadmium stearate is commonly used in combination with other salts to retard the degradation processes which occur in PVC and related polymers on exposure to heat and ultraviolet light (sunlight). The stabilizers consist of mixtures of barium, lead and organic cadmium salts, usually cadmium stearate or cadmium laurate, which are incorporated into the PVC before processing and which arrest any degradation reactions as soon as they occur. They ensure that PVC develops good initial colour and clarity and allow high processing temperatures to be employed; they also ensure longer service life.

Barium–cadmium stabilizers typically contain 1–15% cadmium and usually constitute about 0.5–2.5% of the final PVC compound. They are incorporated into PVC used, for example, in rigid profiles for window and door frames, water and drain pipes, hoses and electrical insulation (Parker, 1978; Cadmium Association/Cadmium Council, 1991).

(*h*) *Cadmium sulfate*

Cadmium sulfate is used in electroplating and as a starting material for pigments, stabilizers and other cadmium compounds that can be precipitated from aqueous solution. It is also used to produce fluorescent materials, in analytical chemistry and as a nematocide. Cadmium sulfate solution is a component of Weston cells (portable standards for electromagnetic frequency) (Schulte-Schrepping & Piscator, 1985; Sax & Lewis, 1987; Budavari, 1989).

(*i*) *Cadmium sulfide*

The main use of cadmium sulfide is for pigments. Pure yellow cadmium sulfides are formulated with red cadmium selenides in varying proportions to make chemically pure toners ranging from yellows and oranges with a low selenium content to reds and maroons with a high selenium content. Cadmium colourants are used in special paints (especially artists' colours, such as cadmium yellow), for colouring textiles, paper, rubber, plastics, glasses and ceramic glazes and in fireworks. Red and yellow cadmium sulfide–zinc sulfide fluorescent and phosphorescent pigments are also produced. Cadmium sulfide is used in the conversion of solar energy to electrical power. Its photoconductive and electroluminescent properties have been applied not only in photocells but also in a wide variety of phosphors, light amplifiers, radiation detectors, thin film transistors and diodes, electron beam-pumped lasers and household smoke detectors (Parker, 1978; Sax & Lewis, 1987; Budavari, 1989).

(*j*) *Cadmium oxide*

The main use of cadmium oxide is in the manufacture of nickel–cadmium batteries. In the first step in the preparation of negative electrodes (paste preparation), cadmium oxide is hydrated to form a paste of cadmium hydroxide. The dried paste is then mixed with graphite, iron oxide and paraffin, milled and finally compacted between rollers (Malcolm, 1983; Adams, 1992).

Cadmium oxide is used as a starting material for PVC heat stabilizers and for other inorganic cadmium compounds. It is also used as a catalyst in oxidation–reduction reactions, dehydrogenation, cleavage, polymerization, the production of saturated alcohols, hydrogenation of unsaturated fatty acids and as a mixed catalyst component to produce methanol from carbon monoxide and water. Further uses are in resistant enamels, metal coatings for plastics, heat-resistant plastics and selenium ruby glass. Cadmium oxide combined with an alkali-metal cyanide is the salt mixture used in baths for cadmium electroplating. High-purity cadmium oxide is used as a second depolarizer (in addition to silver oxide) in silver–zinc storage batteries. It is temperature resistant and, together with silver, useful in heavy-duty electrical contacts. In veterinary medicine, it has been used as a nematocide, vermicide and ascaricide in swine (Parker, 1978; Schulte-Schrepping & Piscator, 1985; Sax & Lewis, 1987; Budavari, 1989; Cadmium Association/Cadmium Council, 1991).

Other cadmium compounds used industrially include: cadmium cyanide (electroplating), cadmium carbonate (starting material for pigments), cadmium arsenides (electronic devices), cadmium selenide (photocells, luminous paints, colourant in glass), cadmium telluride (photocells, infra-red optics) and cadmium tungstate (X-ray screens, phosphors) (Parker, 1978; Schulte-Schrepping & Piscator, 1985).

1.3 Occurrence

1.3.1 *Natural occurrence*

Cadmium is widely but sparsely distributed over the Earth's surface; it is found most commonly as the mineral greenockite (cadmium sulfide) and in weathered ores such as otavite (cadmium carbonate). Other minerals that contain cadmium are hawleyite (cadmium sulfide), xanthocroite (cadmium sulfide hydrate), cadmoselite (cadmium selenide) and monteponite (cadmium oxide). It occurs in nature associated mainly with zinc but also with lead or copper; in minerals and ores, cadmium and zinc are present typically in a ratio of 1:100 to 1:1000 (Fairbridge, 1974; Alessio *et al.*, 1983; Förstner, 1984).

Cadmium is a relatively rare element, comprising about 0.1–0.5 mg/kg of the Earth's crust; however, higher concentrations (15 mg/kg) are present in some sedimentary rocks. Trace quantities of cadmium can also be found in fossil fuels and oils (Bowen, 1966; WHO, 1992a,b).

1.3.2 *Occupational exposure*

Workers may be exposed to cadmium and cadmium compounds in a variety of occupational settings (Table 6). The major sources of such exposure are smelting and refining of zinc, lead and copper ores, electroplating, manufacture of cadmium alloys and of pigments and plastic stabilizers, production of nickel–cadmium batteries and welding.

Table 6. Occupations in which there is potential exposure to cadmium and cadmium compounds

Alloy production[a]
Battery production[a]
Brazing
Coating
Diamond cutting
Dry colour formulation
Electroplating
Electrical contacts production
Enamelling
Engraving
Glasswork
Laser cutting
Metallizing
Paint production and use
Pesticide production and use
Phosphorus production
Pigment production and use[a]
Plastics production[a]
Plating
Printing
Semiconductor and superconductor production
Sensors production
Smelting and refining[a]
Solar cells production
Soldering
Stabilizer production
Textile printing
Thin film production
Transistors production
Welding[a]

[a]Activities in which risk is highest because atmospheric concentrations of cadmium can be high and because the number of workers employed is relevant (modified from Odone *et al.*, 1983)

It has been estimated that about 510 000 workers in the USA are exposed to cadmium (Thun *et al.*, 1991). In 1987, an estimated 210 000 workers were exposed to concentrations equal to or greater than 1 μg/m^3; 65% were exposed to concentrations of 1–39 μg/m^3, 21% to 40–99 μg/m^3 and 14% to concentrations greater than 100 μg/m^3 (US National Toxicology Program, 1991). Airborne concentrations of cadmium found in occupational settings vary considerably according to the type of industry and to specific working conditions. Cadmium oxide fumes are generated at high temperatures (US Occupational Safety and Health Administration, 1992) and can be absorbed very efficiently through the lung, while deposition and absorption of dust of different cadmium compounds depends on particle size (Alessio *et al.*, 1983; Thun *et al.*, 1991). Improvements in occupational hygiene have led to a

progressive reduction in the concentrations of cadmium in occupational environments, and 5–20 μg/m^3 can now be achieved (Hassler *et al.*, 1983; Friberg *et al.*, 1986a; US Occupational Safety and Health Administration, 1992).

Data on exposure to cadmium and cadmium compounds and the results of biological monitoring in different occupational situations are summarized below. Occupational exposure to cadmium can be assessed both by ambient air monitoring ('external dose') and by biological monitoring ('internal dose'). Individual external doses can be measured only by personal sampling of ambient air; individual uptake is estimated by biological monitoring of cadmium in blood and urine (Alessio *et al.*, 1983; Ghezzi *et al.*, 1985; see also section 4.1).

(*a*) *Cadmium production and refining*

Smith *et al.* (1980) made a detailed assessment of exposures to cadmium in a production facility in the USA where cadmium metal had been refined and cadmium compounds, such as cadmium oxide and yellow cadmium pigment, had been produced since 1925. An epidemiological study carried out at the plant (Thun *et al.*, 1985) is described on pp. 152–153. Exposure to cadmium oxide dusts occurred during sampling, loading and transport of dust between the roasting, mixing and calcining operations and during loading of purified oxide. Exposure to cadmium oxide fume occurred in roaster, calcining, retort and foundry operations. Exposure to cadmium sulfate mist occurred during solution and tankhouse operations. The concentrations of cadmium differed substantially between the departments and with time. The highest exposures (1500 μg/m^3) were estimated to have occurred in the mixing and retort areas prior to 1950 and in the calcining area prior to 1960. Estimates of exposures by inhalation, based on historical data derived from area monitoring and adjusted to reflect actual exposures of workers wearing respirators, were 200–1500 μg/m^3 before 1950 and 40–600 μg/m^3 during 1965–76. In 1946, an average concentration of 18 900 μg/m^3 was reported during grinding of cadmium sulfide and 31 300 μg/m^3 in the cadmium sulfide packaging room (Princi, 1947); cadmium concentrations in the solution room were approximately 3000 μg/m^3 before 1955, 1500 μg/m^3 in 1955–64 and 150 μg/m^3 subsequently (Thun *et al.*, 1985; Commission of the European Communities, 1991a,b).

At a zinc–lead–cadmium smelter in the United Kingdom, mean airborne cadmium concentrations were 80 μg/m^3 in the cadmium plant and 200 μg/m^3 in the sintering plant before 1970, whereas a mean level of 15 μg/m^3 was measured in each department in 1977. These assessments were considered to be accurate within a factor of 2–5. Urinary cadmium concentrations ranged from a geometric mean of 2.5 nmol/mmol creatinine [2.5 μg/g creatinine] for workers in the sinter area to 6.3 nmol/mmol creatinine (6.3 μg/g creatinine) for workers in the cadmium plant. [Some of the workers were exposed to cadmium sulfate and cadmium sulfide, but cadmium oxide is the compound to which they were most likely to have been exposed predominantly.] Copper and, from time to time, arsenic had also been refined in the plant (Kazantzis & Armstrong, 1983; Ades & Kazantzis, 1988). Epidemiological studies at the smelter are described on pp. 154–156.

Concentrations of cadmium were measured in the blood and urine of workers employed at two cadmium-producing factories and at a nickel–cadmium battery plant in Belgium. The cadmium content of the airborne respirable dust was usually below 90 μg/m^3. In 96 workers without kidney damage, the mean urinary concentration of cadmium was 16.3 ± 1.7

(SE) μg/g creatinine and that in blood was 21.4 ± 1.9 μg/L. In 25 workers with kidney lesions, the levels were 48.2 ± 8.5 μg/g creatinine and 38.8 ± 7.7 μg/L, respectively (Lauwerys *et al.*, 1976).

Airborne cadmium concentrations of 2500–6500 μg/m^3 in the crushing and roasting area, 10 800–23 300 μg/m^3 in the dry smelting area, 10–160 μg/m^3 in the cadmium melting area and 2800–4700 μg/m^3 in the ingot making area were measured in 1988 at a Chinese plant which employed about 10 000 workers; 358 were employed in those areas (Nomiyama *et al.*, 1992).

As part of an epidemiological study of Chinese smelter workers (see p. 156), Ding *et al.* (1987) reported a mean air concentration of 186 μg/m^3 in the cadmium shop, where workers were exposed to cadmium oxide, and 14 μg/m^3 in the sintering shop. The concentrations in the cadmium shop were reported to have been much higher (535 μg/m^3) prior to 1980.

(*b*) *Cadmium–copper and silver–cadmium alloy production*

In two plants for the production of cadmium–copper alloys in the United Kingdom, mean exposure concentrations of cadmium oxide as cadmium were 38–106 μg/m^3 in 1953 in one factory (Bonnell *et al.*, 1959) and 13–89 μg/m^3 in the rocker furnace area in the other factory (King, 1955). Concentrations of cadmium oxide were reported to have been at least 1000 μg/m^3 prior to 1953, up to 150 μg/m^3 between 1953 and 1957 and approximately 50 μg/m^3 subsequently (Holden, 1980a,b). Similar levels (mean, 130 μg/m^3) were reported in the 1960s at a Japanese silver–cadmium alloy factory (Tsuchiya, 1967).

In an Italian cadmium alloy plant in 1982, mean concentrations of 67 μg/m^3 and 28 μg/m^3 were detected using personal samplers in two foundries in the same factory; during alloy processing, 3 μg/m^3 were measured. Atmospheric concentrations of cadmium of up to 1500 μg/m^3 were measured with area samplers in 1975 (Ghezzi *et al.*, 1985).

As part of an epidemiological study of copper–cadmium alloy workers in Sweden (see pp. 151–152), the concentration of cadmium in cadmium oxide fumes was reported to be 100–400 μg/m^3 during the 1960s and 50 μg/m^3 during the 1970s (Kjellström *et al.*, 1979).

(*c*) *Battery manufacture*

Although the oxide is the form of cadmium used as the raw material in the manufacture of nickel–cadmium batteries, it is converted to cadmium hydroxide during the process. No information was available in the studies described below about which species of cadmium workers were actually exposed to. Exposures to nickel during the manufacture of nickel–cadmium batteries were described in a previous monograph (IARC, 1990a).

In a nickel–cadmium battery factory in Singapore, atmospheric, urinary and blood concentrations of cadmium were measured. The highest geometric mean atmospheric concentration (870 μg/m^3) was detected during spot welding; measurements during the period 1973–80 showed levels of 31–2900 μg/m^3. The geometric mean concentration of cadmium in blood was 75.2 μg/L for 41 women and 40.4 μg/L for six men; the geometric means in urine were 66.0 and 22.9 μg/g creatinine, respectively. The highest concentrations were detected in the subgroup of spot welders (Chan *et al.*, 1982).

The average concentrations of cadmium in a battery factory in the United Kingdom in 1957 were 500 μg/m^3 in the plate-making department and 100 μg/m^3 in the assembly

department (Adams *et al.*, 1969). In a nickel–cadmium battery factory in the United Kingdom, in which an epidemiological stdy was conducted (see pp. 149–150), the air concentration of cadmium in plate-making and assembly shops was 600–2800 μg/m^3 in 1949. After installation of local exhaust ventilation in 1950, concentrations were reduced to less than 500 μg/m^3 in most parts of the factory. After further improvements in the ventilation systems and the building of new departments in 1975, the levels were below 50 μg/m^3 (Sorahan & Waterhouse, 1983).

In a Swedish nickel–cadmium battery factory, where a series of epidemiological studies were carried out (see pp. 150–151), the concentration of cadmium was about 1000 μg/m^3 before 1947 but decreased gradually thereafter, to about 300 μg/m^3 in 1947–62 and 50 μg/m^3 in 1962–74. After 1975, 20 μg/m^3 was seldom exceeded (Adamsson, 1979; Elinder *et al.*, 1985). In 1977 in the same factory, the arithmetic mean concentration of cadmium in workroom air, based on 181 observations, was 7.6 μg/m^3; the arithmetic mean concentration in samples from 18 workers was 14.1 μg/L in blood and 4.9 μg/g creatinine in urine (Hassler *et al.*, 1983).

(*d*) *Polyvinyl chloride compounding*

A study was carried out in eight PVC production factories in Singapore where cadmium compounds were used as thermal stabilizers in liquid form or as cadmium stearate powder. A geometric mean concentration of 100 μg/m^3 cadmium was measured in the mixing area of one plant, where maintenance and work practices were poor; and < 10 μg/m^3 in the other seven plants. Geometric mean concentrations in samples from 53 male workers were 0.78 ± 2.9 μg/g creatinine in urine and 2.25 ± 2.51 μg/L in blood (Chan *et al.*, 1982).

(*e*) *Pigment manufacture*

Concentrations of cadmium in respirable dust were measured in 1976 and 1977 in a small Australian plant producing cadmium selenosulfide and cadmium sulfide pigments; exposure to cadmium carbonate also occurred. All time-weighted average exposures in the furnace, crushing–cleaning and general duties areas were greater than 1000 μg/m^3 in 1977; about 50% of the dust particles were in the respirable range. Biological monitoring of nine workers was begun in 1976: concentrations of < 0.5–32 μg/L were found for urinary cadmium and 6–54 μg/L for blood cadmium (De Silva & Donnan, 1981).

In a Japanese factory for the manufacture of cadmium pigments, cadmium sulfide and cadmium selenide, the arithmetic mean atmospheric concentrations of cadmium in seven areas of the plant in 1986 ranged from 3 to 350 μg/m^3; the highest values were found in the canning area. The geometric mean urinary cadmium concentrations in nine subjects who worked in the canning area were 1.7 (0.5–5.8) μg/g creatinine in April 1986 and 2.3 (1.3–4.1) μg/g creatinine in September 1986 (Kawada *et al.*, 1989).

(*f*) *Soldering*

One limited investigation in the United Kingdom indicated air concentrations of cadmium in excess of 50 μg/m^3 in five firms involved in the small specialized trade for both the manufacture and repair of metal frames (jigs), which entails soldering with cadmium-containing electrodes in small workrooms without exhaust ventilation. All 32

workers with more than five years of exposure and 11 of 21 with fewer than five years of exposure had 'raised' blood and urinary concentrations of cadmium; 30 had urinary cadmium concentrations in excess of 10 nmol/mmol (μg/g) creatinine (Smith *et al.*, 1986).

(*g*) *Other*

A biological monitoring programme was conducted between 1980 and 1989, involving 919 workers employed in 16 different cadmium-processing industries in The Netherlands. The main industrial processes included in the survey were metal recycling, alloy production, enamelling, printing, production of coloured plastics, stabilizers, paints and pigments, electroplating and manufacture of cathode-ray tubes. The cadmium compounds to which workers were exposed included the oxide, chloride, carbonate, laurate, cyanide, sulfate and phosphate. Urinary cadmium concentrations ranged from 0 to 60.4 μg/g creatinine and those in blood from 0 to 48.4 μg/L. The highest concentrations were measured in workers using silver–cadmium solder (Zwennis & Franssen, 1992).

1.3.3 *Air*

Most of the cadmium that occurs in air is associated with particulate matter in the respirable range. Cadmium oxide is presumed to constitute a large proportion of airborne cadmium, but, in principle, other cadmium salts, such as cadmium chloride, used as stabilizers and pigments in plastics, could enter the environment, especially during incineration. Atmospheric emissions of cadmium from man-made sources exceed those of natural origin by one order of magnitude (UNEP, 1984, 1992). Traditional municipal solid-waste incinerators may make a significant contribution to the concentration of cadmium in ambient air and to its deposition rates. The rates of emission of cadmium from incinerators in Europe, Canada and the USA ranged from 20 to 2000 μg/m^3 from the stacks of traditional incinerators and from 10 to 40 μg/m^3 from advanced incinerators. Such emissions could result in deposition rates of 1–40 and 0.02–0.8 μg/m^2 per day, respectively (WHO, 1988). Cadmium sulfate also occurs in atmospheric emissions from thermal processes involving cadmium (IARC, 1976; Friberg *et al.*, 1985, 1986b).

Estimated emissions of cadmium to the atmosphere from natural and human sources are shown in Table 7. In both the European Economic Community and worldwide, 10–15% of total airborne emissions arise from natural processes, volcanic action being one of the major sources (WHO, 1992a,b). Mean global emission rates were estimated in 1983 to be 1000 tonnes cadmium per year from natural sources and 7570 tonnes from human sources (Nriagu & Pacyna, 1988).

In many countries, cadmium concentrations in the atmosphere are monitored regularly. In European countries, average values were 0.001–0.005 μg/m^3 in rural areas, 0.005–0.015 in urban areas and up to 0.05 μg/m^3 in industrialized areas. Concentrations of 0.003–0.023 μg/m^3 were found in urban areas of the USA, and 0.003–0.0063 μg/m^3 cadmium have been measured in urban areas in Japan (Friberg *et al.*, 1974, 1985, 1986b; WHO, 1992b). Higher concentrations of cadmium have been detected in areas close to atmospheric sources of the metal, such as cadmium-related industries. The nonferrous metal industry accounts for the largest fraction of cadmium emitted (Nriagu & Pacyna, 1988). Fluctuations in the data occur as a result of changing emission characteristics and weather conditions (WHO, 1992b).

Table 7. Estimated atmospheric emissions of cadmium (tonnes/year) from natural and human sources

Source	European Economic Community	Worldwide
Natural source	20	800
Nonferrous metal production		
Mining	NR	0.6–3
Zinc and cadmium	20	920–4600
Copper	6	1700–3400
Lead	7	39–195
Secondary production	NR	2.3–3.6
Iron and steel production	34	28–284
Fossil fuel combustion		
Coal	6	176–882
Oil	0.5	41–246
Refuse incineration	31	56–1400
Sewage sludge incineration	2	3–36
Phosphate fertilizer manufacture	NR	68–274
Cement manufacture	NR	8.9–534
Wood combustion	NR	60–180
Total	130	3900–12 800

Modified from WHO (1992a,b). NR, not reported

In Sweden, weekly mean levels of 0.3 μg/m^3 were recorded 500 m from a factory where cadmium–copper alloys were used. In Japan, a mean level of 0.2 μg/m^3 was recorded 400 m from a zinc smelter (Friberg *et al.*, 1971). In Colorado (USA), the mean annual airborne concentration of cadmium in an area about 1 km from a zinc smelter was 0.023 μg/m^3 (Wysowski *et al.*, 1978).

1.3.4 *Water*

Cadmium enters the aquatic environment from numerous diffuse and point sources and by different routes. At the global level, the smelting of nonferrous metal ores has been estimated to be the largest human source of cadmium released into the aquatic environment (Nriagu & Pacyna, 1988). The cadmium content of ore bodies, mine management policies and climatic and geographical conditions all influence the quantities of cadmium released from individual sites. Contamination can arise from entry into aquifers of mine drainage water, wastewater, overflow from tailing ponds and rainwater run-off from mine areas (WHO, 1992a).

Other human sources are spent solutions from plating operations and phosphate fertilizers, which are known to contain cadmium: cadmium constitutes up to 255 mg/kg of phosphorus pentoxide in West Africa and up to 35 mg/kg in the USA (WHO, 1992a,b). Atmospheric fall-out of cadmium to water courses and marine waters represents the major worldwide source of cadmium in the environment (Nriagu & Pacyna, 1988). Acidification of

soils and lakes may result in mobilization of the metal from soils and sediments toward surface and groundwaters (Impens *et al.*, 1989; WHO, 1992b). Other point sources are mining residue dumps, solid-waste deposits and wastewater of both municipal and industrial origin (Muntau & Baudo, 1992). Cadmium salts such as cadmium carbonate, cadmium chloride and cadmium sulfate may also contaminate surface waters as a result of run-off from industrial processes (IARC, 1976). In polluted rivers, high concentrations can be found in bottom sediments (Muntau & Baudo, 1992).

The concentration of cadmium dissolved in surface waters of the open ocean is less than 0.005 μg/L (WHO, 1992b). Ice samples from the Arctic contained an average of 5 ng/kg, while those from the Antarctic contained 0.3 ng/kg (Wolff & Peel, 1985).

The concentration of cadmium in drinking-water is generally less than 1 μg/L, but it may increase up to 10 μg/L as a result of industrial discharge and leaching from metal or plastic pipes (Friberg *et al.*, 1971).

1.3.5 *Soil and plants*

The sources of cadmium in soil are nonferrous metal mines and smelters, agricultural application of phosphate fertilizers, use of batteries, PVC stabilizers, pigments and alloys, sewage-sludge landfill, sewage-sludge and solid-waste incineration, and application of municipal sewage sludge to agricultural soil (UNEP, 1984, 1992; WHO, 1992a,b). The concentration of cadmium in soil can vary widely. In non-polluted areas, concentrations are usually below 1 mg/kg (Friberg *et al.*, 1971, 1974), whereas in polluted areas levels of up to 800 mg/kg have been detected (Friberg *et al.*, 1985; 1986b; WHO, 1992b). With increasing acidification of soils due to acid rain and the use of fertilizers (and sewage sludge), increased uptake of cadmium from soil may occur (UNEP, 1984; 1992; WHO, 1992b).

Plants may be contaminated with cadmium *via* two routes: (i) soil–plant transfer, due to absorption of mobile forms of cadmium by the roots: increased soil content of cadmium results in increased plant uptake of the metal; the long-term availability of cadmium to plants is uncertain; (ii) air–plant transfer, due to deposition of cadmium particles and to precipitation of soluble forms on the epigeal parts of plants (Impens *et al.*, 1989). Cadmium residues in plants are normally less than 1 mg/kg (Friberg *et al.*, 1986a); however, plants growing in soil contaminated with cadmium may contain significantly higher levels (UNEP, 1984, 1992; WHO, 1992b).

1.3.6 *Cigarette smoke*

Tobacco plants naturally accumulate relatively high concentrations of cadmium in the leaves. The cadmium content of cigarette tobacco is generally 1–2 μg per cigarette, although the concentrations differ among regions. A smoker who smokes 20 cigarettes per day has an estimated daily uptake of 2–4 μg and accumulates 0.5 mg cadmium in one year (Lewis *et al.*, 1972; UNEP, 1984; Friberg *et al.*, 1985; IARC, 1986a; UNEP, 1992; WHO, 1992b).

1.3.7 *Food*

Food is the main source of cadmium for non-occupationally exposed people, although uptake (gastrointestinal absorption) from food is generally much less efficient than from water or air, as cadmium binds to food constituents. Cadmium is present in most foods, and

an extremely wide range of concentrations in foodstuffs has been reported from different countries (Friberg *et al.*, 1986a,b; WHO, 1992b). While average dietary concentrations are usually below the provisional tolerable weekly intake of 7 μg/kg bw proposed by FAO/WHO (1989), they are exceeded in some population groups (UNEP, 1984, 1992).

Meat, eggs, fish and milk products generally contain little cadmium—less than 0.01 μg/g wet weight—whereas internal organs, especially liver and kidney, may contain much more: concentrations of up to 1 μg/g wet weight have been reported in animal organs. Even higher concentrations have been detected in oysters (up to 8 μg/g) and salmon flesh (3 μg/g) (Friberg *et al.*, 1974); internal organs of fish and shellfish may also contain high amounts of the metal (Banat *et al.*, 1972; WHO, 1992b).

In general, vegetable products contain more cadmium than animal products. Two important dietary staples, rice and wheat, accumulate high amounts of the metal, depending on the season (Nordberg & Nordberg, 1988). In unpolluted areas, concentrations of 0.01–0.1 μg/g have been reported in rice and wheat, whereas in Japan and some other Asian countries the cadmium content may be higher (Friberg *et al.*, 1985; Watanabe *et al.*, 1989; Rivai *et al.*, 1990). An analysis of the cadmium content of 207 samples of common rice and glutinous rice collected in various areas of Asia showed no difference; the geometric mean cadmium concentration was about 20 ng/g dry wt (range, 0.8–259.3) (Watanabe *et al.*, 1989).

The average daily intake of cadmium varies among countries, and large individual variations occur. In unpolluted areas, intake is estimated to be 10–60 μg/day; values tend to be lower in Europe and North America than in Japan. In areas of Japan that are considered to be unpolluted, average daily intakes are generally 15–50 μg, whereas in polluted areas values as high as 500 μg have been reported (Friberg *et al.*, 1974; Kowal *et al.*, 1979; Friberg *et al.*, 1985; Watanabe *et al.*, 1985; Louekari *et al.*, 1991; Watanabe *et al.*, 1992; WHO, 1992b).

1.3.8 *Animal tissues* (some of which may be used as food)

High levels of cadmium have been found particularly in seabirds and sea mammals; much of the cadmium occurs in the kidney and liver. Typical concentrations are in the range 0.1–2 mg/kg wet weight in liver and 1–10 mg/kg wet weight in kidney (Elinder, 1992; WHO, 1992b).

Long-lived terrestrial mammals, such as horses and moose, can also have remarkable burdens of cadmium in liver and kidney; concentrations of up to 200 mg/kg have been reported in kidney cortex samples of old horses (Elinder, 1992; WHO, 1992a). In small mammals living in polluted areas, cadmium also accumulates in the liver and kidney: concentrations ranged from 1.5 to 280 mg/kg dry weight in liver and from 7.4 to 193 mg/kg in kidney. In animals from unpolluted sites, concentrations in liver ranged from 0.5 to 25 mg/kg and those in kidney from 1.5 to 26 mg/kg (WHO, 1992a).

1.3.9 *Human tissues and secretions*

Cadmium accumulates in the body. The total body burden of non-occupationally exposed adult subjects has been estimated to range from 9.5 to 40 mg in the USA and Europe. The International Register of Potentially Toxic Chemicals (UNEP, 1984, 1992) considered that the body burden of a proportion of the population is already approaching the

critical value of 10–15 μg, which is the amount that must be retained daily to result in impaired kidney function after 50 years. Cadmium deposition increases with age and is greater in smokers then nonsmokers (Alessio *et al.*, 1983). Concentrations of 1–3 mg/kg wet weight have been detected in liver and 15–50 mg/kg in kidney cortex. Concentrations are usually higher in the Japanese; average concentrations in kidney cortex ranging from about 50 to 100 mg/kg were detected in people 50 years of age (Friberg *et al.*, 1985).

After long-term exposure to low levels, 40–80% of the retained cadmium (mainly bound to metallothionein) was found in liver and kidneys and about one-third in kidneys alone. Concentrations of 100–450 mg/kg wet weight were measured in kidney cortex of cadmium-exposed subjects who showed no renal changes or only slight changes in tubular function. The lungs of non-occupationally exposed subjects contained about 2% of the cadmium body burden (Alessio *et al.*, 1983; WHO, 1992b). In unselected autopsies in Germany, the mean concentrations of cadmium in lungs were found to be 1.48 ± 1.22 μg/g dry weight in the age group 20–45, 1.73 ± 1.42 μg/g in the age group 45–65 and 1.18 ± 1.27 μg/g for people aged > 65 (Kollmeier *et al.*, 1990). Placentas from nonsmokers contained 13.7 ± 6.4 ng/g cadmium, and those from smokers contained 18.1 ± 7.3 ng/g (Kuhnert *et al.*, 1982).

Concentrations of cadmium in urine and blood of subjects non-occupationally exposed to the metal have been reported in only a few studies, most of which were not designed for the definition of reference values but involved control groups for toxicological and epidemiological investigations (Alessio *et al.*, 1992). Mean urinary cadmium concentrations measured in several countries in Europe, Japan and the USA ranged from about 0.4 to 4 μg/L. Urinary cadmium concentrations are significantly higher in smokers than in nonsmokers; on a group basis, they increase with age in nonsmokers. Mean blood concentrations ranged from about 0.2 to 4 μg/L; they were significantly higher in smokers and were influenced by age (Kowal *et al.*, 1979; Bruaux *et al.*, 1983; Elinder *et al.*, 1983; Friberg *et al.*, 1985; Watanabe *et al.*, 1985; Abe *et al.*, 1986; Pocock *et al.*, 1988; Alessio *et al.*, 1990; Buchet *et al.*, 1990; Alessio *et al.*, 1992; Kawada *et al.*, 1992).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines, whether legally binding or not, established in different parts of the world are given in Table 8. Separate engineering control air limits for cadmium in selected industries in the USA are shown in Table 9. WHO (1980, 1987, 1988) estimated the hazards to human health of lifetime exposure to different levels of cadmium in air and concluded that the concentration of cadmium in respirable dust should be well below 20 μg/m^3, and short-term exposures to cadmium oxide fumes and respirable dust should not exceed 250 μg/m^3.

In Sweden, an 8-h time-weighted average concentration of 0.01 mg/m^3 became applicable for respirable dust of cadmium and cadmium compounds in new and renovated plants as of 1 July 1991 (UNEP, 1993).

The American Conference of Governmental Industrial Hygienists (1992) adopted a biological exposure index of 10 μg/g creatinine for cadmium in urine and 10 μg/L for cadmium in blood. They have also proposed a reduction in these values to 5 μg/g creatinine in urine and 5 μg/L in blood, in agreement with the health-based biological limits recommended by WHO (1980).

Table 8. Occupational exposure limits and guidelines for cadmium and cadmium compounds

Country or region	Year valid	Concentration (mg/m^3)	Substances affected	Interpretation[a]
Argentina	1991	0.05	Cadmium and cadmium salts (as Cd)	TWA, potential carcinogen
Australia	1990	0.05	Cadmium, cadmium compounds (as Cd), cadmium oxide, fumes	TWA, probable human carcinogen
Austria	1982	0.05	Cadmium dusts and salts (as Cd)	TWA
Belgium	1990	0.05	Cadmium, cadmium compounds (as Cd), cadmium oxide	TWA
		0.05	Cadmium oxide, fumes	Ceiling
Bulgaria	1984	0.1	Cadmium oxide, fumes (as Cd)	TWA
China	1979	0.1	Cadmium oxide, fumes (as Cd)	TWA
Denmark	1990	0.01	Cadmium, cadmium oxide, fumes	TWA
		0.01	Inorganic cadmium compounds (as Cd)	TWA, suspected carcinogen
Finland	1990	0.02	Cadmium, cadmium compounds (as Cd)	TWA, suspected of having carcinogenic potential
		0.01	Cadmium oxide, fumes	TWA, suspected of having carcinogenic potential
		0	Cadmium (respirable dust), cadmium chloride, inorganic cadmium compounds (as Cd), inorganic cadmium compounds (respirable dust) (as Cd)	Suspected of having carcinogenic potential
France	1990	0.05	Cadmium oxide	TWA
		0.05	Cadmium oxide, fumes	STEL
		0	Cadmium chloride	Suspected carcinogen
Germany	1992	0	Cadmium, cadmium compounds (as Cd), cadmium oxide, cadmium chloride, cadmium sulfate, cadmium sulfide	A2
Hungary	1983	0.05	Cadmium oxide, fumes (as Cd)	TWA
		0.1	Cadmium oxide, fumes (as Cd)	STEL (twice during one work shift)
Indonesia	1978	0.2	Cadmium dusts and salts (as Cd)	TWA
		0.2	Cadmium oxide, fumes (as Cd)	Ceiling
Italy	1978	0.05	Cadmium dusts and salts (as Cd)	TWA
		0.01	Cadmium oxide, fumes (as Cd)	TWA
Japan	1990	0.05	Cadmium, cadmium compounds (as Cd)	TWA

Table 8 (contd)

Country or region	Year valid	Concentration (mg/m^3)	Substances affected	Interpretation[a]
Mexico	1984	0.05	Cadmium dusts and salts (as Cd); cadmium oxide, fumes (as Cd); cadmium oxide, production (as Cd)	TWA
		0.2	Cadmium dusts and salts (as Cd); cadmium oxide, fumes (as Cd); cadmium oxide, production (as Cd)	STEL (15 min four times a day)
Netherlands	1986	0.02	Cadmium and cadmium compounds (as Cd)	TWA, suspected carcinogen
		0.05	Cadmium oxide, fumes (as Cd)	TWA
Poland	1984	0.1	Cadmium oxide, fumes (as Cd)	TWA
Romania	1975	0.2	Cadmium oxide, fumes (as Cd)	STEL
Sweden	1991	0.05	Cadmium (total dust), inorganic cadmium compounds (as Cd) (total dust)	TWA, suspected of having carcinogenic potential
		0.02	Cadmium (respirable dust), inorganic cadmium compounds (respirable dust)	TWA, suspected of having carcinogenic potential
Switzerland	1984	0.05	Cadmium dusts and salts (as Cd), cadmium choride	TWA
		0.05	Cadmium oxide, fumes (as Cd)	Ceiling
Taiwan	1981	0.1	Cadmium dusts and salts (as Cd)	TWA
United Kingdom[b]	1992	0.05	Cadmium and cadmium compounds (dusts and fumes) (as Cd) (except cadmium oxide fumes and cadmium sulfide pigments), cadmium oxide fumes (as Cd)	TWA, MEL
		0.05	Cadmium oxide fumes (as Cd)	STEL, MEL (10 min)
		0.04	Cadmium sulfide pigments (respirable dust) (as Cd)	TWA
USA				
OSHA	1992	0.005	Cadmium	TWA, PEL
		0.015–0.050	Cadmium	SECAL (see Table 9)
ACGIH[c]	1992	0.05	Cadmium dusts and salts (as Cd), cadmium oxide production	TWA, TLV
		0.05	Cadmium oxide fumes (as Cd)	Ceiling

Table 8 (contd)

Country or region	Year valid	Concentration (mg/m^3)	Substances affected	Interpretation[a]
Venezuela	1978	0.05	Cadmium dusts and salts (as Cd)	TWA
		0.15	Cadmium dusts and salts (as Cd), cadmium compounds (as Cd)	Ceiling
		0.05	Cadmium oxide, fumes (as Cd)	Ceiling

From Arbeidsinspectie (1986); Cook (1987); International Labour Office (1991); American Conference of Governmental Industrial Hygienists (ACGIH) (1992); Deutsche Forschungsgemeinschaft (1992); Health and Safety Executive (1992); US Occupational Safety and Health Administration (OSHA) (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. TWA, time-weighted average; STEL, short-term exposure limit; MEL, maximal exposure limit; PEL, permissible exposure limit; SECAL, separate engineering control air limit; TLV, threshold limit value; A2, compounds which in the Commission's opinion have proven so far to be unmistakably carcinogenic in animal experimentation only; namely under conditions which are comparable to those for possible exposure of a human being at the work place, or from which such comparability can be deduced.

[b]New maximal exposure limits have been proposed, to take effect from 1 January 1994: 0.04 mg/m^3 for cadmium sulfide and its pigments, and 0.025 mg/m^3 for cadmium and other cadmium compounds (Anon., 1992).

[c]A change has been proposed in the 'adopted' values: to 0.01 mg/m^3 for total dust or particulates of cadmium and cadmium compounds, and 0.002 mg/m^3 for the respirable fraction of dust (respirable particulate mass), considered to be suspected human carcinogens.

Table 9. Separate engineering control air limits (SECALs) for cadmium processes in selected US industries

Industry	Process	SECAL (mg/m^3)
Nickel–cadmium battery	Plate-making, plate preparation	0.050
	All other processes	0.015
Zinc and cadmium refining[a]	Cadmium refining, casting, melting, oxide production, sinter plant	0.050
Pigment manufacture	Calcining, crushing, milling, blending	0.050
	All other processes	0.015
Stabilizer manufacture[a]	Cadmium oxide charging, crushing, drying, blending	0.050
Lead smelting[a]	Sinter plant, blast furnace, baghouse, yard area	0.050
Plating[a]	Mechanical plating	0.015

From US Occupational Safety and Health Administration (1992)

[a]Processes used in these industries that are not specified in the table must achieve the permissible exposure limit by using engineering controls and changing work practices. Industries that are not listed must meet the permissible exposure limit of 0.005 mg/m^3 (see Table 8).

In Sweden, cadmium workers are required to undergo a medical examination twice a year. Workers who have blood cadmium concentrations exceeding 150 nmol/L (16.5 μg/L) are removed from exposure and are not allowed to return until the concentration is below 100 nmol (11 μg/L) (Arbetarskyddsstyrelsens, 1989).

The guideline for all forms of cadmium in drinking-water recommended by WHO (1984, 1992c) is 3 μg/L. The maximal level of cadmium in drinking-water and the permissible level in bottled water in the USA is 10 μg/L (US Environmental Protection Agency, 1991; US Food and Drug Administration, 1992).

The Joint FAO/WHO Expert Committee of Food Additives (WHO, 1989) proposed a provisional tolerable weekly intake for cadmium of 7 μg/kg body weight. The provisional guidelines set by the Japanese Ministry of Health and Welfare are 0.4 mg/kg in rice and up to 10 μg/L in drinking-water (Förstner, 1984).

Cadmium and cadmium compounds are not permitted in cosmetic products in the countries of the European Economic Community (Commission of the European Communities, 1990, 1991c). A Directive has been adopted aimed at restricting the manufacture and use of certain cadmium-bearing pigments, stabilizers and plating and the discharge of cadmium into the environment (Commission of the European Communities, 1983, 1991d,e; Shagarofsky-Tummers, 1992). In Sweden, cadmium is not allowed for use as a pigment, for surface coatings or as a stabilizer (Svensk Författningssamling, 1979, 1980).

The International Register of Potentially Toxic Chemicals of UNEP included cadmium together with lead and mercury in its listing of environmentally dangerous chemical substances and processes of global significance (UNEP, 1984, 1992).

2. Studies of Cancer in Humans

The occupations covered in the studies reviewed below involve recovery of cadmium from zinc refining, manufacture of cadmium oxide, alloys and pigment and production of nickel–cadmium batteries. The Working Group did not review studies of other occupations, such as electroplating, welding (see IARC, 1990b), painting (see IARC, 1989) and glass-making (see p. 347), in which exposure to cadmium occurs, but which involve lower or more sporadic exposures. The use of cadmium was noted to be increasing in the production of nickel–cadmium batteries (US Occupational Safety and Health Administration, 1992) but decreasing in other applications. In general, the maximal concentrations of cadmium in work-place air decreased by up to 100 times since the 1940s in the work sites studied. Given the long latency of cancer, the health effects noted among long-term workers may reflect former rather than current conditions of exposure.

The Working Group considered other occupational respiratory carcinogens, such as nickel (see IARC, 1990a) in nickel–cadmium battery plants and arsenic (see IARC, 1987c) in localized areas of metallurgical plants, that might introduce a spurious association between exposure to cadmium and lung cancer. Potential confounding by occupational exposures to other substances was not considered in the studies of prostatic cancer.

2.1 Descriptive studies

Shigematsu *et al.* (1982) assessed mortality in four pairs of populations in cadmium-polluted and unpolluted areas of four prefectures of Japan during 1948–77, when exposure to cadmium in the polluted areas occurred through ingestion of cadmium-contaminated rice. Average concentrations ranged from 0.2 to 0.7 ppm in the polluted area and from 0.02 to 0.1 ppm in the unpolluted areas. No difference was seen between the two areas in the rate of mortality from cancers at all sites or from cancers of the stomach or liver. The rate of mortality from prostatic cancer was significantly higher (standardized mortality ratio [SMR], 1.66) in the polluted than in the unpolluted area of one prefecture, as was the incidence of hyperplasia of the prostate. Figures for respiratory cancer were not reported.

Bako *et al.* (1982) studied age-adjusted incidence rates for prostatic cancer in various census divisions of Alberta, Canada, in relation to the occurrence of cadmium in the environment, i.e. in samples of flowing fresh water, municipal waste water, soil, and wheat and barley stems. Significantly high and low incidence rates were seen: the city with high incidence, 53.2 cases per 100 000 population, had consistently higher cadmium concentrations in the samples taken (0.006 ppm in waste water, 0.27 in soil, 0.004 in flowing water); and the city with the lowest incidence, 10.6 cases per 100 000 population, had consistently low concentrations (< 0.001, 0.19 and 0.001 ppm, respectively). Other environmental parameters also differed.

Campbell *et al.* (1990) reported analyses of a comprehensive cross-sectional survey of possible risk factors for primary liver cancer in 48 counties in China. County mortality rates were correlated positively with mean daily cadmium intake (0–90 μg/day) from foods of plant origin, as estimated by dietary surveys.

2.2 Cohort studies (see Tables 10 and 11, pp. 157 *et seq.*)

The relation between exposure to cadmium and cancers of the lung and prostate has been studied in six occupational cohorts in Europe and the USA, most of which covered overlapping populations, and in one in China. The cohorts are generally small, particularly when restricted to long-term, highly exposed workers with prolonged follow-up. Recent studies have expanded the number of subjects by including many short-term, minimally exposed or recently hired workers, so that the need for subanalyses by dose and latency is increased. In order to facilitate interpretation, the studies are grouped according to plant; the published data on cancer of the lung are summarized in Table 10 and those for prostatic cancer in Table 11.

2.2.1 *Nickel–cadmium battery manufacture, United Kingdom*

Workers from two nickel–cadmium battery plants in the United Kingdom, one of which operated from 1923 to 1947 and the other from 1937 to the present, were the subject of a series of studies. The plants were amalgamated in 1947. The concentrations of cadmium in cadmium oxide (hydroxide) dust in high-exposure jobs (plate-making and assembly shops) were 0.6–2.8 mg/m^3 [236 mg/m^3 in the negative active material department where cadmium oxide is prepared (Potts, 1965)] in 1949, $\leq$ 0.5 mg/m^3 between 1950 (when extensive local exhaust ventilation was installed) and 1967 (when a new plate-making department was built), < 0.2 mg/m^3 from 1968 to 1975 and < 0.05 mg cadmium/m^3 after 1975 (Sorahan & Waterhouse, 1983). [The Working Group noted that the process was probably similar to those in the Swedish study described below, where exposure to nickel hydroxide dust was reported to be higher than that to cadmium oxide.]

Potts (1965) identified three deaths from cancer of the prostate and one from lung cancer out of eight deaths among 74 men who had been exposed to cadmium oxide dust in the plant for at least 10 years before 1965. No referent rates were used to compute the expected number of fatal cancers. [The Working Group had no information on the completeness of ascertainment and whether, therefore, the 74 men were representative of the exposed population.]

Kipling and Waterhouse (1967) assembled a cohort of 248 men with at least one year of exposure to cadmium oxide at the same plants, including the 74 men reported by Potts (1965). [The Working Group had no published information on exposure levels in these jobs; however, in subsequent studies of the same plants, these job titles were classified as involving high exposure.] They compared cancer incidence rates through 1966 with regional rates from the local cancer registry. One new case of prostatic cancer was detected. This case, combined with the three deaths reported by Potts (1965), exceeded the 0.58 expected (standardized incidence ratio [SIR], 6.90 [95% confidence interval (CI), 1.86–17.66]). The incidence of lung cancer was not significantly elevated (5 observed, 4.4 expected; SIR, 1.14 [95% CI, 0.37–2.65]). [The Working Group noted that there was no analysis of incidence by latency or duration of exposure.]

Sorahan and Waterhouse (1983) enlarged the cohort to include 3025 people (2559 men) first employed at the plants between 1923 and 1975 for a minimum of one month. An initial study of mortality from prostatic cancer reported eight deaths between January 1946 and

January 1981, whereas 6.6 were expected on the basis of mortality rates in the general population of England and Wales (relative risk [RR], 1.21 [95% CI, 0.52–2.39]). In a later study, Sorahan and Waterhouse (1985) identified 15 incident cases of prostatic cancer entered into the Birmingham Regional Cancer Registry between 1950 and 1980; comparison with the 11.0 cases expected from regional rates gave an RR of 1.36 [95% CI, 0.76–2.25]. Eight of the cases occurred in a subgroup of 458 workers who had been employed for at least one year in jobs entailing high exposure to cadmium oxide dust (8 observed, 1.99 expected; RR, 4.02 [95% CI, 1.73–7.92]). Four of the eight cases were additional to those reported by Kipling and Waterhouse (1967); this number was greater than that expected but not significant (4 observed, 1.78 expected; RR, 2.25 [95% CI, 0.60–5.75]).

Sorahan (1987) examined lung cancer mortality between 1946 and 1984 in the same workforce of 3025 workers. Overall, 110 deaths from lung cancer were observed, while 84.5 were expected (RR, 1.30 [95% CI, 1.07–1.57]). The RRs for lung cancer in high-exposure jobs were slightly greater (1.3–1.5) than that for workers with no or minimal exposure but did not increase with years of employment in high-exposure jobs (Table 10). [The Working Group noted that the analysis did not incorporate exposure measurements, nor was the intensity of exposure considered simultaneously with duration. Tobacco smoking was controlled for indirectly in internal dose–response comparisons. Exposure to nickel hydroxide could not be controlled for, since few workers were exposed to cadmium in the absence of nickel.]

2.2.2 *Nickel–cadmium battery manufacture, Sweden*

Concentrations of cadmium in air containing cadmium oxide dust at a single nickel–cadmium battery plant in Sweden, where a series of studies was done, averaged about 1 mg/m^3 before 1947, 0.3 mg/m^3 between 1947 and 1962, 0.05 mg/m^3 between 1962 and 1974 and 0.02 mg/m^3 after 1975 (Elinder *et al.*, 1985). Exposures to nickel hydroxide dust were reported to have been 2–10 times higher than those to cadmium oxide, although no measurements were reported (Kjellström *et al.*, 1977).

Kjellström *et al.* (1979) studied 228 men who had been employed at the plant for five or more years between 1940 and 1959, who were followed up from 1959 to 1975. Incident cancers among the workers were identified from the Swedish National Cancer Registry, which started in 1959, and were compared with national rates of incidence. The numbers of new cases were as follows: lung, 2 observed, 1.35 expected (RR, 1.48 [95% CI, 0.17–5.35]), prostate, 2 observed, 1.2 expected (RR, 1.67 [95% CI, 0.19–6.02]) and nasopharynx, 2 observed, 0.20 expected (RR, 10.0 [95% CI, 1.23–36.1]). [The Working Group noted that cancers of the nasal cavity and sinuses and not nasopharyngeal cancers are associated with exposure to nickel, and that only cases of cancers that occurred after 1959 were included.]

Andersson *et al.* (1984) and Elinder *et al.* (1985) extended the cohort to include 522 male workers who had been exposed to cadmium for at least one year between 1940 and 1980, and who were still alive in 1951; follow-up was from 1951 to 1983. In that period, there were eight deaths from lung cancer (6.01 expected; RR, 1.33 [95% CI, 0.57–2.62]), four from prostatic cancer (3.70 expected; RR, 1.08 [95% CI, 0.29–2.77]) and one from cancer of the nasopharynx (expected near 0). Seven of the eight cases of lung cancer occurred among workers with five or more years of exposure and 20 years' latency (7 observed, 4.0 expected;

RR, 1.75 [95% CI, 0.70–3.61]). [The Working Group noted that the small number of cases precluded a dose–response analysis.]

2.2.3 *Copper–cadmium alloy plants, United Kingdom*

Holden (1980a,b) described cadmium exposures at two plants, in rural and urban locations in the United Kingdom, where copper–cadmium alloy was produced from 1922 to 1966 and from 1925 to the present, respectively. The numbers of workers in each plant were not given; a total of 347 workers at the two plants had been employed for at least one year. Exposure to cadmium fume at the urban plant exceeded 1 mg/m^3 before 1953, with a peak of 3.6 mg/m^3, was < 0.15 mg/m^3 from 1953 to 1957 and was < 0.05 mg/m^3 thereafter. Although air concentrations at the rural plant were not described, proteinuria was common in workers at both plants before 1950, indicating high exposures to cadmium (Holden, 1980b).

Mortality from respiratory cancer, followed from 1921 to 1978, was higher among urban cadmium workers [number not given] than in the general population of England and Wales (8 observed, 4.50 expected; RR, 1.78 [95% CI, 0.77–3.50]) but was significantly lower among the rural workers [number not given] (2 observed, 7.85 expected; RR, 0.25 [95% CI, 0.03–0.92]). One death from prostatic cancer was observed in the combined workforce (1.58 expected; RR, 0.63 [95% CI, 0.01–3.52]). In the same study, 624 'vicinity' workers from the urban plant, who produced arsenical copper and other alloys in the same workshop, were followed up. Their mean cadmium exposures were low (≤ 0.07 mg/m^3; King, 1955), but their arsenic exposures were high [figures not given]. These workers had significantly higher mortality rates from both respiratory (36 observed, 26.08 expected; RR, 1.38 [95% CI, 0.97–1.91]) and prostatic cancer (8 observed, 3.0 expected; RR, 2.67 [95% CI, 1.15–5.26]) than the general population of England and Wales (Holden, 1980a,b). [The Working Group noted that no regional comparison was made, and it is unclear whether the general population is comparable with the rural population with respect to smoking. It is unlikely, however, that urban–rural differences would completely explain the low risk for lung cancer in the rural workers.]

Kazantzis *et al.* (1989) reported briefly the results of a nested case–control study of cancer of the lung in the same copper–cadmium alloy cohort described above. Long-term employees were reported also to have been exposed to arsenic in the production of arsenical copper. An analysis in which 50 lung cancer deaths were compared with 158 controls matched on age and year at hire showed a stronger association between lung cancer and exposure to arsenic (odds ratio, 2.15; 90% CI, 1.22–3.79) than with exposure to cadmium (odds ratio, 1.27; 90% CI, 0.61–2.51). [The Working Group found the report difficult to interpret with respect to cadmium, because it lacks information on exposure classification and no statement is made about control for urban *versus* rural location or simultaneous control of exposure to cadmium and arsenic in the analysis.]

2.2.4 *Copper–cadmium alloy plants, Sweden*

Kjellström *et al.* (1979) investigated the incidence of prostatic cancer among 94 workers employed for five or more years between 1940 and 1978 at a cadmium–copper alloy plant in

Sweden. Production of the alloy was begun in the 1930s. The levels of cadmium oxide fume in air were 0.1–0.4 mg/m^3 in the 1960s and about 0.05 mg/m^3 in the 1970s. Mortality from prostatic cancer between 1940 and 1975 was above that expected from national rates (4 observed, 2.69 expected; RR, 1.49 [95% CI, 0.40–3.81]). A reference group of 328 workers not exposed to cadmium had lower mortality from prostatic cancer than expected (4 observed, 6.42 expected; RR, 0.62 [95% CI, 0.17–1.60]).

2.2.5 *Cadmium recovery plant in the USA*

Several mortality studies have been conducted at a US plant where cadmium oxide, sulfide and metal were made from cadmium oxide dust recovered from the waste of nonferrous smelters since 1926 (especially zinc smelters). Estimated average air concentrations of cadmium in dust and fumes in high-exposure departments were 1.16 mg/m^3 before 1950, 0.50 mg/m^3 in 1950–59, 0.34 mg/m^3 in 1960–64 and 0.26 mg/m^3 in 1965–76 (Smith *et al.*, 1980). As extensive measurements had been made throughout the plant since 1943, mortality could be analysed by both intensity and duration of exposure to cadmium. Other metals, such as lead, arsenic, indium and thallium, had been produced intermittently in localized areas of the plant, and the facility had been an arsenic smelter in 1918–25 and a lead smelter from 1886 to 1918. Some contamination of incoming feed material with arsenic persisted after 1926: The proportion of arsenic in feedstock was $\geq$ 50% before 1926, about 7% in 1926–27, 1.5–5.6% in 1928–33, 1.9–3.7% in 1934–40 and 1.0–2.0% after 1940 (Thun *et al.*, 1985, 1986). In 1973, arsenic was present at 0.3–1.1 µg/m^3 in the pre-melt department and 1.4 µg/m^3 in the retort department; the respective values for cadmium were 74.8–90.3 and 1105 µg/m^3. Bulk samples of preprocessed ore contained 70% cadmium, 6.0% zinc, 4.3% lead and 0.3% arsenic; after initial roasting, bulk samples contained 42.2% cadmium, 3.53% zinc, no lead and 0.02% arsenic. Additional refining steps reduced the levels of impurities further, so that exposure of workers to trace metals other than cadmium was considered to be insignificant (Lemen *et al.*, 1976).

Lemen *et al.* (1976) studied 292 white male hourly workers exposed for two or more years between 1940 and 1969 and followed from 1940 through to 1973. There were four deaths from cancer of the prostate (1.15 expected; RR, 3.48; [95% CI, 0.94–8.91]). Mortality from this cancer was significantly increased in workers with $\geq$ 20 years latency (4 observed, 0.88 expected [RR, 4.55; 95% CI, 1.22–11.64]). The number of deaths from respiratory cancer also exceeded that expected (12 observed, 5.11 expected; RR, 2.35 [95% CI, 1.21–4.10]). [The Working Group noted that the association with lung cancer was not examined in relation to cumulative exposure to cadmium or exposure to other work-related exposures, including arsenic.]

Thun *et al.* (1985) expanded the cohort to a total of 602 white men who had been employed in cadmium production between 1940 and 1969 for at least six months. Estimates of exposure based on air measurements over time were combined with work exposure categories to estimate cumulative exposures to cadmium. No additional death from prostatic cancer had occurred during the extended follow-up from 1974 to 1978. As the cohort was limited to cadmium production workers, one of the four prostatic cancer deaths observed by Lemen *et al.* (1976) was excluded from the analysis. The remaining three deaths from prostatic cancer occurred among workers with two or more years of employment and 20 or

more years of latency (3 observed, 1.41 expected; RR, 2.13; 95% CI, 0.44–6.22). [The Working Group noted that increased screening for prostatic cancer could result in early detection and therefore greater survival, thus biasing the results of mortality studies of this cancer.]

Lung cancer mortality was examined first through 1978 (Thun *et al.*, 1985) and later through 1984 (Stayner *et al.*, 1992). All analyses of lung cancer mortality in relation to exposure to cadmium were restricted to 576 men who were first employed after 1 January 1926, when the plant ceased arsenic smelting, although (as noted above) some arsenic remained in the material being processed, decreasing with time. Death rates from lung cancer in the overall cohort through 1984 were slightly greater than those expected from US white male rates (24 observed, 16.07 expected; RR, 1.49 [95% CI, 0.96–2.22]), and the RR increased with estimated cumulative exposure to cadmium: 0.34, 1.63, 2.17 and 2.72 in workers with cumulative exposures of $\leq$ 584, 585–1460, 1461–2920 and > 2920 mg/m^3-days (Table 10). The mortality rates for lung cancer among the workers were compared with Colorado State rates for white men for the follow-up period through 1978. The RRs were higher for this follow-up period when compared with local rather than national rates: The RR in the most highly exposed group was 3.87 when compared to State rates (7 observed, 1.81 expected [95% CI, 1.55–7.97]) and 2.80 when national rates were used for comparison (Thun *et al.*, 1986).

Several authors have examined whether exposure to cigarette smoking or arsenic could account for the excess mortality from lung cancer at the US plant. Nearly half of the cadmium workers were men of Mexican–American descent, who in the 1980s smoked fewer cigarettes per day on average and had less than half the incidence of lung cancer of other US white males (US National Cancer Institute, 1986). Lower rates from lung cancer among Mexican–Americans as compared with other whites were also reported in earlier years in Denver, where the plant is located: The RR was about 0.3 in 1969–71 and 0.7 in 1979–81, when men with Latino surnames were compared with other whites (Savitz, 1986). Stayner *et al.* (1992) showed that the excess mortality from lung cancer at the US plant is confined to non-Mexican–American cadmium workers when compared to US white males (21 observed, 9.95 expected; RR, 2.11 [95% CI, 1.31–3.23]), and no excess was seen in Mexican–American workers (3 observed, 6.12 expected; RR, 0.49 [95% CI, 0.10–1.43]). Comparisons with the US population, however, result in overestimates of the expected number of deaths among Mexican–Americans and underestimates of the effect of occupation. The tobacco smoking habits of the non-Mexican–American workers were similar to those of all US white males, yet 11 excess deaths from lung cancer were observed (RR, 2.11; $p < 0.01$) (US Occupational Safety and Health Administration, 1992). [The Working Group noted that confounding by cigarette smoking is unlikely to explain a dose–response relationship and strength of association of this magnitude in an occupational cohort study (Axelson, 1978; Siemiatycki *et al.*, 1988).]

A second extraneous factor that could contribute to mortality from lung cancer at the US plant is arsenic. Three studies were designed to isolate the effect of cadmium from that of arsenic in the cohort by using year of hire before or after 1940 as a proxy for exposure to arsenic. These analyses are based on identical exposure data and overlapping study populations.

Lamm *et al.* (1992) performed a nested case–control analysis in which 25 cases of fatal lung cancer diagnosed through 1982 were each matched with three controls on year of hire; no association was found between exposure to cadmium and risk for lung cancer. The mean cumulative exposure of the cases (9.24 mg/m^3-year) was not different from that of the controls (mean, 9.29 mg/m^3-year). [The Working Group found the results difficult to interpret, in that exposure data identical to those for the full cohort were used and therefore the same results as in the full cohort should have been obtained. One possible explanation is that matching was done on year of hire, but no matched analysis was done, thereby potentially biasing the results.]

In further analyses, Stayner *et al.* (1992) categorized the 576 cadmium workers employed after January 1926 into pre-1940 and post-1940 and included this variable in Poisson and proportional hazards analyses of lung cancer rates. Dose–response relationships between exposure to cadmium remained significant in nearly all multivariate analyses after controlling for age, Mexican–American ethnicity (a proxy for lighter tobacco use) and period of hire.

As noted by Doll (1992), part of the explanation for the differences between the results of Lamm *et al.* (1992) and Stayner *et al.* (1992) could be that the two studies had only 21 cases in common. Lamm's series also included four cases hired before 1926, which were excluded by Stayner *et al.* Three cases included by Stayner *et al.* died of lung cancer between 1982 and 1984 and were therefore not reported by Lamm *et al.* [The Working Group noted that the methodological differences between the studies of Lamm *et al.* and Stayner *et al.* may account for the contradictory results reported.]

In a subsequent analysis, Stayner *et al.* (1993) conducted a nested case–control analysis using approximately 50 controls per case. The odds ratio increased with increasing cumulative exposure to cadmium, as in the full cohort. They also presented an odds ratio analysis of workers hired after 1940, when arsenic exposures were low. For non-Mexican–Americans, the odds ratio was 0.32 [95% CI, 0.0–1.78] at < 584 mg/m^3-days, 2.81 [1.02–6.10] at 585–1460 mg/m^3-days and 4.70 [1.51–10.97] at 1461–2920 mg/m^3-days. No lung cancer death was observed in the highest exposure category (> 2920 mg/m^3-days), but only 0.6 were expected. [The Working Group noted that the dose–response pattern was stronger in workers hired after 1940, indicating that the result was not likely to be due to exposure to arsenic.]

Thun *et al.* (1986) addressed the question of the extent to which exposure to arsenic could be held responsible for the excess of lung cancer observed in the cohort. They estimated average cumulative exposure to arsenic in relation to a potency estimate for exposure to arsenic and lung cancer used by the US Occupational Safety and Health Administration and concluded that 0.77 lung cancer deaths could be attributed to arsenic. In a more detailed analysis, the US Occupational Safety and Health Administration (1992) estimated that exposure to arsenic would have resulted in 0.52–0.97 lung cancer deaths in the cohort.

2.2.6 *Cadmium processing plants in the United Kingdom*

Armstrong and Kazantzis (1983) and Kazantzis *et al.* (1988) studied mortality among workers at 17 plants in the United Kingdom where cadmium is produced or used, including

primary production, copper–cadmium alloy production, silver–cadmium alloy production, pigments and oxide production and stabilizer production. The cohort comprised 6958 men born before 1940 and employed for more than one year on or near a cadmium process between 1942 and 1970. The plants at which nickel–cadmium batteries and copper–cadmium alloys were produced and which were described by Sorahan (1987) and Holden (1980b) were excluded. Jobs were assessed for each relevant year as involving high, medium or low exposure to cadmium on the basis of discussions with hygienists and others with knowledge of past working procedures, taking into account available results of biological or environmental monitoring. The years at risk of the study population were divided on the basis of these categories and recorded job histories into three groups; 'ever high' (minimum one year), 'ever medium' (minimum one year) and 'always low'. A total of 198 workers (3%; Kazantzis *et al.*, 1992) were classified as having had 'ever high' exposure, 17% were considered to have had 'ever medium' exposure, and the exposures of 80% were classified as 'always low' (Armstrong & Kazantzis, 1983). Kazantzis *et al.* (1992) stated that in these epidemiological studies consideration should be given to concomitant exposure to other potential carcinogens, in particular to arsenic, but also to beryllium (see p. 41), nickel (see IARC, 1990a), chromium (see IARC, 1990c) and emissions from a variety of heated mineral oils (see IARC, 1987d) in the various plants.

Kazantzis *et al.* (1988) described mortality from 1943 to 1984 in this cohort, and Kazantzis and Blanks (1992) and Kazantzis *et al.* (1992) extended follow-up through 1989 for 6910 workers. No increased risk for death from prostatic cancer was observed in the overall cohort (37 observed, 49.5 expected; RR, 0.75; 95% CI, 0.53–1.03). One death from prostatic cancer was seen in the 'ever high' exposure group (1.0 expected; RR, 0.97), but none was observed in the 'ever medium' group (6.2 expected; RR, 0; 95% CI, 0–0.59). Mortality from lung cancer was significantly increased in the overall cohort (339 observed, 304.1 expected; RR, 1.12; 95% CI, 1.00–1.24), with some evidence of a trend across exposure categories; these do not, however, attain significance (low: 270 observed, 249.9 expected; RR, 1.08; 95% CI, 0.96–1.22; medium: 55 observed, 45.6 expected; RR, 1.21; 95% CI, 0.91–1.57; high: 14 observed, 8.6 expected; RR, 1.62; 95% CI, 0.89–2.73). With regard to duration of exposure, mortality from lung cancer was significantly raised for men employed for 20–29 years in the cohort as a whole (65 observed, 49.6 expected; RR, 1.31; 95% CI, 1.01–1.67) and in the low-exposure category (54 observed, 38.4 expected; RR, 1.41; 95% CI, 1.06–1.84). In the 'ever high' exposure category, mortality from lung cancer was significantly increased among men first employed between 1930 and 1939 (4 observed, 1.0 expected; RR, 3.81; 95% CI, 1.03–9.76). There is suggestive evidence of a relationship with both intensity of exposure and duration of employment for workers employed before 1940, but no such pattern was seen for workers who started work after 1950. A significantly increased risk was observed for stomach cancer in the cohort as a whole (106 observed, 85.3 expected; RR, 1.24; 95% CI, 1.02–1.50), but this was not related to intensity of exposure, with 91 of the deaths occurring in the low-exposure group (71.4 expected; RR, 1.28; 95% CI 1.03–1.57). As in the earlier studies of this cohort, an increased risk significantly related to intensity of exposure was observed only for bronchitis.

Ades and Kazantzis (1988) reported separately on the experience of 4393 men who had been employed for at least one year at a lead–zinc smelter that comprised 64% of the entire

United Kingdom cadmium cohort and at which no exposure was classified as 'ever high'. There was excess mortality from lung cancer overall when compared with regional rates (182 observed, 146.2 expected; RR, 1.25; 95% CI, 1.07–1.44) and when updated by Kazantzis *et al.* (1992): 237 observed, 194.3 expected; RR, 1.22, 95% CI, 1.02–1.39. A significant trend in SMR was seen with increasing duration of employment. A nested case–control analysis and matched logistic regression were used to compare 174 fatal cases of lung cancer with 2717 controls matched to the cases on year of birth, date of starting work (within three years) and length of follow-up (at least 10 years). The odds ratio for lung cancer increased by 1.23 fold per mg/m^3-years of exposure to cadmium, but the trend was not significant. The trend in RR was significant for exposure to arsenic and lead. Only 21 (12%) cases had ever worked in the two departments (sinter and cadmium plant) where exposures to cadmium generally exceeded 0.010 mg/m^3.

2.2.7 *Smelter in China*

Cancer mortality among male workers employed for at least one year in a smelter in China was followed from 1972 to 1985 and compared with rates for the city in which the smelter was located (Ding *et al.*, 1987). When the plant was divided into five areas, industrial hygiene sampling indicated that exposures to cadmium were highest in the cadmium shop and the sintering shop, with mean air concentrations of 0.186 and 0.014 mg/m^3, respectively. The levels in the cadmium shop were reported to have been much higher prior to 1980 (0.535 mg/m^3). Exposure to arsenic was also reported to have occurred in the sintering area (0.196 mg/m^3 As_2O_3). One case of lung cancer (0.15 expected, SMR, 6.65) and two of liver cancer (0.11 expected, SMR, 17.9) were observed among cadmium shop workers. Four lung cancers (0.24 expected, SMR, 16.8; $p < 0.05$), one stomach cancer (0.31, SMR, 3.18) and three liver cancers (0.18 expected, SMR, 17.0) were observed among sintering shop workers. The men who died of cancer were reported to have had 10–30 years of exposure. Mortality from lung cancer was also increased in the other three areas. The authors stated that there was no obvious association with smoking. [The Working Group noted that the numbers of workers employed were not given.]

2.3 Case–control studies

Abd Elghany *et al.* (1990) conducted a population-based case–control study of exposure to cadmium based on 358 cases of prostatic cancer newly diagnosed in 1984–85 and 679 controls in four urban Utah (USA) counties. Analyses were also conducted for the subgroup of cases classified as aggressive tumours, in order to differentiate more clearly the cases from the controls (which may have included some latent prostatic tumours). In general, there was little evidence of an increased risk for prostatic cancer associated with occupations with potential exposure to cadmium (odds ratio, 0.9; 95% CI, 0.7–1.2), with cigarette smoking (odds ratio, 1.1; 95% CI, 0.8–1.4) or with diet (odds ratio, 1.4; 95% CI, 1.0–2.1). A composite measure of potentially high exposure to cadmium from any source was not associated with prostatic cancer in general (odds ratio, 1.0; 95% CI, 0.7–1.3) but was associated with aggressive tumours (odds ratio, 1.7; 95% CI, 1.0–3.1).

A hypothesis-generating case–control study of 20 cancer sites was conducted in the Montréal (Canada) metropolitan area (Siemiatycki, 1991) and is described in detail in the

Table 10. Cohort studies of lung cancer in workers exposed to cadmium

Type of plant, country (reference)	Population (duration of exposure)	Lung cancers (obs/exp)	Exposure level	Cadmium levels: Years	Cadmium levels: Estimated levels (mg/m³)			Relative risk (95% CI[a])	Comment
Nickel–cadmium battery (cadmium oxide)									
United Kingdom									
Potts (1965)	74 men (≥ 10 years)	1/NR	Overall					Cannot be calculated	Mortality through 1965 No referent group
Kipling & Waterhouse (1967)	248 men (≥ 1 year)	5/4.40	Overall	1949	0.6–2.8		(Sorahan & Waterhouse, 1983)	1.14 [0.37–2.65]	Incidence through 1966 at same plant as Potts (1965)
Sorahan (1987)	3025 men and women (≥ 1 month)	110/84.5	Overall	1950–67	< 0.5		(Sorahan & Waterhouse (1983)	1.30 [1.07–1.57]	Mortality 1946–84
			None[b]	1968–75	< 0.2			1.0	Dose–response based on years employed in high-exposure jobs. Trend not significant
			< 2 years	> 1975	< 0.05			1.4	
			2–					1.3	
			5–					1.3	
			≥ 15					1.5	
Sweden									
Kjellström *et al.* (1979)	228 men (≥ 5 years)	2/1.35	Overall	< 1947	1		(Elinder *et al.* 1985)	1.48 (0.17–5.35)	Incidence 1959–75
Elinder *et al.* (1985)	522 men (> 1 year)	8/6.01	Overall	1947–62	0.3		(Elinder *et al.*, 1985)	1.33 [0.57–2.62]	Mortality 1940–80 at same plant
			> 5 years and ≥ 20 years latency	1962–74	0.05			1.75 [0.70–3.61]	
				> 1975	0.02				
Copper–cadmium alloy									
United Kingdom									
Holden (1980a)	Urban ≥ 1 year	8/4.50	Overall	< 1953	1			1.78 [0.77–3.50]	Mortality, number of workers not stated
	Rural ≥ 1 year	2/7.85	Overall	1953–57	< 0.15			0.26 [0.03–0.92]	Expected deaths based on national rates
	624 vicinity ≥ 1 year	36/26.08	Overall	> 1957	< 0.05			1.38 [0.97–1.91]	Vicinity workers also exposed to arsenic
Cadmium recovery									
USA					(personal)	(ambient)			
Lemen *et al.* (1976)	292 men (≥ 2 years)	12/5.11		< 1950	1.16	1–45	(Smith *et al.*, 1980)	2.35 [1.21–4.10]	Mortality 1940–73
				1950–59	0.50	0.1–20			
Stayner *et al.* (1992)	579 men (≥ 6 months)	24/16.07	Overall	1960–64	0.34	0.4–0.5		1.49 (0.95–2.21)	Mortality 1940–84
			≤ 584[c]	1965–76	0.26	0.05–0.6		0.34	Excludes workers hired before 1 January 1926
			585–1460					1.63	Test for trend significant
			1461–2920					2.17	
			> 2920					2.72	

Table 10 (contd)

Type of plant, country (reference)	Population (duration of exposure)	Lung cancers (obs/exp)	Exposure level	Cadmium levels		Relative risk (95% CI[a])	Comment
				Years	Estimated levels (mg/m^3)		
Cadmium recovery (contd)						Odds ratio	
						Non-Mexican-American (no.)	Mexican-American (no.)
USA (contd) Stayner *et al.* (1993)	Subgroup of cohort of Stayner *et al.* (1992) hired after 1940		< 584			0.32 (1)	0.42 (1)
			584–1460			2.81 (6)	0 (0 exp.)
			1461–2920			4.70 (5)	0.82 (1)
			> 2920			0 (0.6 exp.)	2.46 (2)
Cadmium processing							
United Kingdom Kazantzis *et al.* (1992); Kazantzis & Blanks (1992)	6910 men > 1 year	339/304.1	Overall			1.12 (1.00–1.24)	Mortality 1943–89; 17 plants; 3% of workers had ever high exposure.
		270	Always low			1.08 (0.96–1.22)	
		55	Ever medium			1.21 (0.91–1.57)	
		14	Ever high			1.62 (0.89–2.73)	

NR, not reported
[a]Approximate 95% confidence intervals calculated by the Working Group are given in square brackets.
[b]Referent group includes jobs with no or 'minimal' exposure to cadmium.
[c]Units are mg/m^3-days

Table 11. Cohort studies of prostatic cancer in cadmium workers

Type of plant, country (reference)	Population (duration of exposure)	Prostatic cancers (obs/exp)	Exposure level	Relative risk (95% CI[a])	Comment
Nickel–cadmium battery (cadmium oxide)					
United Kingdom					
Potts (1965)	74 men (≥10 years)	3/NR	Overall	Cannot be calculated	Mortality through 1965 No referent group
Kipling & Waterhouse (1967)	248 men (≥1 year)	4/0.58	Overall	6.90 [1.86–17.66]	Incidence through 1966 includes three deaths from Potts (1965).
Sorahan & Waterhouse (1983)	2559 men (≥1 month)	8/6.6	Overall	1.21 [0.52–2.39]	Mortality 1946–80
Sorahan & Waterhouse (1985)	2559 men (≥1 month)	15/11.02	Overall > 1 year and high	1.36 [0.76–2.25] 4.02 [1.73–7.92]	Incidence 1950–80 including 4 cases from Kipling & Waterhouse (1967)
Sweden					
Kjellström *et al.* (1979)	228 men (≥5 years)	2/1.2	Overall	1.67 [0.19–6.02]	Incidence 1959–75
Elinder *et al.* (1985)	522 men (> 1 year)	4/3.70	Overall > 5 years and ≥ 20 years' latency	1.08 [0.29–2.77] 1.48 [0.40–3.79]	Mortality 1951–83
Copper–cadmium alloy					
United Kingdom					
Holden (1980a)	347 male cadmium workers (≥1 year)	1/1.58	Exposed	0.63 [0.01–3.52]	Mortality
	624 vicinity workers (≥1 year)	8/3.0	Less exposed	2.67 [1.15–5.26]	

Table 11 (contd)

Type of plant, country (reference)	Population (duration of exposure)	Lung cancers (obs/exp)	Exposure level	Relative risk (95% CI[a])	Comment
Copper–cadmium alloy (contd)					
Sweden					
Kjellström *et al.* (1979)	94 men (≥ 5 years)	4/2.69	Exposed	1.49 [0.40–3.81]	Mortality 1940–75. Data described as preliminary
	328 controls	4/6.42	Unexposed	0.62 [0.17–1.60]	
Cadmium recovery					
USA					
Lemen *et al.* (1976)	292 men (≥ 2 years)	4/1.15	Overall	3.48 [0.94–8.91]	Mortality 1940–73
			≥ 20 years' latency	[4.55 (1.22–11.64)]	
Thun *et al.* (1985)	602 men (≥ 6 months)	3/1.41	≥ 2 years' employment and ≥ 20 years' latency	2.13 (0.44–6.22)	Mortality 1940–78
Cadmium processing					
United Kingdom					
Kazantzis *et al.* (1992); Kazantzis & Blanks (1992)	6910 men (> 1 year)	37/49.3	Overall	0.75 (0.53–1.03)	Mortality 1943–89 Regional adjustment
		36	Always low	0.85 (0.60–1.18)	
		0	Ever medium	0 (0.0–0.59)	
		1	Ever high	0.97 (0.01–5.40)	

NR, not reported
[a]Approximate 95% confidence intervals calculated by the Working Group are given in square brackets.

monograph on exposures in the glass manufacturing industry (p. 347). The prevalence of exposure to cadmium compounds was 1%. Bladder was the only cancer site to be associated with exposure to cadmium compounds (six exposed cases; odds ratio, 1.6; 90% CI, 0.7–3.8). When the analysis was restricted to substantial exposure, only four cases of bladder cancer had been exposed (odds ratio, 4.9; 90% CI, 1.2–19.6). No association was found with cancers of the lung or prostate.

3. Studies of Cancer in Experimental Animals

The carcinogenic and toxicological effects of cadmium have been reviewed (Oberdörster, 1986; Peters *et al.*, 1986; Kazantzis, 1987; Oberdörster, 1989; Waalkes & Oberdörster, 1990; Heinrich, 1992; Nordberg *et al.*, 1992; Waalkes *et al.*, 1992a).

3.1 Oral administration

3.1.1 *Mouse*

A group of 48 male and 39 female weanling Swiss mice (Charles River strain) received 5 ppm [5 mg/L] cadmium as **cadmium acetate** in the drinking-water for life. A group of 44 male and 60 female control mice were given 'metal-free' drinking-water. Body weight was generally similar in treated and control animals. Cadmium treatment did not result in an increased incidence of any type of tumour, and the incidence of lung tumours in treated males was reduced compared to controls (0/48 *versus* 8/44; $p < 0.01$, χ^2 test); no such effect was observed in females (5/39 *vs* 9/60) (Schroeder *et al.*, 1964). [The Working Group considered that the single exposure level used was too low for an evaluation of carcinogenicity.]

Groups of 50 eight-week-old male specified pathogen-free (SPF) Swiss mice were administered 0.44, 0.88 or 1.75 mg/kg bw cadmium as **cadmium sulfate** (3 $CdSO_4.8H_2O$) in distilled-water by gavage once a week for 18 months, at which time the experiment was terminated. A control group of 150 male mice received distilled-water alone. No difference in survival or weight gain was observed between cadmium-treated mice and controls. Among the mice surviving after 18 months of treatment, groups of 20 animals were selected at random from the high-dose group and from the control group for histological analysis of selected tissues, including urogenital tract, stomach, lung, liver and kidney, while only macroscopically abnormal tissues were examined from other animals. Tumour incidence was no different in treated and control animals. Special attention was paid to the prostate, but no neoplastic or preneoplastic lesion was observed in this organ (Levy *et al.*, 1975). [The Working Group noted the low dose levels used and the limited histopathological examination in terms of numbers of animals and tissues.]

3.1.2 *Rat*

Groups of 69 male and 58 female weanling Long–Evans rats received 0 or 5 ppm [5 mg/L] cadmium as **cadmium acetate** in the drinking-water until death. Body weights and survival did not differ significantly among treated and control groups; about 50% of test and

control animals survived more than 24 months. Histopathology was performed on gross lesions. Tumour incidences in various organs in the 48 treated male and 36 treated female rats examined were similar to those in the 35 male and 35 female controls examined (Schroeder *et al.*, 1965). [The Working Group noted that the single exposure level used was too low for an evaluation of carcinogenicity.]

A group of 47 weanling Long–Evans rats [sex distribution unspecified] received 5 ppm [mg/L] cadmium as **cadmium acetate** in the drinking-water for life. A control group of 34 rats received drinking-water alone. Growth rate and survival were similar. Only macroscopically visible tumours were sectioned for histological analysis. Tumour incidence (as analysed by χ^2) in the cadmium-treated animals was similar to that in the control group (Schroeder *et al.*, 1963; Kanisawa & Schroeder, 1969). [The Working Group noted the single, low exposure level, the lack of sex-specific data and that histopathology was performed only on macroscopic lesions.]

Three groups of 30 male SPF CB hooded rats, 12 weeks of age, received weekly gastric instillations of 0.09, 0.18 and 0.35 mg/kg bw cadmium as **cadmium sulfate** ($3CdSO_4.8H_2O$) dissolved in sterile distilled-water for 104 weeks, at which time surviving animals were killed. A control group of 90 rats received weekly gastric instillations of sterile distilled-water. Histopathological examination was performed on all animals. There was no difference in body weights or survival. Tumour incidence was similar in cadmium-exposed animals and controls (Levy & Clack, 1975). [The Working Group noted the low doses used and that the spontaneous incidence of interstitial-cell tumours of the testis (seen in 75% of animals) may have obscured any cadmium-induced effects within that tissue.]

Groups of 50 male and 50 female Wistar (W74) rats, four to five weeks of age, were fed diets containing 1, 3, 10 or 50 ppm (mg/kg diet) Cd^{2+} as **cadmium chloride** ($CdCl_2.H_2O$) for a period of 104 weeks. Control groups of 100 rats of each sex were used. Survival was not affected by cadmium treatment, and body weights were significantly reduced only in high-dose males [exact extent or time point not given]. Histological examination was performed on all animals, and tumour incidence data were tested by the Fisher exact test. The incidences of testicular and prostatic tumours and of other tumour types were similar in treated groups and controls (Löser, 1980a).

Groups of 30 male Wistar (TNO/W74) rats, 13–16 weeks old, received a single intragastric dose of 50 mg/kg bw or 10 weekly doses of 5 mg/kg bw cadmium as **cadmium chloride** ($CdCl_2.H_2O$) in distilled-water. Two groups of 10 controls received vehicle only. Five animals in each group of treated animals and two or three animals of each group of control animals were killed at 12 and 18 months, and the remaining animals were killed at 133 weeks. Survival was similar in all groups. Following the single administration of 50 mg/kg bw, growth was slightly retarded [data not shown, extent or time point not given]. Testis, epididymis, seminal vesicles, prostates and gross lesions were examined histologically. Rats treated with cadmium did not have an increased incidence of testicular tumours or of tumours at other sites (Bomhard *et al.*, 1987). [The Working Group noted the short duration of exposure.]

In a study on the effect of chronic dietary deficiency of zinc on the carcinogenicity of orally administered cadmium, groups of 28 male Wistar (WF/NCr) rats, eight weeks of age, were fed diets containing either adequate zinc (60 ppm [60 mg/kg diet]) or a zinc concentration (7 ppm [7 mg/kg diet]) that produced a significant reduction (40%) in serum zinc in

the absence of overt toxicity. Starting two weeks later, these diets were fed together with cadmium at 0, 25, 50, 100 or 200 (maximum-tolerated dose) ppm [mg/kg diet] as **cadmium chloride** hemipentahydrate, for 77 weeks, at which time the study was terminated. Histological examination was performed on all animals and lesions. Zinc deficiency alone did not affect food consumption, weight gain or survival; cadmium did not affect survival or food consumption, and body weight was consistently reduced only at the highest doses (100 and 200 mg/kg diet), by 10% and 12–17%, respectively. At the two highest doses of cadmium, rats fed zinc-deficient diets had a significantly increased food consumption when compared with zinc-deficient controls. The combined incidence of prostatic proliferative lesions (hyperplasia and adenoma), but not those of the lesions separately, was significantly ($p < 0.05$; Fisher exact test) greater in rats given zinc-adequate diets containing 50 ppm cadmium (5/22; 22.7%) than in controls (1/28; 3.6%), and in rats receiving zinc-deficient diets (4/26; 15.4%) than in controls (0/26). At higher doses of cadmium (100 and 200 ppm), an increased incidence of prostatic atrophy was observed in the rats receiving zinc-deficient diets, which may have been responsible for the lower incidence of prostatic lesions seen in rats fed zinc-deficient diets. Cadmium treatment resulted in a dose-related (Cochran–Armitage trend tests) increase in the incidence of leukaemia in rats fed zinc-deficient diets throughout the dose range and in rats fed zinc-adequate diets receiving up to and including 100 ppm. The highest incidence of leukaemia occurred in rats receiving 200 ppm cadmium and the zinc-deficient diet (7/25; 28%), when compared with controls (2.27; 7.4%). Exposure to cadmium at a concentration of 200 ppm in conjunction with the zinc-adequate diet also induced a significant increase in testicular interstitial-cell tumours (6/27, 22.2% compared with controls, 1/28, 3.6%) (Waalkes & Rehm, 1992).

3.2 Inhalation exposure[1]

3.2.1 *Mouse*

Groups of 48 female Han:NMRI mice [age unspecified] were exposed to cadmium at 30 or 90 μg/m^3 as **cadmium chloride**, 30 or 90 μg/m^3 as **cadmium sulfate**, 90, 270 or 1000 μg/m^3 as **cadmium sulfide**, 10, 30, 90 or 270 μg/m^3 as **cadmium oxide dust** or 10, 30 or 90 μg/m^3 as **cadmium oxide fume**. The mass median aerodynamic diameter of all compounds was 0.2–0.6 μm [geometric standard deviation, 1.6]. For each treated group, a control group of 48 animals receiving filtered air was available. Exposure was for 19 or 8 h per day for five days a week, and the exposure time ranged from six to 69 weeks; exposure was terminated in some groups when the mortality rats started to increase. The duration of the study was 71–107 weeks; controls were followed for about 106 weeks. Histological examination was performed on all animals. Survival was reduced in 12 of the 19 experimental groups; survival was similar to that of controls in groups exposed to 90 or 270 μg/m^3 as cadmium sulfide, to 10, 30 or 90 μg/m^3 as cadmium oxide fume and to 10 or 270 μg/m^3 as cadmium oxide dust. The incidence of lung tumours was significantly increased in the groups receiving 30 and 90 μg/m^3

[1]The Working Group was aware of a study by inhalation in progress in rats and mice (Ghess *et al.*, 1992).

as cadmium oxide fumes and 10 μg/m^3 as cadmium oxide dust, but not in the group given 270 μg/m^3 as cadmium oxide (see Table 12). In six other groups receiving cadmium oxide dust at various concentrations, survival was significantly decreased, but the probability of dying with a lung tumour was greater than in the controls (by life-table analysis) (Heinrich *et al.*, 1989; Heinrich, 1992). [The Working Group noted the variable spontaneous lung tumour rate and that the histopathological types of tumours were not reported.]

3.2.2 *Rat*

Four groups of 40 male SPF Wistar (TNO/W75) rats, six weeks old, were exposed to 12.5, 25 or 50 μg/m^3 cadmium as **cadmium chloride** aerosol (mass median aerodynamic diameter, 0.55 μm; geometric standard deviation, 1.8) for 23 h a day on seven days a week for 18 months. Animals were observed for an additional 13 months, at which time the experiment was ended. A group of 41 rats exposed to filtered air served as controls. Histological examination was performed on all animals. Body weights and survival were not affected by cadmium treatment. A dose-related increase in the incidence of malignant pulmonary tumours (mostly adenocarcinomas) was observed in cadmium chloride-treated rats (12.5 μg/m^3, 6/39 [15%]; 25 μg/m^3, 20/38 [53%]; 50 μg/m^3, 25/35 [71%]) compared with controls (0/38). Multiple pulmonary tumours were observed frequently; several tumours showed metastases or were regionally invasive. The incidence of adenomatous hyperplasia was also increased by cadmium treatment (Takenaka *et al.*, 1983).

Groups of 20–40 male and 20 female Wistar (BOR-WISW) [formerly called TNO/W75] SPF rats, nine weeks of age, were exposed to aerosols of **cadmium chloride, cadmium sulfate, cadmium sulfide, cadmium oxide dust** or **cadmium oxide fume** (for all compounds, mass median aerodynamic diameter, 0.2–0.5 μm; geometric standard deviation, 1.6) for up to 18 months and observed for up to an additional 13 months (see Table 13). Two additional groups received both zinc oxide dust and cadmium oxide dust at two different levels. Exposure was generally for 22 h a day for seven days a week, although some groups received continuous exposure for 6 months or discontinuous exposure for 40 h per week for 6 months. Inhalation and observation periods were terminated when mortality reached $\geq$ 25% or $\geq$ 75%, respectively, or at 31 months. Histological examination was performed on all rats. Mortality rates were generally greater in rats treated with the high dose of cadmium [body weights not given]. Generally, all forms of cadmium appeared to increase the incidence of primary pulmonary tumours over that in controls [statistical analysis not performed], to a maximum of 90% (cadmium sulfate in females) compared to 0 in controls; in general, no male:female difference was observed. Except in males exposed to 90 μg/m^3 cadmium oxide and 900 μg/m^3 zinc oxide, zinc oxide reduced the carcinogenicity of cadmium oxide at that dose. The tumours observed were mostly adenomas and adenocarcinomas, but a few rats had bronchioloalveolar adenomas and squamous-cell carcinomas (Glaser *et al.*, 1990). [The Working Group noted that the groups exposed to cadmium oxide fume had significantly lower lung tumour incidences than the groups exposed to the other cadmium compounds ($p < 0.0001$; likelihood ratio by χ^2 test). Animals exposed to cadmium oxide fume, however, had only about half the cadmium content in their lungs as animals exposed to the same concentration of the other cadmium compounds over the same period, which was attributed

Table 12. Percentages of animals bearing lung tumours among mice exposed to cadmium with no reduction in mean survival time

Cadmium compound	Concentration ($\mu g/m^3$ Cd)	Exposure time (weeks)		50% survival (weeks)		Experimental time (weeks)	% Tumour-bearing animals	
		h/day	Weeks	Treated	Controls		Treated	Controls
Cadmium sulfide	90	19	64	76	70	98	21.1	14.6
	270	8	26	78	80	101	25	36.9
Cadmium oxide fume	10	19	55	75	71	98	20.9	20.0
	30	19	50	68	71	93	29.6*	20.0
	90	8	64	74	70	105	34.0*	14.6
Cadmium oxide dust	10	19	64	76	70	105	26.1*	14.6
	270	8	59	66	89	107	25.5	27.7

Modified from Heinrich (1992)
*$p < 0.05$ (χ^2 test)

Table 13. Lung tumour incidence in animals with long-term exposure to cadmium by inhalation

Group	Cadmium aerosol ($\mu g/m^3$)	Duration (months)[a]		Animals bearing primary lung tumours/animals examined
		Exposure	Study	
Males				
Control	0	0	31	0/40
Cadmium chloride	30	18	30	15/20
	90	6	30	11/20
Cadmium sulfate	90	14	31	11/20
Cadmium sulfide	90	18	30	17/20
	270	16	30	14/20
	810	7	30	11/20
	2430	4	30	7/16
	270[b]	6	27	3/20
Cadmium oxide dust	30	18	31	28/39
	90	7	31	12/39
	90[b]	6	31	4/20
	30[c]	18	29	25/38
Cadmium oxide fume	10	18	31	0/40
	30	18	31	8/38
Cadmium oxide/zinc oxide	30/300	18	31	0/20
	90/900	18	31	8/20
Females				
Control	0	0	31	0/20
Cadmium chloride	30	18	31	13/18
	90	6	29	3/18
Cadmium sulfate	90	18	29	18/20
Cadmium sulfide	90	18	31	15/20
	270	16	30	16/19
	810	10	29	13/20
	2430	3	31	6/19
	270[b]	6	29	3/20
Cadmium oxide dust	30	18	31	15/20
	90	11	31	14/19
	90[b]	6	31	3/20
Cadmium oxide/zinc oxide	30/300	18	31	0/20
	90/900	18	31	7/20

Modified from Glaser *et al.* (1990)

[a]Exposure was stopped when 25% mortality had occurred, and the study was terminated when 75% of the animals had died.

[b]Discontinuous exposure for 40 h per week

[c]Rats maintained on a zinc-deficient (24 ppm) diet

to a lower pulmonary deposition (Oberdörster & Cox, 1990) of the chain-like electric arc-generated fume particles. The Working Group was also aware of the fact that the generation of cadmium sulfide aerosols in this study from an aqueous suspension had resulted in the generation of a cadmium sulfate:cadmium sulfide mixture (50:50), due to photo-oxidation of cadmium sulfide, which may have confounded the number of tumours induced by cadmium sulfide (Glaser *et al.*, 1992; König *et al.*, 1992; Oberdörster & Cherian, 1992)].

3.2.3 *Hamster*

Groups of 24 male and 24 female Syrian golden [Hoe:SYHK] hamsters [age unspecified] were exposed to cadmium at 30 or 90 μg/m^3 as **cadmium chloride**, 30 or 90 μg/m^3 as **cadmium sulfate**, 90, 270 or 1000 μg/m^3 as **cadmium sulfide**, 10, 30, 90 or 270 μg/m^3 as **cadmium oxide dust** or 10, 30 or 90 μg/m^3 as **cadmium oxide fume** (mass median aerodynamic diameter, 0.2–0.6 μm [geometric standard deviation, 1.6]) for 19 or 8 h per day on five days a week; the exposure time ranged from 13 to 65 weeks and the total experimental time from 60 to 113 weeks. Control groups received filtered air. Exposure was terminated earlier when mortality started to increase; the experimental time was 61–87 weeks for exposed females and 60–113 weeks for males, as increased mortality occurred earlier in females than in males. Survival was reduced in 12 of the 19 groups of exposed male hamsters, but none showed an increased incidence of lung tumours. Histological examination was performed on all animals. In only six of the exposed groups (males and females combined) was there one or, in one case, two animals with a papilloma or a polypoid adenoma of the trachea; one papilloma was also found in the control group (Heinrich *et al.*, 1989; Heinrich, 1992). [The Working Group noted the limited reporting of the data on tumours and the insensitivity of the hamster to induction of tumours of the lung in studies by long-term inhalation.]

3.3 Intratracheal administration

Rat: Groups of male Fischer 344 rats received either a single intratracheal instillation of 25 μg **cadmium oxide** (median diameter, 0.5 μm) suspended in saline at 70 days of age (48 rats), one instillation at both 70 and 100 days of age (total dose, 50 μg/rat; 46 rats) or one instillation at 70, 100 and 130 days of age (total dose, 75 μg/rat; 50 rats) and were compared with 46 rats receiving intratracheal instillations of saline only. [The dose of 25 μg/rat was approximately 75% of the single intratracheal LD_{50}.] Animals were observed for up to 880 days, and all were examined histologically. Cadmium treatment did not affect survival [body weights not given]. Two pulmonary adenocarcinomas were seen in rats given 50 μg (nonsignificant; χ^2) but none in other groups. Increased incidences of mammary gland fibroadenomas were reported in all groups receiving cadmium oxide: 25 μg/rat, 7/44 (16%); 50 μg/rat, 5/41 (12%); 75 μg/rat, 11/48 (23%); controls, 3/45 (7%). No other significant difference in tumour incidence was seen (Sanders & Mahaffey, 1984). [The Working Group noted that the mammary tumours that occurred in treated groups had to be pooled in order to reach statistical significance.]

Groups of about 40 female Wistar (WU/Kiβlegg) rats, 11 weeks of age, received 20 weekly intratracheal instillations in saline of 1 or 3 μg or 15 weekly instillations of 9 μg

cadmium as **cadmium chloride** hydrate (purity, 99%) or **cadmium oxide** [purity not given] (total doses, 20, 60 or 135 μg/rat for both compounds) or 10 weekly instillations of 63, 250 or 1000 μg cadmium as **cadmium sulfide** (> 99.9% pure; total doses, 630, 2500 or 10 000 μg/rat) and were observed for up to 124 weeks. Concurrent controls received saline only. [Body weights were not given.] Only the lungs and trachea were examined histologically. Cadmium chloride induced moderate, dose-related increases in the incidence of lung tumours: controls, 0/40; 20 μg/rat, 0/38; 60 μg/rat, 3/40 (7.5%); 135 μg/rat, 2/36 (5.6%) [$p < 0.01$; trend test]. Cadmium oxide also induced some lung tumours: 20 μg/rat, 2/37 (5.4%); 60 μg/rat, 2/40 (5.0%); 135 μg/rat, 0/39 (not significant). Cadmium sulfide induced a dose-related increase in the incidence of lung tumours: 2/39 (5.1%) at 630 μg/rat, 8/36 (22.2%) at 2500 μg/rat and 7/36 (19.4%) at 10 000 μg/rat [$p < 0.005$; trend test]. The authors reported that mortality was increased at the highest dose. The lung tumours induced were primarily adenocarcinomas, although a few adenomas and squamous-cell carcinomas were also observed (Pott *et al.*, 1987). [The Working Group noted that the cadmium sulfide particles had been administered in an aqueous suspension, which may have resulted in photo-oxidation of some fraction of the cadmium sulfide to cadmium sulfate; however, even under the assumption of worst-case conditions—24-h exposure of cadmium sulfide suspension to light—the amount of cadmium sulfate should not have exceeded 3% of the total cadmium in the middle dose (Oberdörster & Cherian, 1992). Therefore, photo-decomposition of cadmium sulfide to cadmium sulfate could not have accounted for the carcinogenic response observed.]

3.4 Subcutaneous and/or intramuscular administration

3.4.1 *Mouse*

In a study to examine the effect of zinc on the carcinogenicity of cadmium, a group of 26 male Charles River mice, eight weeks of age, received a single subcutaneous injection of 0.03 mmol/kg bw (5.5 mg/kg bw) **cadmium chloride** [vehicle unspecified] in the interscapular region and were observed for 14 months. Control groups consisted of 25 untreated mice and 25 mice that received a single subcutaneous injection of 0.03 mmol/kg bw cadmium chloride and three concurrent subcutaneous injections of 1.0 mmol/kg zinc acetate (total dose, 3.0 mmol/kg; 550 mg/kg bw) at three different sites over a period of 25 h before and after the cadmium injection. No injection-site tumour was reported. Only testes were examined histologically [weight gains and survival not reported]. Of the mice that received cadmium alone, 77% (20/26) had interstitial-cell tumours of the testis; none occurred in cadmium–zinc treated animals or in untreated controls. Zinc also prevented the induction by cadmium of non-neoplastic lesions of the testes in almost all of the animals (Gunn *et al.*, 1961, 1963).

A group of 20 male CB mice, six to seven weeks of age, received 11 weekly subcutaneous injections of 0.05 mg **cadmium sulfate** tetrahydrate in 0.2 ml sterile distilled-water into the right flank (total dose of cadmium, 0.22 mg). A group of 20 untreated animals served as controls [body weights not reported]. Only gross and testicular lesions were taken for histological analysis. None of the cadmium-treated mice developed tumours at the site of injection, and the incidence of tumours at other sites did not exceed control rates [statistical analysis not given]; however, non-neoplastic changes typical of cadmium treatment, such as

testicular degeneration and interstitial-cell hyperplasia, were observed in 6/16 [17 in table] animals that survived for eight months or more and in none of 15 control mice surviving at least to the same time point. [The Working Group noted the short duration of the study.] In a separate study, 10 six-week-old male CB mice received three weekly subcutaneous injections of 5 mg cadmium sulfate-precipitated rat ferritin into the right flank, followed six weeks later by 12 weekly injections of 0.5 mg of the same preparation (total dose, 0.36 mg cadmium). No tumour was observed at the site of injection during the following 20 months (Haddow *et al.*, 1964; Roe *et al.*, 1964).

3.4.2 *Rat*

The earliest suspicion that cadmium might be carcinogenic came from a brief report by Haddow *et al.* (1961), who detected malignant tumours at the injection site (subcutaneous or intramuscular) of ferritin prepared from rat liver by cadmium precipitation in 8/20 male rats [strain unspecified]. Additionally, 10/20 of these rats had interstitial-cell tumours of the testes.

Groups of 10 female hooded rats, two to three months old, received a single intramuscular injection of 14 or 28 mg **cadmium metal** powder (dimensions: 1.7 μm diameter for spheres, 85 μm × 50 μm for ellipsoids and rods and 220 μm × 50 μm × 50 μm for other shapes) suspended in 0.4 ml fowl serum into the thigh muscle. The total duration of the study was 84 weeks. [Weight gain was not determined and necropsy protocol was not stated.] Two of the rats receiving 28 mg cadmium powder were killed within two week of injection in order to study acute local reactions. Malignant tumours developed at the site of injection in 9/10 rats given 14 mg and in 6/8 rats given 28 mg cadmium powder. Most of the tumours were rhabdomyosarcomas; some fibrosarcomas were seen which metastasized to lymph nodes (Heath *et al.*, 1962; Heath & Daniel, 1964). [The Working Group noted that, while the authors stated that zinc or tungsten metal powders did not induce local sarcomas at the injection site, no details were reported.]

A group of 25 male Wistar rats, 12 weeks of age, received a single subcutaneous injection of 0.03 mmol/kg bw [5.5 mg/kg bw] **cadmium chloride** [vehicle unspecified] in the interscapular region and were observed for 11 months. Control groups consisted of 20 untreated rats and 17 rats that received a single subcutaneous injection of 0.03 mmol/kg bw cadmium chloride and three concurrent subcutaneous injections of 1.0 mmol/kg zinc acetate (total dose, 3.0 mmol/kg; 550 mg/kg bw] in the lumbosacral area over a period of 25 h before and after the cadmium injection. Only testes were examined histologically. [Weight gains and survival were not stated.] Of the rats that received cadmium alone, 17/25 (68%) had interstitial-cell tumours of the testes; 2/17 occurred in cadmium–zinc treated animals, and 0/20 occurred in controls (Gunn *et al.*, 1961, 1963, 1965).

Ten six-month-old female Wistar CB rats received subcutaneous injections of 25 mg **cadmium sulfide** (diameter, 0.5 μm; equivalent to 20 mg cadmium) suspended in 0.25 ml saline into both sides of the dorsal midline. Ten three-month-old rats received subcutaneous injections of 0.25 ml saline and served as controls. [Body weights and necropsy protocol were not stated.] Over the following 12 months, 6/10 treated rats and none of the controls developed fibrosarcomas (Kazantzis, 1963). In a further study, 15 male and 15 female Wistar CB rats, nine months of age, received subcutaneous injections of 25 mg cadmium sulfide

suspended in 0.25 ml saline into both sides of the dorsal midline. Of the 26 rats that survived for more than six months, six developed sarcomas at the site of injection. In a separate experiment, seven male and seven female rats, eight months old, were given a single intramuscular injection of 50 mg cadmium sulfide suspended in 0.5 ml saline into the thigh. [Body weights and necropsy protocol not stated.] Four animals died during the first nine months after injection. Sarcomas at the site of injection developed in 6/14 rats over a 17-month period. In a further study, 10 three-month-old female rats received subcutaneous injections of 25 mg cadmium oxide suspended in 0.25 ml saline into both sides of the dorsal midline; 8/10 developed fibrosarcomas at the site of injection within one year (Kazantzis & Hanbury, 1966).

A group of 22 four-month-old male Wistar rats received single subcutaneous injections of 0.03 mmol/kg bw [5.5 mg/kg bw] **cadmium chloride** (equivalent to 1.35 mg cadmium [vehicle not stated]) into the interscapular region and were observed for 10 months. Only testes and subcutaneous tumours at the site of injection were examined histologically. Sarcomas developed at the site of injection in 9/22 rats, while 21/22 rats developed interstitial-cell tumours of the testis. A group of 17 rats received the same treatment with cadmium chloride and subcutaneous injections of 1 mmol/kg bw (183.5 mg/kg bw) zinc acetate in the lumbosacral area; the zinc acetate treatment resulted in lower incidences of sarcomas at the site of injection (2/17) and of testicular tumours (3/17) than those induced by cadmium. No interstitial-cell tumour of the testis developed in 18 untreated controls (Gunn *et al.*, 1964).

A group of 20 male CB rats, three weeks of age, received an initial subcutaneous injection of 20 mg **cadmium sulfate**-precipitated rat liver ferritin [vehicle unspecified] into the right flank followed by another injection of 20 mg 46 days later and then 2 mg once a week for eight weeks, all in approximately the same area. A group of 16 untreated rats served as controls. Only gross lesions were taken for histological examination. Of the cadmium–ferritin-treated rats, 7/20 (35%) developed injection-site sarcomas and 11/15 (73%) examined developed interstitial-cell tumours of the testis over the total observation period of 28 months. No such lesion was observed in 15 control rats that survived to a similar time (Haddow *et al.*, 1964; Roe *et al.*, 1964). In a subsequent study, no tumour at the site of injection and no testicular tumour was induced in CB Wistar rats by cadmium-free ferritin (Roe *et al.*, 1968). A separate group of 20 male CB rats, six to seven weeks old, received 10 weekly subcutaneous injections into the right flank of 0.5 mg cadmium sulfate tetrahydrate in 0.1 ml sterile distilled-water. By 20 months, 14/20 rats had developed sarcomas at the site of injection (Haddow *et al.*, 1964), while 10/18 examined had developed interstitial-cell tumours of the testis (Roe *et al.*, 1964).

A group of 49 male Wistar rats, four months of age, received a single injection of 1.8 mg cadmium as **cadmium chloride** [vehicle unspecified] either subcutaneously into the interscapular region (23 rats) or intramuscularly into the thigh (26 rats) and were observed for 14 months. No concurrent controls were available [body weights and necropsy protocol not given]. More sarcomas occurred at the site of injection when cadmium was injected subcutaneously (10/23; 43.5%) than intramuscularly (3/26; 11.5%) (Gunn *et al.*, 1967).

Six male Sprague–Dawley rats, three months of age, received a single subcutaneous injection of 10 mg/kg **cadmium chloride** [site and vehicle unspecified] and were observed for

a further 13 months. A group of 16 untreated rats of the same age served as controls. All six cadmium-treated rats developed interstitial-cell tumours of the testis. Baseline urinary testosterone concentrations in cadmium-treated rats bearing tumours were 26–29% those of control animals (Favino *et al.*, 1968). [The Working Group noted the limited reporting of the study.]

Eighty 12-week-old male Wistar rats received a a single subcutaneous injection of 0.03 mmol/kg bw [5.5 mg/kg bw] **cadmium chloride** as the dihydrate (3.4 mg/kg bw cadmium) dissolved in sterile distilled-water into the hip area and were observed for up to two years. Twenty untreated rats served as controls. Animals were examined grossly and histologically [body weights not stated]. Dermal atrophy, ulcerative necrosis, acute and chronic inflammation, fibrosis and mineralization were observed at the site of injection during the two months following administration of cadmium. Of the rats that survived to seven months (the time of appearance of the first sarcoma at the site of injection), 6/45 had local spindle-cell sarcomas after 18 months (Knorre, 1970a,b). In a second experiment with 104 male rats treated by the same schedule, interstitial-cell tumours of the testis were found by 698 days in 10/25 rats still alive at 355 days (when the first tumour of the testis appeared) (Knorre, 1971). One sarcoma at the site of injection metastasized to the peritoneum [possibly invasion], and several others metastasized to regional lymph nodes (Knorre, 1970a). A single cadmium-induced histologically confirmed testicular interstitial-cell tumour metastasized to the colon and liver [a rare event]. No interstitial-cell tumour of the testis was seen in 32 control animals (Knorre, 1971).

A group of 15 male Wistar rats weighing 100–300 g received single subcutaneous injections [site unspecified] of 0.02–0.03 mmol/kg bw [3.7–5.5 mg/kg bw] **cadmium chloride** and were observed for 11 months. Interstitial-cell tumours of the testis developed in 13/13 rats still alive at 11 months, and two rats developed pleomorphic sarcomas at the site of injection (Lucis *et al.*, 1972) .

Three groups of 25 male SPF CB hooded rats, 12 weeks of age, received weekly subcutaneous injections of 0.05, 0.1 or 0.2 mg **cadmium sulfate** (3 $CdSO_4.8\ H_2O$; 0.02–0.09 mg Cd) dissolved in sterile distilled-water into alternate flanks over a period of two years. The control group consisted of 75 animals that received weekly injections of distilled-water alone. Extensive macroscopic and microscopic examinations were performed, with special attention to the genital gland complex. Body weights were suppressed ($p < 0.001$) [test unspecified; data not shown; extent not stated] in the high-dose group after two years. Sarcomas at the site of injection were found in 1/25 rats given the low dose, 1/25 given the medium dose and 4/25 given the high dose. No neoplastic change was seen in any other tissue, including the prostate. All groups, including controls, had high incidences of testicular interstitial-cell tumours (67–77%) [which may have obscured any effect of cadmium on that tissue]. The concentration of cadmium in the kidney in the highest dose group was about 500 μg/g tissue [analysed polarographically after dithizone extraction] (Levy *et al.*, 1973).

Twenty male Fischer 344 rats, four to five weeks old, received a single subcutaneous injection of 0.03 mmol/kg bw **cadmium chloride** [5.5 mg/kg bw], and 10 control rats received subcutaneous injections of saline [body weight, survival data and necropsy protocol not given]. Interstitial-cell tumours of the testis (11 bilateral) developed in 16/20 treated rats over the one-year observation period, while none developed in control rats (Reddy *et al.*,

1973). [The Working Group noted that the Fischer 344 strain generally has a > 80% spontaneous incidence of interstitial-cell tumours of the testis by two years of age.]

In a 110-week study to examine the potential effects of calcium and magnesium salts on the carcinogenicity of cadmium, groups of 25 male Wistar rats weighing 120–150 g were kept for two weeks and then given subcutaneous injections of 0.02 or 0.04 mmol/kg bw [3.67 or 7.34 mg/kg bw] **cadmium chloride** hemipentahydrate into the nape of the neck. Rats received either no further treatment or treatment with calcium acetate or magnesium acetate, either in the diet (3%) two weeks prior and two weeks after cadmium chloride treatment or by three separate subcutaneous injections (calcium acetate, 0.16 mmol/kg bw [25.3 mg/kg bw]; magnesium acetate, 4.0 mmol/kg bw [570 mg/kg bw]) in the same area as the cadmium chloride 24 h before, at the same time as and 24 h after cadmium chloride injection. Control rats received saline injections instead of cadmium chloride. All animals were examined histologically. The highest dose of cadmium chloride caused slight weight suppression but only up to 12 weeks after injection. Survival was not affected by any of the treatments. Tumours at the site of injection (predominantly fibrosarcomas) occurred to a similar extent (approximately 33% of rats at risk) in all groups receiving cadmium chloride, regardless of the dose or of other treatments, with the exception of injected magnesium acetate which significantly reduced (to 0; $p < 0.02$; χ^2) the response to cadmium at the injection site. Both levels of cadmium chloride increased the incidence of testicular interstitial-cell tumours (approximately 85%) over that in controls (30%); the increase was generally unchanged by other treatments, with the exception of dietary calcium acetate, which resulted in a lower incidence than in animals receiving cadmium chloride alone, but only at the high dose. When all groups receiving cadmium chloride were considered together, a significantly ($p < 0.02$) higher incidence of pancreatic islet-cell tumours (mainly adenomas) occurred (22/258 rats; 8.5%) when compared with rats not receiving cadmium chloride (3/137; 2.2%) (Poirier *et al.*, 1983).

Groups of 30 male Wistar Crl:(WI)BR rats, six weeks of age, received a single subcutaneous injection of 1.0, 2.5, 5.0, 10.0, 20.0 or 40.0 μmol/kg bw [0.18–7.3 mg/kg bw] **cadmium chloride** dissolved in saline into the dorsal thoracic midline area and were observed for two years. Other groups received either four separate subcutaneous injections of 5 μmol/kg cadmium chloride on days 0, 2, 4 and 7 or a subcutaneous injection of 5 μmol/kg [0.9 mg/kg] cadmium chloride followed two days later by a dose of 10 or 20 [1.8 or 3.6] μmol/kg bw. A group of 45 controls received subcutaneous injections of saline alone. All animals were examined histologically. Cadmium chloride did not modify survival in any group. The highest dose (40 μmol/kg) reduced body weight by about 5–10%. The incidences of sarcomas at the site of injection were found to depend on accumulated dosage at the site and approached 45% incidence at the highest dose of cadmium. The incidences of testicular tumours (mostly interstitial-cell tumours) were correlated with the extent of testicular degeneration induced by cadmium and showed a positive dose-dependence with single doses of cadmium: 83% at 40 μmol/kg and 72% at 20 μmol/kg, as compared with 18% in controls ($p \leq 0.05$; Cochran–Armitage test). The 5-μmol/kg and 20-μmol/kg doses did not increase the incidence of testicular tumours. Prostatic tumour incidence was significantly elevated at the 2.5 μmol/kg dose (8/26; 31%; $p \leq 0.05$, Fisher exact test) compared with controls (5/44; 11%), and a positive dose–effect relationship was seen between 0 and 2.5 μmol/kg in both

tumour incidence and multiplicity ($p \leq 0.05$; Cochran–Armitage test). A reduction to the control level in the tumour response of the prostate to higher doses of cadmium (≥ 5.0 μmol/kg) was attributed by the authors to testicular degeneration and consequent loss of androgenic support. Cadmium chloride suppressed the induction of tumours of the pancreas (both islet-cell and acinar-cell) from 60% in controls to 20% in animals receiving 40 μmol/kg cadmium, with a negative dose dependence ($p \leq 0.05$, Cochran–Armitage test) (Waalkes *et al.*, 1988a).

Groups of 30 male Wistar Crl:(WI)BR rats, six weeks of age, received a single subcutaneous injection of 30 μmol/kg bw (5.5 mg/kg bw) **cadmium chloride** dissolved in saline into the dorsal thoracic midline area and three subcutaneous injections of 0.1, 0.3 or 1.0 mmol/kg [18.4, 55.1 or 183.5 mg/kg bw] zinc acetate in saline into the right, left and midline lumbosacrum 6 h before, at the same time as and 18 h after the cadmium treatment. Animals were observed for up to two years. Two other groups of 30 rats received either 30 μmol/kg cadmium chloride intramuscularly plus 1.0 mmol/kg zinc subcutaneously into the right, left and midline lumbosacrum 4 h before, at the same time as and 18 h after the cadmium treatment or 30 μmol/kg cadmium chloride subcutaneously and, starting two weeks previously, 100 ppm [100 mg/L] zinc as zinc acetate in the drinking-water for the duration of the study. A control group of 84 rats received saline injections and tap water. All animals were examined histologically. The treatments did not modify survival in any group. Injection-site sarcomas occurred in 12/30 rats given only the subcutaneous injection of cadmium, and the incidence was significantly ($p \leq 0.05$; Fisher exact test) reduced by the highest subcutaneous dose of zinc (6/29) and by administration of zinc in the drinking-water (1/30). Intramuscular injection of cadmium produced sarcomas at the site of injection in 3/29 rats given cadmium alone and in 1/29 rats also given zinc subcutaneously. Testicular tumours (mostly interstitial-cell tumours) were observed in 22/30 (73%) rats given only the subcutaneous injection of cadmium chloride and in 3/28 (11%) rats receiving both cadmium chloride subcutaneously and three subcutaneous doses of 1 mmol/kg zinc; 9/83 (11%) were observed in saline control rats. The incidence of testicular tumours overall showed a negative dependence on the subcutaneous dose of zinc ($p \leq 0.05$; Cochran–Armitage test), although zinc in the drinking-water had no effect on induction by subcutaneous cadmium chloride (25/30 rats, 83%). Subcutaneous administration of cadmium caused extensive testicular degeneration, which was prevented in a dose-related fashion by subcutaneous zinc. Intramuscular administration of cadmium did not increase the incidence of tumours of the testis. Prostatic adenoma incidence was elevated in the groups receiving cadmium subcutaneously and the high dose of zinc (8/27; 30%; $p \leq 0.05$, Fisher exact test), intramuscular cadmium (11/26; 42%; $p \leq 0.05$) or intramuscular cadmium and subcutaneous zinc (7/28; 25%; $p \leq 0.05$), compared with controls (8/83; 10%). The tumour response of the prostate to cadmium in animals given the highest dose of zinc was attributed by the authors to prevention of cadmium-induced testicular degeneration and consequent loss of androgenic support (Waalkes *et al.*, 1989).

A group of 70 male Fischer F344/NCr rats, eight weeks old, received a single subcutanous injection of 30.0 μmol/kg bw [5.5 mg/kg bw] **cadmium chloride** hemipentahydrate dissolved in saline into the dorsal thoracic midline area and were observed for 90 weeks. Fifty control animals received a single subcutaneous injection of saline only. In the

33 animals still alive at the time of appearance of the first tumour (32 weeks), cadmium chloride reduced survival but not body weight. Cadmium chloride induced sarcomas (primarily fibrosarcomas) at the site of injection in 21/32 rats (1/50 in controls). The incidence of testicular interstitial-cell tumours was 97% in cadmium chloride-treated rats and 84% in controls. The incidence of large granular lymphocytic leukaemia (2/31) was reduced ($p = 0.028$) by cadmium chloride from that in controls (12/47) (Waalkes *et al.*, 1991a).

Groups of 28 male Wistar Hsd:(WI)BR rats, eight weeks of age, were fed diets either adequate in zinc (60 ppm [60 mg/kg diet]) or marginally zinc-deficient (7 ppm [7 mg/kg diet]), as defined by significant reductions (40%) in serum zinc in the absence of overt weight suppression. The diets were given for two weeks prior to a single subcutaneous injection of 0, 5.0, 10.0 or 30.0 μmol/kg bw (0.92–5.5 mg/kg bw) **cadmium chloride** hemipentahydrate dissolved in saline into the dorsal thoracic midline area. Animals were observed for the next 92 weeks. All animals were examined histologically. Zinc deficiency alone did not affect food consumption, weight gain or survival. Cadmium chloride affected weight gain only at the highest dose (30 μmol/kg), at which body weight was reduced approximately 15%, only for the first 10 weeks after injection; thereafter, weights were not different from those of controls. Survival was reduced in rats fed zinc-adequate diets and given the highest dose of cadmium chloride ($p \leq 0.05$). Injection-site sarcomas occurred in 7/25 rats receiving 30 μmol cadmium chloride and zinc-deficient diets ($p < 0.05$), in 3/24 rats given 30 μmol cadmium chloride and zinc-adequate diets and in 0/49 controls. Dietary zinc level did not affect the incidence of cadmium-induced interstitial-cell tumours of the testis, and a dose–response relationship in tumour incidence occurred with cadmium up to a maximum incidence of approximately 70% (control, < 10%) at both levels of dietary zinc. Rats receiving zinc-deficient diets showed an increased multiplicity of testicular interstitial-cell tumours (Waalkes *et al.*, 1991b).

3.5 Other routes of administration

3.5.1 *Mouse*

In a screening study based on the accelerated induction of lung adenomas in a strain highly susceptible to development of this neoplasm, groups of 20 male and female strain A/Strong mice, six to eight weeks old, received thrice weekly intraperitoneal injections of **cadmium acetate** in saline for a total of 23 injections, while controls received a total of 24 injections of saline alone. The total doses of cadmium acetate were designed to be 7, 14 and 28 mg/kg bw. All mice given 28 mg/kg bw died prior to completion of the study (30 weeks). Lung adenomas occurred in 6/14 (43%) animals given 7 mg/kg bw and in 3/10 (30%) animals given 14 mg/kg bw, compared with 37% of controls. The average number of lung tumours per mouse was unaltered by treatment ($p > 0.05$; Student's *t* test) (Stoner *et al.*, 1976).

3.5.2 *Rat*

A group of 207 male Wistar rats, six weeks of age, received injections of 0.15 ml of a 1-mol [*sic*] solution of **cadmium chloride** [16.86 mg/rat; 241 mg/kg bw] in saline directly into

the prostate. A further group of 50 rats received one to five subcutaneous injections of 0.05 ml of the 1-mol solution of cadmium chloride [5.62–28.1 mg/rat; 80–401 mg/kg bw] in saline [site unspecified]. Concurrent controls were not included [body weights, survival, necropsy protocol and observation time not specified]. Prostatic tumours, generally carcinomas, developed in 17/207 (8.2%) rats given injections directly into the prostate. In the animals given cadmium chloride subcutaneously, a possible early adenocarcinoma of the prostate was observed (Scott & Aughey, 1978). [The Working Group noted that the absence of concurrent controls makes these data difficult to interpret.]

A group of 125 inbred male rats of the Okamoto-toki strain, 12 months of age, were anaesthetized and injected with 0.44 mg cadmium (1.2 mg/kg bw) as **cadmium chloride** in saline into the right lobe of the ventral prostate. Twenty saline-injected rats of the same age served as controls. Animals were observed for 270 days after cadmium chloride injection [body weights and survival not given]. Lesions of the prostate were classified as hyperplasia, atypical hyperplasia, carcinoma *in situ* (Hoffmann *et al.*, 1985a) [modified to atypical hyperplasia with severe dysplasia by Hoffmann *et al.*, 1985b] and invasive carcinoma. The first case of invasive prostatic carcinoma was detected 56 days after treatment, and a total of five cases occurred in 100 rats examined in this group. Other prostatic changes induced by cadmium chloride treatment included 'carcinoma *in situ*' in 11 rats (Hoffmann *et al.*, 1985a), atypical hyperplasia in 29 rats and simple hyperplasia in 38. Of the 20 controls examined, five had simple hyperplasia and one had atypical hyperplasia (Hoffmann *et al.*, 1985a,b). [The Working Group noted the small number of controls and the short obervation period.]

Female Wistar WU/Kiβlegg rats [number not given], 12 weeks of age, each received a single intraperitoneal injection of 50 mg cadmium as **cadmium sulfide** (81 rats examined) or two weekly intraperitoneal injections of 0.125 mg cadmium as **cadmium oxide** (47 rats examined) dissolved in saline. Animals were observed for up to 123 weeks. No concurrent controls were reported. Only gross lesions of the peritoneal cavity were examined histologically. Three of the rats given cadmium oxide and 54/81 given cadmium sulfide had peritoneal cavity tumours, described as sarcomas, mesotheliomas and carcinomas of the abdominal cavity [no further details reported]. In the 204 rats injected with saline alone (combined controls), five intraperitoneal tumours (one carcinoma, one mesothelioma and three sarcomas) were observed (Pott *et al.*, 1987).

Groups of male Okamoto-aoki rats, 12 months of age, were injected twice with 2.25 mg/kg bw (10 rats) or three times with 3.35 mg/kg bw (20 rats) **cadmium chloride** [time course and vehicle unspecified] into the right lobe of the ventral prostate. No concurrent controls were used. Animals were killed after 170 or 240 days, respectively. Prostatic carcinomas occurred in 2/8 rats receiving the lower dose of cadmium and in 9/15 rats given the higher dose (Hoffmann *et al.*, 1988). [The Working Group noted that the absence of a control group makes this study difficult to interpret.]

3.6 Administration with known carcinogens

3.6.1 *Mouse*

Groups of 25 three-week-old female Swiss mice received 5, 10 or 50 ppm [mg/L] cadmium as **cadmium chloride** in deionized water or drinking-water alone (controls) for

15 weeks. After three weeks of exposure, all mice received an intraperitoneal injection of 1.5 mg/g bw [1.5 g/kg bw] urethane in saline. At the end of the 15-week exposure period, all mice were killed. Treatment did not affect average body weight gain or water consumption. Only lungs were examined histologically. Cadmium did not modify the size or number of pulmonary adenomas induced by urethane per animal (Blakley, 1986).

A group of 100 female hybrid CBA × C57Bl/6 mice, weighing 10–12 g, received 0.01 mg/L **cadmium chloride** together with 10 ppm [mg/L] *N*-nitrosodimethylamine (NDMA) in the drinking-water *ad libitum* for nine months, at which time the experiment was terminated. A positive control group of 50 mice received NDMA alone. The total dose of cadmium chloride received from drinking-water was stated to be 0.007 mg. Survival was similar in both groups [body weights not given]. All animals were examined histologically. Treatment with cadmium chloride plus NDMA significantly increased ($p \leq 0.05$, χ^2) the proportion of animals with tumours of any type (95.3%) over that of mice given NDMA alone (80.0%) among animals that survived to the time of appearance of the first tumour. The tumours were primarily pulmonary adenomas, renal adenomas and hepatic haemangiomas and haemangioendotheliomas (Litvinov *et al.*, 1986). [The Working Group noted the high incidence of tumours in the group given NDMA alone and the absence of a concurrent untreated control group and of a group receiving cadmium chloride alone.]

In a study of promotion, groups of 50 male B6C3F1 mice, five weeks of age, were given a single intraperitoneal injection of 90 mg/kg bw *N*-nitrosodiethylamine (NDEA) in tricaprylin or vehicle alone followed two weeks later by administration of 0, 500 or 1000 ppm [mg/L] **cadmium chloride** hemipentahydrate in drinking-water. Groups of 10 mice were killed at 16, 24 and 36 weeks, and the remainder were killed at 52 weeks. Cadmium chloride markedly suppressed body weight gain in the group given 1000 mg/L. All animals were examined histologically. Cadmium chloride was not associated with an increased incidence of tumours, regardless of NDEA treatment, and animals treated with cadmium chloride had a dose-related reduction in NDEA-induced pulmonary adenomas of alveolar-cell origin and liver tumours (typically basophilic adenomas) (Waalkes *et al.*, 1991c).

In a study of initiation, groups of male B6C3F1 mice, five weeks of age, were given a single subcutaneous injection of vehicle (30 mice) or cadmium at 20.0 (30 mice) or 22.5 (60 mice) μmol/kg bw (2.25 or 2.53 mg/kg bw) as **cadmium chloride** hemipentahydrate in saline, followed two weeks later by administration of water or 500 ppm [mg/L] sodium barbital in the drinking-water (540 mice in all). Both doses of cadmium chloride caused focal hepatocellular necrosis; the 20.0 μmol/kg dose caused 8% (5/60) mortality and 22.5 μmol/kg caused 39% (47/120) mortality within the first two days (all treated groups combined). Final body weights were similar in animals that survived the acute toxicity. Groups of 10 mice were killed 40 weeks after cadmium injection, and the remainder were killed at 92 weeks. Histological examination was performed, with special emphasis on liver lesions. Cadmium chloride treatment was not associated with increases in the incidence of any tumours; it reduced ($p \leq 0.05$) liver tumour incidence and the numbers of tumours/liver, but not tumour size (Waalkes *et al.*, 1991c).

3.6.2 *Rat*

Groups of 15 male Fischer 344 rats, seven weeks old, were administered 500 mg/L *N*-nitrosoethyl-*N*-hydroxyethylamine in drinking-water for two weeks followed by 100 mg/L **cadmium chloride** hemipentahydrate for 25 weeks. Cadmium chloride did not affect body weight or survival. Only kidneys and liver were examined histologically. Cadmium chloride did not increase the kidney tumour incidence significantly but it significantly ($p \leq 0.05$; Student's *t* test) increased the mean number of renal dysplastic foci/cm^2 of tissue (0.69 $\pm$ 0.32) in comparison with nitrosamine-treated controls (0.23 $\pm$ 0.28) (Kurokawa *et al.*, 1985, 1989). [The Working Group noted the short duration of the study.]

Groups of 40 male Wistar (Sim:Wistar) rats, nine weeks of age, were treated with estimated daily dietary doses of 50 mg/kg of diet [ppm] cyproterone acetate for three weeks followed by three daily subcutaneous injections of 25 mg testosterone propionate and then a single intravenous injection of 50 mg/kg bw *N*-methyl-*N*-nitrosourea (MNU). One group then received 100 ppm (100 mg/L) **cadmium chloride** in the drinking-water, and another received standard drinking-water and served as controls. Survival and body weight were not affected by cadmium, and the mean survival time was 58 weeks. All animals were examined histologically. One intraductal carcinoma of the prostate occurred in a cadmium-treated rat, but none occurred in controls. The incidences of tumours at other sites were not affected by cadmium (Nakao, 1986). [The Working Group noted the short duration of the study, the minimal effect of MNU alone and the absence of concurrent untreated controls or controls receiving cadmium chloride alone.]

Groups of 20 male Wistar rats [age at onset unspecified] were given 100 ppm [mg/L] *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in their drinking-water and fed a diet supplemented with 10% sodium chloride for eight weeks to initiate stomach tumour formation. **Cadmium chloride** was then given in the drinking-water at a concentration of 100 ppm [mg/L] for the following 32 weeks. A group of 28 rats received the nitrosamine then distilled drinking-water and served as controls. Cadmium chloride did not modify the incidence of gastroduodenal tumours or preneoplastic lesions (Kurokawa *et al.*, 1989).

Groups of 20 male Fischer 344 rats [age at onset unspecified] were given 50 ppm [mg/L] NDEA in the drinking-water for four weeks followed by 100 ppm [mg/L] **cadmium chloride** in the drinking-water for the following 30 weeks. Controls received NDEA followed by drinking-water. Cadmium chloride significantly ($p < 0.01$) reduced the incidence of hepatocellular carcinomas induced by NDEA (Kurokawa *et al.*, 1989).

Groups of 42–58 female hooded rats, 10–12 weeks of age, were given one treatment of either crocidolite alone (1.82 mg/rat suspended in Tyrode's solution by intratracheal instillation), crocidolite plus cadmium (0.18 mg cadmium/rat as powdered **cadmium metal** suspended in Tyrode's solution by intratracheal instillation), crocidolite plus cadmium plus *N*-nitrosoheptamethyleneimine (NHMI; 1 mg/rat dissolved in saline given subcutaneously into the dorsal thoracic area six weeks after intratracheal instillation of crocidolite and cadmium for 12 weeks) or NHMI alone. Survival was similar in all the cadmium-treated groups. The overall lung tumour incidence in animals receiving crocidolite, cadmium and NHMI (14/45) was significantly ($p \leq 0.05$) higher than that in groups receiving NHMI alone (10/58), crocidolite and cadmium (2/51) or crocidolite and NMHI (7/42). The tumours were

primarily squamous-cell carcinomas (Harrison & Heath, 1986). [The Working Group noted that concurrent untreated controls and groups treated with cadmium metal only were not available.]

Groups of male Wistar Cr1:[WI]BR rats, 22 weeks old, were given a single intraperitoneal injection of 18 mg/kg bw NDMA followed 4 h and four days later by intramuscular injections of **cadmium chloride** into the thigh (total doses of cadmium, 1.5 mg/kg bw [20 rats] or 3.0 mg/kg bw [30 rats]) or no further treatment (20 rats). Two other groups of 20 rats were given cadmium alone, and a group of five untreated rats served as controls. The animals were observed for 52 weeks. Cadmium chloride alone was not acutely lethal; NDMA alone caused 5% mortality, low-dose cadmium plus NDMA induced 10% mortality and high-dose cadmium plus NDMA induced 30% mortality. All treatments markedly reduced body weight [extent not stated] within one week of exposure, but by the end of the experiment the weights were similar to those of untreated controls. Only rats surviving to week 30 were included in the tumour analysis. Cadmium chloride increased ($p \leq 0.05$, Fisher exact test) the incidence of renal tumours induced by NDMA (NDMA alone, 2/18 rats examined; NDMA plus low-dose cadmium chloride, 10/18; NDMA plus high-dose cadmium chloride, 11/21) but did not induce significant numbers when given alone (low-dose, 1/20; high-dose, 0/20). Cadmium chloride also increased the incidence of hepatocellular adenoma (NDMA alone, 1/18; NDMA plus pooled cadmium chloride groups, 9/39). In a second experiment, 30 rats (same strain, six weeks old) were given intramuscular injections of cadmium as cadmium chloride at a dose of 1 mg/kg bw into the thigh on days 0, 4, 5 and 6 and of 2 mg/kg bw on day 12; one day later, the animals received an intraperitoneal injection of 18 mg/kg bw NDMA. Further groups received NDMA alone (20 rats), cadmium chloride alone (20 rats) or remained untreated (four rats). Survival and body weights were similar in all groups. Cadmium chloride increased ($p \leq 0.05$, Fisher exact test) the incidence of NDMA-induced renal tumours (NDMA alone, 2/19; NDMA plus cadmium chloride, 15/26) but did not induce any renal tumours when given alone (0/20). The incidences of hepatocellular adenomas were: NDMA alone, 3/19; NDMA plus cadmium chloride, 0/26; cadmium chloride alone, 1/20 (Wade *et al.*, 1987).

4. Other Relevant Data

The extensive literature on cadmium has been reviewed (Friberg *et al.*, 1985, 1986b; Nordberg & Nordberg, 1988; Nordberg *et al.*, 1992; US Occupational Safety and Health Administration, 1992; WHO, 1992b). The following summary comprises illustrative studies only.

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Cadmium may enter the body by ingestion, inhalation and, to a very limited extent, by passage through the skin, but few studies have examined fractional absorption of cadmium in humans. In one study, rice was cultured in a nutrient solution containing cadmium-115

[compound unspecified] and then cooked and administered to a healthy male subject. Whole-body counting for three days and counting in faeces and urine suggested that 5% of the cadmium had been absorbed. When cadmium-115 was administered in an acid solution [presumably on an empty stomach], the absorption was almost 30% (Yamagata *et al.*, 1975). In another study, faecal elimination of cadmium-115 was detected up to 20–30 days after oral intake of the tracer as the chloride, probably reflecting sloughing of mucosal cells containing cadmium; the remaining whole-body retention averaged 4.6% (McLellan *et al.*, 1978). A higher absorption rate has been seen in women, in whom fractional absorption of ^{115}Cd-cadmium chloride was correlated inversely with serum ferritin concentration (Flanagan *et al.*, 1978).

The extent of deposition in the lungs depends on particle size and shape, ventilatory parameters and airway geometry. The fact that smokers have higher cadmium levels in the body shows that cadmium is absorbed in the lungs (see section 1.3.9). In a study of autopsy specimens, lower pulmonary concentrations of cadmium were observed in ex-smokers than in smokers. A half-time for pulmonary cadmium of 9.4 years was calculated from these data (Paäkkö *et al.*, 1989).

Low excretion rates of cadmium lead to efficient retention in the body. Analysis of cadmium in autopsied organs shows that most of the body burden is retained in the kidneys and liver. The biological half-time in kidneys was estimated to be 12–20 years (Elinder *et al.*, 1976; Tsuchiya *et al.*, 1976; Kjellström & Nordberg, 1978; Roels *et al.*, 1981; WHO, 1992b) and that in the liver somewhat shorter (Tsuchiya *et al.*, 1976; Kjellström & Nordberg, 1978). Neutron activation analysis has been used to determine cadmium concentrations in liver and kidney of cadmium-exposed workers *in vivo*. In workers without kidney dysfunction, the cadmium concentrations in the two organs correlated well, and both correlated well with urinary cadmium excretion (Roels *et al.*, 1981). As also reflected in other studies (Lauwerys *et al.*, 1980), urinary cadmium excretion can be regarded as a measure of the body burden of this metal in individuals with normal kidney function. In 64 active and retired smelter workers without kidney dysfunction, urinary excretion of metallothionein also correlated well with the cadmium burdens of liver and kidneys (Shaikh *et al.*, 1990). In workers with cadmium-induced kidney dysfunction, urinary cadmium excretion is higher, and kidney burdens tend to decrease relative to the concentrations in the liver (Roels *et al.*, 1981).

The concentration of cadmium in the blood depends mainly on recent absorption of the metal and tends to stabilize within a few months after a change in exposure (Lauwerys *et al.*, 1980). The concentrations of cadmium in blood were measured over more than 10 years in five workers in a copper–cadmium alloy factory who had had high exposures to cadmium in the past. The data fitted a two-compartment model, with a first mean half-time of 75–128 days and a second of 7.4–16 years. Two workers with proteinuria had shorter half-times than workers without kidney dysfunction (Järup *et al.*, 1983).

Urinary excretion of absorbed cadmium is the major route of elimination, but it is also excreted in the bile (Friberg *et al.*, 1986b). In an autopsy study of deceased smelter workers, increased lung concentrations of cadmium were found. High concentrations were related particularly to tobacco smoking (Gerhardsson *et al.*, 1986).

Cadmium concentrations in the prostate (50–500 ng/g wet weight) were < 1% of those found in the kidneys (8000–39 000 ng/g wet weight) in five men aged 61–76 years, but within

the prostate the concentrations varied considerably, with the highest concentrations at the base (Lindegaard *et al.*, 1990).

A placental barrier seems to exist: at delivery, cadmium concentrations in umbilical cord blood were about half of those occurring in maternal blood, and cadmium concentrations in human placenta reached a level about 10-fold higher than that seen in maternal blood (Hubermont *et al.*, 1978). Placental transfer was also demonstrated in more recent studies (Kuhnert *et al.*, 1982, 1987).

4.1.2 *Experimental systems*

In mice given ordinary food pellets, average fractional absorption of a single dose of cadmium chloride was 0.2% of non-toxic doses; five to eight times higher absorption rates were recorded in mice on a semisynthetic diet resembling human food (Andersen *et al.*, 1992).

In a study of male Wistar rats exposed by inhalation to cadmium aerosols (see pp. 164, 166–167), the cadmium concentrations in lung tissue homogenate and lung cytosol supernatant were about twice as high for cadmium oxide as for cadmium chloride, both at the end of the 30-day exposure period and two months later. Exposure to a cadmium sulfide aerosol (a combination of sulfide and sulfate) at a 10-fold higher level (1 mg/m^3) resulted in cytosol cadmium concentrations similar to those caused by administration of cadmium oxide at 0.1 mg/m^3. The amount of absorbed cadmium that was retained in the liver and kidneys was higher if delivered as cadmium oxide than if given as cadmium chloride at the same concentration (Glaser *et al.*, 1986).

In a study of Long–Evans and Fischer 344 rats exposed to aerosols of cadmium chloride, oxide dust and sulfide dust, pulmonary retention of cadmium chloride and sulfide (half-time, 85 days and 11–76 days, respectively) was similar, whereas that of cadmium oxide dust was somewhat longer (half-time, 217 days). In contrast, there was no transfer to the kidney or liver of cadmium administered as cadmium sulfide, but the levels in faeces were high. Monkeys (*Macaca fascicularis*) did not accumulate cadmium in the kidney after inhaling cadmium sulfide dust but did so after inhaling cadmium oxide (Oberdörster & Cox, 1989).

A low-molecular-weight protein, metallothionein, occurs mainly in liver and kidney and binds cadmium. Its synthesis is induced by cadmium and other divalent metals. Metallothionein-bound cadmium released from the liver is cleared by glomerular filtration and taken up by the renal tubules (Nordberg *et al.*, 1971; Nordberg, 1972). Metallothionein production in the intestinal mucosa was induced by oral administration of zinc to Wistar rats. Subsequent oral administration of cadmium increased the retention of cadmium in the kidneys but decreased retention in the liver in comparison with non-pretreated rats (Min *et al.*, 1991). Induced mallothionein production was not detectable in rat ventral prostate, and cadmium in these cells seems to bind to other (non-inducible) proteins. In male Wistar rats, subcutaneous injection of cadmium stimulated expression of the metallothionein-I gene in the liver and the dorsal prostate, while gene expression in the ventral prostate remained unchanged (Waalkes *et al.*, 1992a,b).

Zinc deficiency may affect tissue deposition of cadmium. In male Wistar rats given a diet low in zinc (7 ppm) for nine weeks with different levels of cadmium for the last six weeks, retention of cadmium was enhanced in liver, kidney and testis, with concomitant, marked

reductions in renal and testicular zinc concentrations. Zinc deficiency also decreased cadmium-induced metallothionein retention in the kidneys (Waalkes, 1986). After acute exposure to cadmium, low doses, which probably become bound to metallothionein, are retained mainly in the kidneys, while higher doses show a retention pattern that probably reflects saturation of metallothionein binding (Lehman & Klaassen, 1986).

Metallothionein-bound cadmium-109 given orally to male C57Bl/6J mice initially showed the same fractional absorption as cadmium chloride, but the relative retention in the kidney was greater (Cherian *et al.*, 1978). Kidney retention of cadmium-109 in male CF-1 mice was similar after oral intake of metallothionein-bound cadmium generated in different ways; heat-treatment of the material did not affect the retention pattern (Maitani *et al.*, 1984).

The reported half-times of cadmium in the body vary from weeks to two years (or as long as half the lifespan of the animal); the biological half-time of cadmium in the kidney and whole body decreases when renal tubular dysfunction has developed (WHO, 1992b).

After inhaling cadmium chloride aerosols at a concentration of 100 $\mu g/m^3$ for four weeks, male Fischer 344 rats showed no significant increase in the concentration of metallothionein in lung tissue; the concentration was increased in female BALB/c mice treated similarly. Metallothionein concentrations were higher, however, in lung cells obtained by bronchoalveolar lavage from the exposed rats than in those from the mice (Oberdörster *et al.*, 1993).

The rate of cadmium uptake in Chinese hamster V79 variant cells resistant to cadmium was about 10–15% of that seen in the parental line; however, metallothionein induction and the rate of glutathione synthesis after depletion were similar in the two cell types. Depletion of glutathione enhanced the sensitivity of wild-type cells to cadmium ion but had no effect on the resistant variant. Inhibition of protein synthesis by cycloheximide did not affect cadmium uptake, but blocking of sulfhydryl groups with *N*-ethylmaleimide suppressed cadmium uptake (Ochi, 1991).

Cadmium has been observed to cross the hamster placenta on day 8 but not on day 9 of gestation (Dencker, 1975). No cadmium was seen in rat fetuses after their dams had received an injection of a sub-embryolethal dose of cadmium chloride (40 μmol [7.3 mg]/kg) on day 12 of gestation (Saltzman *et al.*, 1989). Concentrations in rat fetuses after injection of a teratogenic dose of cadmium (1.25 mg/kg) to the dam on day 12 of gestation have been reported to be 1% of those in the placenta (Webb & Samarawickrama, 1981). Christley and Webster (1983) reported similar percentages of embryonic cadmium uptake when mice were injected with cadmium at 0.66, 40 or 2400 μg/kg as cadmium chloride on gestation day 9.

4.2 Toxic effects

4.2.1 *Humans*

A worker who inhaled high concentrations of cadmium fumes died five days later. Both lungs showed acute pneumonitis (Lucas *et al.*, 1980).

Long-term exposure to cadmium may result in kidney disease. Twenty-three workers with cadmium-induced kidney dysfunction were examined at various times after their

removal from exposure. Over a five-year period, a significant increase was noted in the concentrations of β_2-microglobulin and creatinine in serum, indicating considerable progression in kidney dysfunction despite cessation of exposure (Roels *at al.*, 1989). Similar progression was observed in a population residing in a cadmium-polluted community (Kido *et al.*, 1988). Cadmium-induced kidney dysfunction may, however, be reversible, depending on the severity of the damage (Kasuya *et al.*, 1986; Saito, 1987; WHO, 1992b). In Japan, ingestion of cadmium-contaminated rice resulted in a disease (*itai-itai* or 'ouch-ouch' disease) characterized by kidney damage (mainly in proximal tubuli but also in other parts of the nephron) and osteomalacia, which mainly affected women who had given birth to many children (Shigematsu *et al.*, 1982; Williams *et al.*, 1983; Kasuya *et al.*, 1992).

Ten patients with cadmium-induced kidney dysfunction had decreased serum concentrations of 24,25-dihydroxyvitamin D; the five patients with the most severe kidney dysfunction also had decreased concentrations of 1α,25-dihydroxyvitamin D, while serum 25-hydroxyvitamin D levels were similar to those seen in five controls (Nogawa *et al.*, 1990).

A group of 101 men who had worked for at least one year at a copper–cadmium alloy manufacturing company were examined for respiratory symptoms by questionnaire, lung function testing and chest X-ray and were compared with a control group matched for age, sex and employment status; the two groups contained a similar proportion of smokers. Individual exposure to cadmium was estimated from data on cumulative exposure or from activation analysis of liver cadmium concentrations *in vivo*. The forced expiratory volume in 1 sec (FEV_1) and carbon monoxide transfer (diffusion capacity) were significantly decreased in the cadmium-exposed workers; more frequent radiographic signs of emphysema were also recorded. The difference from the controls in carbon monoxide transfer coefficient increased linearly with increasing cumulative exposure; exposure of 2000 $\mu g/m^3$-years resulted in a decrement of 0.05–0.3 mmol/min × kPa × L (Davison *et al.*, 1988).

In a study of men employed in two Belgian zinc–cadmium plants, the concentration of cadmium in the liver increased with years of past exposure (range, 3–40 years). The concentration of cadmium in the renal cortex increased up to a level of about 250 ppm after 10–15 years of exposure and decreased with longer duration of exposure. Most of the men with more than 20 years' mean exposure, but none of the men with fewer than 10 years' mean exposure, had signs of renal dysfunction. These findings were interpreted as evidence of accumulation of cadmium in the liver and kidneys up to the onset of renal dysfunction, which is followed by a progressive loss of the cadmium in the kidneys (Roels *et al.*, 1981). Ellis *et al.* (1985), in a study of workers occupationally exposed to cadmium, reported that cumulative exposure concentrations higher than 400–500 $\mu g/m^3$-years (corresponding to about 40 ppm [mg/kg] in the liver) were associated with renal abnormalities.

Workers in the cadmium recovery plant studied by Thun *et al.* (1985) (described in detail on pp. 136 and 152–153) had slightly elevated mortality from nonmalignant respiratory disease (SMR, 1.54; 95% CI, 0.88–2.51). In the study of cadmium-exposed workers in 17 plants in the United Kingdom (Kazantzis & Blanks, 1992; see pp. 154–156), the rate of mortality from bronchitis was significantly increased in the cohort as a whole (SMR, 1.20; 95% CI, 1.03–1.39) and in the highly exposed group (SMR, 3.16; 1.68–5.40). In the whole cohort, the SMR for emphysema was elevated (1.37; 95% CI, 0.84–2.12), but that for nephritis and nephrosis was not (0.77; 95% CI, 0.45–1.23). Increased mortality from

nephritis and nephrosis was, however, reported among workers in a Swedish nickel–cadmium battery plant (SMR, 3.00; not significant) (Elinder *et al.*, 1985; see pp. 150–151).

Possible excess mortality due to diabetes and 'neuralgia' [not defined] was seen over periods of 6–30 years in Japanese communities with significant cadmium pollution (Shigematsu *et al.*, 1982). In another study, mortality was recorded for an average of 6.3 years for 185 Japanese individuals over 50 years of age who had increased excretion of retinol-binding protein, indicating kidney dysfunction due to environmental cadmium pollution. The mortality rate was compared with that of a group of 2229 individuals who had no sign of proteinuria. Of the 76 deaths that occurred in the group with kidney dysfunction, five were due to respiratory disease (as compared to 1.30 expected), four in men to nephritis and renal insufficiency (0.14 expected) and three in women to diabetes (0.50 expected). These excesses were significant (Nakagawa *et al.*, 1987).

In 12 women with *itai-itai* disease, immunoglobulin serum concentrations were normal and lymphocyte transformation and phytohaemagglutinin cytotoxicity responses *in vitro* were similar to those in a control group (Williams *et al.*, 1983).

4.2.2 *Experimental systems*

Acute exposure of rodents to cadmium produces hepatotoxicity (Dudley *et al.*, 1982), while chronic administration causes kidney damage. Cadmium-induced kidney dysfunction produced in experimental animals is very similar to the low-molecular proteinuria seen in cadmium workers. Histopathological examination of kidneys from horses and sea birds exposed environmentally to cadmium showed changes indicative of chronic interstitial nephritis (WHO, 1992a). In experimental animals, acute renal toxicity can be prevented by pretreatment with small doses of the metal (Nordberg *et al.*, 1975). After repeated exposures resulting in cadmium concentrations in the kidney cortex greater than about 200 mg/kg, rats tend to develop proteinuria (WHO, 1992b); subsequently, no further accumulation of cadmium occurs in the kidneys, presumably because of the increased urinary excretion of cadmium that occurs with the induced proteinuria (Axelsson & Piscator, 1966). Interspecies differences in the critical concentrations of cadmium in the kidney have been reported (Nomiyama & Nomiyama, 1984; WHO, 1992b).

Injection into male Wistar rats of metallothionein with the same amount of bound cadmium but different amounts of bound zinc showed that renal toxicity decreased with increasing amounts of zinc (Kojima *et al.*, 1991).

Inbred strains of mice show different susceptibility to cadmium-induced hepatotoxicity: C3H/He mice are sensitive, while DBA/2 mice are resistant; however, hepatic concentrations of metallothionein isoforms were similar in the two strains after injection of cadmium chloride. Susceptibiity is therefore not mediated by metallothionein (Kershaw & Klaassen, 1991).

In a carcinogenicity study (described in detail on pp. 164, 166–167), exposure (22 h per day for 6–18 months) to different cadmium compounds by inhalation increased mortality in Wistar rats in a dose-related fashion, mainly from pulmonary toxicity (Glaser *et al.*, 1990).

Alveolar hyperplasia and interstitial fibrosis were recorded in mice and golden hamsters exposed by inhalation to similar aerosols (Heinrich *et al.*, 1989; see pp. 163–164, 167). The

earliest effect of cadmium chloride and cadmium oxide aerosols seems to be type I cell necrosis, which is followed by an increase in the number of macrophages and proliferation of type II cells. Cadmium sulfide appears to be much less toxic (Oberdörster, 1989). Dose-dependent increases in the volume density of hyperplastic areas occurred in male hamsters exposed to cadmium oxide. The volume density of hyperplastic areas was also increased in males exposed to 90 $\mu g/m^3$ cadmium sulfide and in females exposed to 30 $\mu g/m^3$ cadmium sulfate (Aufderheide *et al.*, 1990).

Many studies have been carried out to elucidate the pathogenesis of *itai-itai* disease. In female rhesus monkeys given a diet low in vitamin D, calcium (0.3%), phosphorus (0.3%) and protein (14%) with a cadmium content of 3 mg/kg (as cadmium chloride) during the first 12 months, followed by 30 mg/kg, osteomalacia developed at 12 months and proteinuria was detected at 36 months (Kimura *et al.*, 1988). When cadmium is included in hydroxyapatite, the main calcium-containing mineral in bone, the solubility of the crystal is considerably decreased (Christoffersen *et al.*, 1988).

In female B6C3F1 mice given water containing 0, 10, 50 or 250 ppm (mg/L) cadmium chloride for 90 days, T- and B-lymphocyte proliferation was significantly reduced. Increased susceptibility to herpes 2 virus was also recorded (Thomas *et al.*, 1985). In SPF female rats of the Brown–Norway and Lewis strains given subcutaneous injections of 0.8 mg/kg bw cadmium chloride five times a week for 15 days, the amount of cadmium that reached the thymus was similar; however, only Brown–Norway rats had a significant decrease in S-phase thymocytes and increases in the number of thymus cells in G_2 phase and in mitosis (Morselt *et al.*, 1988).

At concentrations below 10 μmol/L [1 mg/L], cadmium selectively inhibited concanavalin A-induced T-cell proliferation but not bacterial lipopolysaccharide-induced B-cell proliferation of spleen cells from male BALB/c mice. The effect could be prevented by adding 30 μmol zinc to the culture medium, but the intracellular cadmium concentration and the cadmium-induced metallothionein level were not affected (Otsuka & Ohsawa, 1991).

Natural killer cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity of human peripheral blood lymphocytes *in vitro* were inhibited by cadmium concentrations of 1 μM [0.1 mg/L] and above. The inhibition of natural killer activity could be prevented partially by adding calcium or zinc to the culture medium, zinc being most effective (Cifone *et al.*, 1991).

4.3 Reproductive and developmental effects

In a review of occupational exposures and defects of the central nervous system, Roeleveld *et al.* (1990) noted that cadmium could induce malformations of the brain in experimental animals but that no data were available on the effects of prenatal or postnatal exposure to cadmium in humans.

4.3.1 *Humans*

In a study of 77 pregnant smokers and 125 nonsmokers who delivered infants in Cleveland Metropolitan General Hospital (USA), samples of blood were obtained from the mothers within 1 h of delivery and from the umbilical cord immediately after delivery;

placental samples were obtained immediately after delivery. Cadmium concentrations were determined in maternal whole blood, placenta and placental, maternal and cord-vein plasma; zinc was determined in maternal and cord-vein red blood cells. Smoking status was confirmed by measuring plasma thiocyanate. The potential confounding variables that were taken into account in the analysis included maternal age, gravidity, parity, gestational age, sex of offspring, race, maternal red blood cell count, maternal haemoglobin concentration, haematocrit and cord-vein haemoglobin concentration. The birth weights of the infants of smokers were significantly reduced (3143 g *versus* 3534 g), and maternal whole blood cadmium and thiocyanate concentrations were negatively related to birth weight. After the confounding variables had been controlled for, thiocyanate concentration explained 5.8% of the birth weight variance among the infants of smokers, maternal whole blood cadmium concentration explained 8.5%, and cord-vein red blood cell zinc concentration explained 1.7%. All of variables together explained more than 30% of the variance in birth weight (Kuhnert *et al.*, 1987). [The Working Group noted that it was not clear whether the differences in birth weight could be fully explained by differences in smoking, since smoking increases blood cadmium levels, and thiocyanate measurements are only qualitative measures of smoking.]

The relationship between placental cadmium concentration and the birth weight of the children of a population of nonsmoking women living near a lead smelter in former Yugoslavia was compared with that in a neighbouring town. There were 106 placentas from the smelter region and 55 from the control region. The analysis was adjusted for ethnicity, gender of children, maternal age, height, parity and education, mid-pregnancy blood lead levels and alcohol consumption. The average placental cadmium concentrations were 0.73 nmol [82 ng]/g dry weight in the exposed area and 0.50 nmol [56 ng]/g in the control area. There was no association between placental cadmium levels and either birth weight or gestational age (Loiacono *et al.*, 1992).

4.3.2 *Experimental systems*

The effects of cadmium and cadmium compounds on reproduction in experimental systems have been reviewed (Barlow & Sullivan, 1982; Carmichael *et al.*, 1982; Pařízek, 1983; Shepard, 1992).

Haemorrhagic necrosis of the ovaries was observed in Cr:RGH hamsters, in one strain of mice (DBA), but not in three others, and in immature Fischer 344/NCr and WF/NCr rats injected with 47.5 µmol/kg [8.7 mg/kg] cadmium chloride (Rehm & Waalkes, 1988). A single intraperitoneal injection of 2 mg/kg cadmium chloride to (101 × C3H)F_1 or (SEC × C57Bl)F_1 × X^{Gsy} female mice had no dominant lethal or other effect on fertility, except that it induced superovulation (Suter, 1975).

Dietary exposure to up to 10 (Lorke, 1978) or 68.8 ppm (Zenick *et al.*, 1982) cadmium chloride did not affect reproductive performance in male rats. Injection of cadmium chloride to adult male rats induced an acute vascular response in the testis, leading to oedema and, ultimately, necrosis of the seminiferous epithelium (Pařízek, 1960). Vas deferens sperm concentration, release of human chorionic gonadotropin-stimulated testosterone 14 days after exposure and testicular weight 60 days after exposure were found to be the most sensitive of a variety of reproductive parameters in exposed male rats. Younger (30- or

50-day-old) male rats were less sensitive than older (70-day-old) rats to the effects of cadmium (Laskey *et al.*, 1984, 1986). Rat Sertoli cells in culture were at least four times more sensitive to cadmium than interstitial (primarily Leydig) cells, suggesting a direct action of cadmium on cells in the seminiferous epithelium (Clough *et al.*, 1990). Laskey and Phelps (1991) also showed a direct effect on rat Leydig cell function following exposure *in vitro* to cadmium chloride.

Metallothionein was not induced by cadmium in rat, mouse or monkey testis or in hamster ovary (Ohta *et al.*, 1988; Waalkes & Perantoni, 1988; Waalkes *et al.*, 1988b,c,d), which may determine the susceptibility of these organs to cadmium (Waalkes & Goering, 1990). In contrast, Abel *et al.* (1991) demonstrated a cadmium-induced increase in metallothionein concentration in a murine Leydig cell line and in purified rat Leydig cells.

Female mice received cadmium in their diet for six consecutive 42-day rounds of pregnancy and lactation. Litter size at birth and pup growth were reduced at 50 but not at 25 ppm [mg/kg] (Whelton *et al.*, 1988). When male and female rats were gavaged with up to 10 mg/kg bw cadmium chloride per day for six weeks prior to mating and females during pregnancy, the high dose reduced the incidence of copulation and of pregnant females and the numbers of implants and live fetuses. Fetuses of dams given the high dose were anaemic. No effect on male fertility was reported (Sutou *et al.*, 1980a,b).

In multigeneration studies in rats in which cadmium was incorporated into the diet, offspring body weight was reduced at 100 ppm [mg/kg] (Lorke, 1978; Löser, 1980b) and the number of litters per female was reduced in a group receiving a diet containing 6.9 μg/kg bw more than the control levels of 4.4 μg/kg bw (Wills *et al.*, 1981). In a multigeneration study in which rats received up to 5 ppm (mg/L) cadmium in the drinking-water, reductions in male body weights (day 130), liver weights (1 ppm, days 50 and 130), epididymal sperm content (5 ppm, day 130), serum progesterone in term F_1 females (5 ppm), kidney weights in F_1 neonates (5 ppm) and F_2 litter weights [no data presented] were reported. A significant decrease in the incidence of preimplantation death was observed in the F_1 females given 5.0 ppm (Laskey *et al.*, 1980). Exposure of rats by inhalation to 100 μg/m^3 cadmium chloride (as an aerosol) for three generations increased lung weight in males and females of all three generations, increased leukocyte counts in males of the first two generations and in females of all three generations, increased proteinuria in males of the first and third generations and decreased body weight in males of the second and third generations and in females of the third generation. No effect on reproduction was reported (Weischer & Greve, 1979).

Pre- and postimplantation mouse and rat embryos cultured *in vitro* were severely affected by the presence of microgram per millilitre concentrations of cadmium chloride or sulfate (Schmid *et al.*, 1983; Warner *et al.*, 1984; Yu *et al.*, 1985; Abraham *et al.*, 1986; Yu & Chan, 1987; Naruse & Hayashi, 1989; Müller *et al.*, 1990).

Danielsson and Dencker (1984) found decreased vitamin B_{12} transport to the fetuses of mice within 1 h of injection of an embryolethal dose of cadmium chloride (4 mg/kg bw) on gestation day 16; lower doses did not affect fetal development, but vitamin B_{12} transport was reduced within 24 h of exposure to doses as low as 0.5 mg/kg. Transport of α-aminobutyric acid and deoxyglucose across the placenta were largely unaffected by the treatment. A teratogenic dose of cadmium (1.25 mg/kg bw) reduced thymidine incorporation into embryonic DNA at 4 h and leucine incorporation into embryonic protein at 20 h (Webb &

Samarawickrama, 1981). Injection of rats on gestation day 12 or 18 with 40 μM/kg [7.3 mg/kg] cadmium chloride reduced blood flow from the uterus to the chorioallantoic placenta beginning some time between 12 and 16 h after exposure (Levin & Miller, 1981; Levin *et al.*, 1987; Saltzman *et al.*, 1989).

Lobes of placentas from normal-term deliveries of nonsmoking women were dually perfused *in vitro* with cadmium at 0, 10, 20 or 100 nmol/ml [0–11 μg/ml] for up to 12 h. The synthesis and release of human chorionic gonadotropin was decreased by all concentrations of cadmium, beginning at 4 h, and necrosis of the fetal vasculature was seen 5–8 h after perfusion with the high dose. Zinc transfer to the fetal circuit was decreased by addition of 10 nmol/ml cadmium to the maternal perfusate (Wier *et al.*, 1990).

Exposure of QS/CH mice to 40 ppm (mg/L) cadmium in the drinking-water throughout gestation resulted in reduced maternal water intake and fetal growth retardation during gestation; the newborn mice were severely anaemic. Fetal body weights were reduced by concentrations of 10 ppm and above (Webster, 1978). No effect on fetal viability, weight or morphology was reported in a study in which albino rats received 100 ppm (mg/L) cadmium as cadmium acetate in the drinking-water throughout gestation (Saxena *et al.*, 1986). Fetal growth retardation was observed in the offspring of Sprague–Dawley rats receiving 50 or 100 ppm (mg/L) cadmium as cadmium chloride in the drinking-water from day 6 to 20 of pregnancy; no effect was seen with 5 ppm. The higher doses also reduced the average daily body weight gain of dams; after adjustment for maternal weight at day 20, fetal weight deficit was seen only at 50 ppm. No gross defect was noted (Sorell & Graziano, 1990). Exposure of Wistar rats by inhalation to 0.2–0.6 mg/m^3 cadmium (median aerodynamic diameter, 0.6 μm) throughout gestation decreased maternal weight gain and increased lung weight. The fetuses of dam given the high dose were retarded in growth, and both high- and low-dose groups had nonsignificant decreases in haematocrit (Prigge, 1978). No effect on fetal development was reported following dietary exposure of Long–Evans rats to up to 100 ppm (mg/kg in diet) on days 6–15 of gestation (Machemer & Lorke, 1981). Exposure of rats during gestation by oral gavage to doses of 40 mg/kg bw per day and above was severely toxic to the dams; doses as low as 2 mg/kg per day had some maternal effects (Machemer & Lorke, 1981; Barański *et al.*, 1982). Reductions in fetal body weight were seen in Wistar rats with doses as low as 8 mg/kg per day (Barański *et al.*, 1982) and in Long–Evans rats at 30 mg/kg per day (Machemer & Lorke, 1981). Fetal hydropericardium was seen with 4 mg/kg per day and above (Barański *et al.*, 1982), and at 30 mg/kg per day a variety of fetal defects (e.g. dysplasia of the facial bones and of the rear limbs, oedema, cleft palate) were observed in rats (Machemer & Lorke, 1981).

Parenteral administration of < 10 mg/kg of cadmium salts on single days during pregnancy induced a wide range of malformations (e.g. craniofacial, eyes, limbs) in hamsters (Gale, 1979), mice (Layton & Layton, 1979; Webster & Messerle, 1980; Murdoch & Cowen, 1981; Messerle & Webster, 1982; Feuston & Scott, 1985; Naruse & Hayashi, 1989; De *et al.*, 1990; Padmanabhan & Hameed, 1990) and rats (Parzyck *et al.*, 1978; Samarawickrama & Webb, 1979, 1981; Holt & Webb, 1987). Direct injection of cadmium into rat fetuses late in gestation resulted in lower fetal mortality than was expected from the body burden (Levin & Miller, 1980). Daston and coworkers (Daston & Grabowski, 1979; Daston, 1981a,b, 1982) demonstrated selective retardation in morphological and biochemical maturation of fetal rat

lung at doses of cadmium chloride as low as 2 mg/kg per day injected intraperitoneally on days 12–15 of gestation. Respiratory distress was seen in the offspring at birth.

The postnatal consequences of exposure to cadmium *in utero* have been studied by several investigators. Barański *et al.* (1983) reported no effect on postnatal growth of rats following exposure of dams to up to 4 mg/kg per day by oral gavage beginning five weeks prior to and during gestation, but they observed reduced exploratory locomotor activity in females at two months of age after exposure of dams to doses as low as 0.04 mg/kg per day. Ali *et al.* (1986) followed the offspring of rats that had received cadmium in the drinking-water (4.2 or 8.4 μg/ml) during gestation and found impaired postnatal growth, delayed development of cliff avoidance and swimming behaviour, elevated locomotor activity on postnatal days 14 and 21 and reduced locomotor activity on postnatal day 60. Lehotzky *et al.* (1990) injected rats subcutaneously with cadmium chloride at 0.2, 0.62 or 2 mg/kg bw per day on days 7–15 of gestation and found reduced litter size at birth but no effect on growth. Horizontal motor activity was decreased on day 38, among offspring of dams given 0.62 or 2 mg/kg and in all groups on day 90. Saillenfait *et al.* (1991) examined renal function in the offspring of rats exposed to up to 2.5 mg/kg bw cadmium chloride by intraperitoneal injection on days 8, 10, 12 and 14 of gestation. Indications of compromised renal function were observed in offspring of each sex on postnatal day 3 and in male offspring on postnatal day 49 but not on postnatal day 12.

4.4 Genetic and related effects (see also Table 14, pp. 195 *et seq.* and Appendices 1 and 2)

4.4.1 *Humans*

The genetic effects of cadmium and cadmium compounds in exposed humans have been reviewed (Vainio & Sorsa, 1981; Fleig *et al.*, 1983; Bernard & Lauwerys, 1986).

(*a*) *Itai-itai* patients

Twelve female *itai-itai* patients had markedly higher incidences of chromosomal aberrations of all types in peripheral blood lymphocytes than a group of nine age-matched control subjects (six females and three males [no further detail provided]). The patients were women aged 52–72 years who had been living in cadmium-polluted areas of Japan for more than 30 years and had been exposed to cadmium in the diet (water, rice, fish). Eight of the patients were sampled two to three times at three-month intervals. All types of chromatid and chromosomal aberrations were observed in the exposed women; the mean frequency of cells with any abnormality was 26.7% (range, 8.9–51.2%) in the exposed and 2.6 (range, 1.5–3.8%) in controls. The incidence of aneuploidy was four times or more that of the control group [smoking habits were not described] (Shiraishi, 1975).

In contrast, Bui *et al.* (1975) found no significant difference in the frequencies of cells with structural aberrations in cultures from blood of four female *itai-itai* patients and from four controls (three females, one male) living in an area of Japan known not to be cadmium-polluted; both had high frequencies of structural aberrations: 6.6 and 6.0%, respectively. The average age of the patients was 65 and that of controls, 75 years; blood cadmium levels ranged from 16 to 29 ng/g whole blood in exposed and 4.4–6.1 ng/g in controls. The samples were assayed in Sweden 96 h after sampling. The subjects were not

suffering from viral diseases and had not been exposed to X-rays or cytostatic drugs. [The Working Group noted the long delay between sampling and culturing. Two of six samples were haemolysed and therefore discarded.]

(*b*) *Environmental and dietary exposure*

Nogawa *et al.* (1986) examined the frequency of sister chromatid exchange in peripheral lymphocytes from two groups of Japanese men and women. Group 1 (eight men and 16 women) lived in the cadmium-polluted Kakehashi river basin in Ishikawa Prefecture and had been diagnosed as having cadmium-induced renal damage. The comparison group 2 (two men and four women) came from Uchinada-machi, which was not contaminated by cadmium. The mean age was 76.6 years in group 1 and 68.3 years in group 2. The men, but not the women, in both groups had smoked tobacco. None of the subjects had used any known clastogenic drug or had undergone radiotherapy, and none had clinical evidence of viral infection at the time of examination. The mean cadmium concentrations in whole blood from men and women were 9.6 ± 5.8 (μg/L) in group 1 and not detectable in group 2; the mean concentrations in urine were 9.1 μg/g creatinine in group 1 and 2.7 μg/g creatinine in group 2. No difference was seen between the groups in the number of sister chromatid exchanges per cell: group 1, 8.0 ± 0.94; group 2, 9.0 ± 3.13.

Tang *et al.* (1990) investigated the frequency of chromosomal aberrations in a cadmium-polluted region of China. Twenty-one men (urinary cadmium concentration, 3.32 ± 1.46 μg/L) and 19 women (urinary cadmium, 3.83 ± 1.82 μg/L) living at Suichang in Zhejiang Province (soil cadmium, 1.103 ppm) for 11–62 years were compared with nine men (urinary cadmium, 2.34 ± 1.59 μg/L) and two women (urinary cadmium, 1.85 ± 0.65 μg/L) from an unpolluted region in the same general area (soil cadmium, 0.20 ppm). None of the subjects had been exposed to chromosome damaging drugs or radiotherapy and did not have viral infections. The frequency of abnormal cells, including structural aberrations, aneuploidy and endoreduplication, was not significantly different in the exposed group (5.80 ± 3.44) than in the controls (2.80 ± 1.99). (Statistical analysis using transformed data gave $p < 0.01$.) More individuals in the cadmium-polluted group (63.5%) had a high aberration prevalence (> 5%) than in controls (18.2%), and more severe structural aberrations, such as dicentrics, translocations and multiradials, were observed in the exposed group. A significant dose–effect relationship between urinary cadmium content and chromosomal aberration frequency was observed (linear regression equation given). Most men in the region were smokers, while none of the women smoked; no effect of smoking was observed.

(*c*) *Occupational exposure*

Deknudt and Léonard (1975) examined chromosomal aberrations in peripheral lymphocytes from three groups of workers in a cadmium plant: group 1, 23 cadmium workers with an average exposure of 12 years; group 2, 12 rolling-mill workers with an average exposure of 11 years; group 3, 12 controls (administrative department in the same plant). The materials to which exposure was considered to be relevant were: group 1, lead (60% w/w) and cadmium (10% w/w) in the absence of zinc; and group 2, mostly zinc but also low levels of lead (max. 4% w/w) and cadmium (max. 1% w/w). Both lead and cadmium concentrations in blood were measured in groups 1 and 2 at the time of sampling for cytogenetic analysis; the

mean concentrations (in μg/L) were: group 1—lead, 446 ± 122.9; cadmium, 31.7 ± 33.11; group 2—lead, 208 ± 44.3; cadmium, 6.3 ± 5.51. Much of the variation in the concentration of cadmium of group 1 was due to a single individual who had 179 μg/L blood. [The Working Group noted that neither lead nor cadmium concentrations were measured in the blood of controls.] The proportions of cells (per 100 examined) with structural abnormalities were: group 1, 2.00; group 2, 3.96; and group 3, 3.04. The numbers of chromatid exchanges and chromosomal translocations, rings or dicentrics per 100 cells were: group 1, 0.89; group 2, 0.54; and group 3, 0.13. The exposed groups thus showed no increase in total aberrations but had a significantly increased frequency of more severe aberrations; however, the individual with a very high blood cadmium level had no aberration or gap. Seven workers in group 1 who had previously been employed in coal mines for 2.5–13 years had a mean rate of severe aberrations of [1.36/100 cells], compared with [0.69/100 cells] in the remainder of the group. [This effect was, however, due almost entirely to the rate of a single individual.] [The Working Group noted the absence of any record of other relevant exposures, such as tobacco smoking, viruses, X-rays and medicaments.]

Bui *et al.* (1975) examined chromosomal aberrations in peripheral lymphocytes from five men who had been employed in the electrode department of an alkaline battery factory for 5–24 years. The average cadmium concentration in the general air of the department during 1969–72 was 35 μg/m^3, and about twice this value was estimated in personal air samples. The control group consisted of three male office workers of about the same age as the exposed workers and from the same factory. Cadmium concentrations were measured in urine and blood [but it is not clear whether this was done at the same time as blood sampling for chromosomal analysis]. The subjects were not known to be suffering from viral disease and had not been exposed to X-rays or known clastogenic drugs. The mean cadmium concentrations in whole blood were 37.7 ± 15.5 ng/g in the exposed and 2.3 ± 0.9 ng/g in the controls; the concentrations in urine were 11.5 ± 11.5 μg/g creatinine in exposed and 2.5 ± 1.3 μg/g creatinine in controls. Lymphocytes were examined after culture times of both 48 h and 72 h: At neither time was there an increase in the frequency of cells with either structural chromosomal aberrations or numerical changes in the exposed group when compared with the control group.

Chromosomal aberrations were studied in peripheral lymphocytes from 24 male workers at a zinc smelting plant who had spent 3–6.5 years in zinc electrolysis, where they were exposed to fumes and dust containing zinc, lead and cadmium (Bauchinger *et al.*, 1976). The exposed workers had a mean lead blood concentration of 192.9 ± 66.2 μg/L and a cadmium concentration of 3.95 ± 2.68 μg/L but had no clinical sign of metal toxicity and had had no previous exposure to cytostatic drugs or X-irradiation. Fifteen (11 men, 4 women) unexposed healthy members of the general population not exposed to these metals were used as controls; the blood levels of lead and cadmium in this group were not measured but were assumed to be the average for industrial workers—120–130 μg/L lead and 1.5 μg/L cadmium. The numbers of cells with structural aberrations was significantly increased in the exposed group ($p < 0.001$, Mann–Whitney rank test). The percentages of cells with structural aberrations were 1.35 ± 0.99 (0.018 ± 0.015 assigned breaks/cell) for exposed workers and 0.47 ± 0.92 (0.0053 ± 0.011 assigned breaks/cell) for the controls.

No significant difference in chromosomal or chromatid aberration frequency was observed between 40 workers in a cadmium pigment plant (blood cadmium, 19.5 μg/L; range, < 2–140 μg/L) and 13 administrative and laboratory personnel at the same plant, used as controls (blood cadmium, < 2–29 μg/L), although four cells (out of 3740) with chromatid interchanges were observed in the exposed group only. No correlation was found between extent of damage and exposure levels or duration [data not shown]. Exposures ranged from six weeks to 34 years, and workers had not previously been exposed to chromosome damaging drugs or radiation (O'Riordan *et al.*, 1978).

Fleig *et al.* (1983) also found no significant difference in the incidence of chromosomal aberrations (chromosome and chromatid type) in 14 workers exposed to cadmium-containing dusts for 6–25 years in cadmium pigment and stabilizer production plants (1.5% of cells with structural aberrations) when compared with 14 age-matched office workers (1.3% of cells with structural aberrations). The concentrations of cadmium in the blood of the workers (14–38 μg/L) were measured three years before the study; the levels for controls were not stated. The exposed workers had not been exposed to chromosome damaging drugs or radiotherapy.

Dziekanowska (1981) reported small increases in the incidence of chromosomal aberrations (8.91 ± 4.99), especially structural rearrangements (dicentrics, translocations), and disturbance of spiralization in 11 cadmium-exposed workers compared with 32 healthy non-smelter controls (6.66 ± 2.38). No difference was found in the frequency of sister chromatid exchange (cadmium-exposed group, 15.14 ± 4.7; controls, 16.9 ± 5.82). [The Working Group noted the high control value for sister chromatid exchange. It is not clear whether smoking habits were considered.]

The rates of abnormal metaphases (excluding gaps) were significantly higher in peripheral blood lymphocytes of a group of 40 male workers (10 nonsmokers, 24 smokers, 6 ex-smokers) exposed to fumes and dusts in the production of cadmium, zinc, copper and silver alloys in a single factory (2.6%) than in controls matched for age and smoking habits (1.7%, $p < 0.05$), whereas the total rates of abnormal metaphases did not differ between the two groups. Chromosome-type aberrations accounted for most of the observed increase. The mean cadmium concentration in blood, measured at the time of cytogenetic assay, was 5.10 ± 5.15 μg/L (range, 0.3–28.3), and the urinary concentration was 10.63 ± 7.99 μg/L (range, 1.5–31.6) in workers; levels for controls were not stated. When a cumulative exposure index was calculated for each subject (mean yearly atmospheric cadmium concentration × years of exposure), only high-intensity, long-term exposure was associated with a significant increase in the frequency of chromosome-type aberrations: Six of seven complex aberrations (dicentrics and rings) observed were found in the eight subjects of this group. The workers had not been exposed to radiation therapy, treatment with cytotoxic drugs, recent viral diseases or occupational exposure to known clastogens (Forni *et al.*, 1990). [The Working Group noted that neither the exposure levels nor the blood and urine concentrations of other metals were measured.]

4.4.2 *Experimental systems*

The genetic effects of cadmium compounds in experimental systems have been reviewed (Degraeve, 1981; Hansen & Stern, 1984; Sunderman, 1984; Baker, 1985; IARC, 1987b;

Swierenga *et al.*, 1987), as have the mechanistic aspects of the effects (Léonard, 1988; Magos, 1991; Snow, 1992; Rossman *et al.*, 1992).

Most experimental systems have been used to study cadmium chloride. Some data are also available on cadmium acetate, cadmium oxide, cadmium sulfate, cadmium nitrate and cadmium sulfide, and the genetic and related effects of those compounds are listed separately in Table 14. The results are summarized here according to the solubility of the compounds in water, before they are added to biological media. Thus, cadmium sulfide, oxide and carbonate are very poorly soluble, while all of the other cadmium compounds are water-soluble at all concentrations tested. Water solubility does not, however, necessarily reflect solubility *in vivo*.

(*a*) *Cadmium compounds readily soluble in water (acetate, chloride, nitrate, sulfate)*

Cadmium chloride induced DNA strand breaks but not prophage in bacteria. Both cadmium chloride and cadmium sulfate, but not cadmium nitrate, induced differential toxicity in *Bacillus subtilis* and *Escherichia coli* strains. The compounds did not induce bacterial mutation reliably; precipitation in the bacterial media may have affected bio-availability. A few positive responses were reported with cadmium chloride and sulfate tested in *Salmonella typhimurium* strains (particularly TA102) and with cadmium nitrate in *E. coli* DG1153.

Cadmium chloride and cadmium sulfate induced gene conversion in *Saccharomyces cerevisiae*, but cadmium chloride did not induce reverse mutation in *S. cerevisiae* or aneuploidy in either *S. cerevisiae* or *Aspergillus nidulans*.

Cadmium chloride induced micronuclei in *Vicia faba* and water hyacinth and aneuploidy in Chinese spring wheat.

Cadmium chloride and cadmium nitrate did not induce mutation in *Drosophila melanogaster*, and cadmium chloride did not induce aneuploidy in one study but did in another, more sensitive assay.

Cadmium acetate and cadmium chloride induced DNA strand breaks in several cultured, non-human mammalian cell lines. Cadmium sulfate induced DNA strand breaks in primary cultures of rat hepatocytes, and cadmium chloride and cadmium nitrate induced unscheduled DNA synthesis in the same type of cell. Cadmium chloride did not induce DNA strand breaks in primary cultures of rat Leydig cells, which are an important target *in vivo* (see section 4.2).

Cadmium chloride and cadmium sulfate are mutagenic to cultured, non-human mammalian cells. The mutagenic activity of the chloride salt has been demonstrated at the *hprt* locus in Chinese hamster V79 cells and at the *tk* locus in mouse lymphoma L5178Y cells.

In non-human mammalian cells *in vitro*, cadmium chloride induced a dose-dependent increase in sister chromatid exchange frequency in one study but not in two others, in which only single doses were used; in one of the two studies, neither cadmium acetate nor cadmium nitrate induced sister chromatid exchange. A much higher degree of reproducibility has been observed in the induction of chromosomal aberrations by cadmium chloride and cadmium sulfate and in the induction of cell transformation by cadmium acetate and cadmium chloride. The chloride also induced aneuploidy in some cultured cells.

In cultured human cells, cadmium acetate and cadmium chloride induced DNA strand breaks, but cadmium chloride did not induce chromosomal aberrations. Cadmium acetate was reported to have induced aberrations in one study at very high doses. In the only pertinent study in which a human cell line was used, cadmium chloride induced aneuploidy, as demonstrated by the presence of centromeres in micronuclei. Cadmium chloride, but not cadmium sulfate, induced sister chromatid exchange in human lymphocytes.

Conflicting results have been reported for the genetic effects of cadmium chloride in mice: micronuclei and chromosomal aberrations have been observed in bone-marrow cells in several studies but not in others. Cadmium chloride did not induce aneuploidy in bone-marrow cells or spermatocytes of mice treated *in vivo*, but it induced aneuploidy in oocytes of Syrian hamsters and, in two of three studies, of mice. Cadmium chloride did not induce dominant lethal mutation in male rodents in five of six studies with mice or in a single study with rats and did not induce germ-line cell translocations in mice, either cytologically or in breeding experiments. Cadmium chloride induced morphologically abnormal sperm in mice in three of four studies. The discrepancies in the results of the different studies do not appear to be due to dose levels or frequency or route of treatment.

(*b*) *Cadmium compounds sparingly soluble in water*

Cadmium oxide [particle size not given] did not induce mutation in *S. typhimurium*, and cadmium carbonate [particle size not given] did not induce micronuclei in cells of *Vicia faba*.

Only cadmium sulfide, which exists in crystalline and amorphous forms, has been tested in cultured mammalian cells. Crystalline cadmium sulfide induced DNA strand breaks [particle size not given] and cell transformation [particle size, 0.64 μm], whereas amorphous cadmium sulfide [particle size, 0.64 μm] did not induce cell transformation. Cadmium sulfide [form unspecified] induced chromosomal aberrations in cultured human lymphocytes.

Considerations with regard to genotoxic mechanisms

As metal ions may be precipitated as their insoluble phosphates by *ortho*-phosphate ions in normal bacteriological culture medium and may not be detected as mutagens, modified media were used in some studies (e.g. Pagano & Zeiger, 1992). Ochi *et al.* (1984) reported a higher chromosomal aberration incidence after treatment in saline than in serum-containing medium, and that a post-treatment recovery period of Chinese hamster cells, which allows DNA synthesis to resume, was needed for efficient detection of cadmium-induced chromosomal aberrations.

Cadmium compounds are very toxic *in vitro*. In a screening study for cytotoxicity in BALB/c 3T3 cells, cadmium ranked second only to methylmercury in toxic potency (Borenfreund & Babich, 1987). Prostatic fibroblasts were more sensitive to cadmium toxicity than prostatic epithelial cells from the same species (Terracio & Nachtigal, 1986).

It was reported in many studies that exposure to cadmium induced DNA strand breaks (see Table 14). Ochi and Ohsawa (1983) reported single-strand breaks and, possibly, DNA–protein cross-links in Chinese hamster cells. *In vitro*, cadmium–metallothionein, but not cadmium alone, caused DNA strand breaks (Müller *et al.*, 1991). [The Working Group noted that the significance of this observation for the cell is questionable, since zinc

pretreatment (which causes induction of metallothionein) resulted in a reduction of cadmium toxicity and DNA strand breaks (Coogan *et al.*, 1992).]

The frequencies of cadmium-induced DNA strand breaks and chromosomal aberrations are reduced in cells treated with antioxidants, suggesting a relationship between single-strand breaks and active oxygen species. Various scavengers of active oxygen species were assayed for their ability to block chromosomal aberrations induced by cadmium chloride; no effect was seen with superoxide dismutase or dimethylfuran (a scavenger of singlet oxygen), but catalase blocked the induction of aberrations in a dose-dependent manner. D-Mannitol, a scavenger of hydroxyl radicals, also blocked aberration induction, as did the antioxidant butylated hydroxytoluene (a diffusible radical scavenger) (see IARC, 1986b). These results suggest that cadmium chloride is genotoxic by producing hydrogen peroxide, which can form hydroxyl radicals in the presence of iron or copper ions (Rossman *et al.*, 1992). Cadmium chloride treatment also reduced the cellular glutathione level (Ochi *et al.*, 1983; Ochi & Ohsawa, 1985; Ochi *et al.*, 1987; Snyder, 1988). Selenium may also inhibit the clastogenic effects of cadmium in mouse bone marrow, but the interaction, if confirmed, appears to be complex (Mukherjee *et al.*, 1988a). [The Working Group considered this an interesting observation, which could contribute to an understanding of the difficulty in reproducing the genetic effects of cadmium compounds *in vivo*, since selenium levels in rodent diets differ with time and place.]

Various studies have shown that cadmium compounds synergistically increase the effects of other chemicals. For example, cadmium increased the induction of micronuclei by NDMA in mice (Watanabe *et al.*, 1982), enhanced ultraviolet-induced mutagenesis in V79 Chinese hamster cells (Hartwig & Beyersmann, 1989), but not in *E. coli* (Rossman & Molina, 1986), enhanced meiotic nondisjunction induced by γ-irradiation in *Drosophila* oocytes (Kogan *et al.*, 1978) and enhanced benzo[*a*]pyrene-induced transformation of Syrian hamster embryo cells (Rivedal & Sanner, 1981). Inhibition of DNA repair by cadmium has been suggested as a mechanism for these interactions (e.g. Zasukhina & Sinelschikova, 1976). Cadmium inhibits human DNA polymerase β (a polymerase implicated in DNA replication) (Popenoe & Schmaeler, 1979) and O^6-methylguanine-DNA methyl transferase (Bhattacharyya *et al.*, 1988). Other effects on DNA repair have been reviewed (Rossman *et al.*, 1992).

Cadmium ion induces a number of genes in animal cells. Doses of 5–10 μM [917–1834 μg] cadmium chloride induced transient accumulation of c-*jun* and c-*myc* mRNA 2–4 h after treatment of L6J1 rat myoblasts (Jin & Ringertz, 1990). Cadmium chloride inhibited differentiation of *Drosophila* embryonic cultures, while inducing the entire set of heat-shock proteins (Bournias-Vardiabasis *et al.*, 1990). It also induced haem oxygenase in human skin fibroblasts (Keyse & Tyrrell, 1989) and rat small intestinal epithelium (Rosenberg & Kappas, 1991) and metallothionein in Leydig cells (Abel *et al.*, 1991). The induction of hepatocytic transdifferentiation by cadmium in rat pancreas (Konishi *et al.*, 1990) and characteristics of the granulocyte phenotype in promyelocytic leukaemic cells (Richards *et al.*, 1988) also suggest that it can modify gene expression.

Various researchers have reported that cadmium affects the spindle apparatus (possibly through interactions with thiol compounds, which have a high affinity for cadmium ion [$pK_d \sim 17$] [Verbost *et al.*, 1989]). Kogan *et al.* (1978) and Ramel and Magnusson (1979)

Table 14. Genetic and related effects of cadmium and cadmium compounds

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
***Itai-itai* patients**				
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		0.029 (blood, max.) 0.031 (per g urinary creatinine, max.)	Bui *et al.* (1975)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		NR	Shiraishi (1975)
AVH, Aneuploidy, human lymphocytes *in vivo*	+		NR	Shiraishi (1975)
Environmental/dietary exposure				
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		0.01 (blood) 0.01 (per g urinary creatinine)	Nogawa *et al.* (1986)
SLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		NR 0.003 (urine, men) 0.004 (urine, women)	Tang *et al.* (1990)
Occupational exposure				
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		NR	Dziekanowska (1981)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	?[b]		0.032 (blood)	Deknudt & Léonard (1975)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		0.061 (blood) 0.031 (per g urinary creatinine, max.)	Bui *et al.* (1975)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	(+)[b]		0.004 (blood)	Bauchinger *et al.* (1976)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		0.020 (blood)	O'Riordan *et al.* (1978)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	(+)		NR	Dziekanowska (1980)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		0.038 (blood)	Fleig *et al.* (1983)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		0.0003–0.0283 (blood) 0.0015–0.0316 (urine)	Forni *et al.* (1990)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium acetate				
DIA, DNA strand breaks, cross-links, hamster fibroblasts *in vitro*	+	0	0.11	Casto (1983)
SIC, Sister chromatid exchange, Chinese hamster DON cells *in vitro*	–	0	0.13	Ohno *et al.* (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*	+	0	0.04	DiPaolo & Casto (1979)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*	(+)	0	0.21	Rivedal & Sanner (1981)
T7S, Cell transformation, SA7/Syrian hamster embryo cells *in vitro*	+	0	0.11	Casto *et al.* (1979)
DIH, DNA strand breaks, cross-links, human cells *in vitro*	+	0	21	Casto (1983)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	(+)	0	11.2	Gasiorek & Bauchinger (1981)
Cadmium chloride				
PRB, λ Prophage induction/SOS/strand breaks/cross-links	–	0	7.2	Rossman *et al.* (1984)
ECB, *Escherichia coli*, DNA strand breaks	+	0	0.34	Mitra & Bernstein (1978)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	280	Nishioka (1975)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	28	Kanematsu *et al.* (1980)
ERD, *Escherichia coli* differential toxicity	+	+	60	De Flora *et al.* (1984a)
SAF, *Salmonella typhimurium* TA1537, forward mutation to 8-azaguanine resistance	+	0	56	Mandel & Ryser (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	150	Bruce & Heddle (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	1120	Tso & Fung (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	56	Mandel & Ryser (1984)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	610	Mortelmans *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA2, *Salmonella typhimurium* TA102, reverse mutation	(+)	(+)	8	De Flora *et al.* (1984b)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	56	Mandel & Ryser (1984)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	610	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	150	Bruce & Heddle (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	0	56	Mandel & Ryser (1984)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	610	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	150	Bruce & Heddle (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	610	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	NR	De Flora *et al.* (1984b)
SAS, *Salmonella typhimurium* TA1975, reverse mutation	(+)	–	56	Mandel & Ryser (1984)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–[c]	0	22.4	Pagano & Zeiger (1992)
SCG, *Saccharomyces cerevisiae*, gene conversion	+	0	11.2	Fukunaga *et al.* (1982)
SCG, *Saccharomyces cerevisiae*, gene conversion	+	0	61	Schiestl *et al.* (1989)
SCR, *Saccharomyces cerevisiae*, reverse mutation	–	0	34	Fukunaga *et al.* (1982)
SCN, *Saccharomyces cerevisiae*, aneuploidy	–	0	50	Whittaker *et al.* (1989)
SCN, *Saccharomyces cerevisiae*, aneuploidy	–	0	9	Albertini (1990)
ANN, *Aspergillus nidulans*, aneuploidy	–	0	610	Crebelli *et al.* (1991)
PLI, *Vicia faba*, micronuclei	+	0	45	De Marco *et al.* (1988)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
PLI, Water hyacinth root tips, micronuclei	+	0	0.006	Rosas *et al.* (1984)
PLN, Chinese spring wheat, aneuploidy	+	0	0.61	Sandhu *et al.* (1991)
DMM, *Drosophila melanogaster*, somatic mutation or recombination	-		240	Rasmuson (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	-		30	Inoue & Watanabe (1978)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	-		112	Kogan *et al.* (1978)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	-		30	Chung & Kim (1982)
DMN, *Drosophila melanogaster*, aneuploidy	-		38	Ramel & Magnusson (1979)
DMN, *Drosophila melanogaster*, aneuploidy	+		12	Osgood *et al.* (1991)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	0	11	Robison *et al.* (1982)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	-	0	112	Hamilton-Koch *et al.* (1986)
DIA, DNA strand breaks, cross-links, Chinese hamster V79 cells *in vitro*	+	0	2.24	Ochi & Ohsawa (1983)
DIA, DNA strand breaks, TRL-1215 rat liver cells *in vitro*	+	0	56	Coogan *et al.* (1992)
DIA, DNA strand breaks, rat primary Leydig cells *in vitro*	-	0	45	Koizumi *et al.* (1992)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus, *in vitro*	+	0	0.11	Ochi & Ohsawa (1983)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus, *in vitro*	(+)	0	0.22	Hartwig & Beyersmann (1989)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus, *in vitro*	+	0	0.001	Kanematsu *et al.* (1990)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus, *in vitro*	(+)	0	0.07	Amacher & Paillet (1980)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus, *in vitro*	+	0	0.09	McGregor *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	-	0	0.045	Deaven & Campbell (1980)
SIC, Sister chromatid exchange, Don Chinese hamster cells *in vitro*	-	0	0.11	Ohno *et al.* (1982)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	0	0.001	Howard *et al.* (1991)
MIA, Micronucleus test (aneuploidy), Chinese hamster lung Cl-1 cells	+	0	1.22	Antoccia *et al.* (1991)
CIC, Chromosomal aberrations, Chinese hamster V79 cells *in vitro*	+	0	0.11	Deaven & Campbell (1980)
CIC, Chromosomal aberrations and polyploidy, Chinese hamster V79 cells *in vitro*	+	0	0.11	Ochi *et al.* (1984)
CIC, Chromosomal aberrations, Chinese hamster V79 cells *in vitro*	+	0	1.12	Ochi & Ohsawa (1985)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.06	Lakkad *et al.* (1986)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.01	Howard *et al.* (1991)
CIT, Chromosomal aberrations, mouse mammary carcinoma cells *in vitro*	-	0	3.58	Umeda & Nishimura (1979)
TBM, Cell transformation, BALB/c 3T3 mouse cells *in vitro*	+	0	0.17	Saffiotti & Bertolero (1989)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
TCL, Cell transformation, rat ventral prostate cells *in vitro*	+	0	0.003 × 7 days	Terracio & Nachtigal (1986)
TCL, Cell transformation, Indian muntjac skin fibroblasts *in vitro*	+	0	0.56 × 20 months	Chibber & Ord (1990)
T7S, Cell transformation, SA7/Syrian hamster embryo cells *in vitro*	+	0	0.22	Casto *et al.* (1979)
DIH, DNA strand breaks, human lymphocytes *in vitro*	+	0	2.8	Zasukhina & Sinelschikova (1976)
DIH, DNA strand breaks, human lymphocytes *in vitro*	–	0	5.6	McLean *et al.* (1982)
DIH, DNA strand breaks, human diploid (HSBP) fibroblasts *in vitro*	+	0	14	Hamilton-Koch *et al.* (1986)
DIH, DNA strand breaks, human diploid (HSBP) fibroblasts *in vitro*	+	0	14	Snyder (1988)
MIH, Micronuclei (aneuploidy), human LEO fibroblasts *in vitro*	+	0	0.03	Bonatti *et al.* (1992)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	0.56	Han *et al.* (1992)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	0	5.6	Deknudt & Deminatti (1978)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+	0	0.51, ip × 1	Mukherjee *et al.* (1988b)
SVA, Sister chromatid exchange, pregnant mouse bone-marrow cells *in vivo*	–	0	7, sc × 1	Nayak *et al.* (1989)
SVA, Sister chromatid exchange, mouse fetal liver and lung cells *in vivo*	–	0	7, transplacentally × 1	Nayak *et al.* (1989)
MVM, Micronuclei, mice *in vivo*	–	0	9.15, ip	Bruce & Heddle (1979)
MVM, Micronuclei, mice *in vivo*	–	0	50, in drinking-water × 7 days	Watanabe *et al.* (1982)

Table 14 (contd)

Test system	Result		Dose (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
MVM, Micronuclei, mice *in vivo*	+	0	0.92, ip × 1	Kozachenko *et al.* (1987)
MVM, Micronuclei, mice *in vivo*	(+)	0	4.12, ip × 1	Mukherjee *et al.* (1988b)
MVM, Micronuclei, mice *in vivo*	–	0	0.06, po × 2	Volkova & Karplyuk (1990)
MVM, Micronuclei, mice *in vivo*	–	0	6.10, ip × 1	Adler *et al.* (1991)
MVM, Micronuclei, mice *in vivo*	+	0	0.43, ip × 1	Han *et al.* (1992)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–	0	44, in diet × 1 month	Deknudt & Gerber (1979)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+	0	0.26, ip × 1	Mukherjee *et al.* (1988b)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+		1.07, po × 7–21 days	Mukherjee *et al.* (1988a)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		30.5, ip × 1	Chopikashvili *et al.* (1989)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+		0.43, ip × 1	Han *et al.* (1992)
CGC, Chromosomal aberrations, mouse spermatocytes *in vivo*	–		1.83, ip × 1	Gilliavod & Léonard (1975)
DLM, Dominant lethal mutation, mice *in vivo*	–		4.3, ip × 1	Epstein *et al.* (1972)
DLM, Dominant lethal mutation, mice *in vivo*	–		1.07, ip × 1	Gilliavod & Léonard (1975)
DLM, Dominant lethal mutation, mice *in vivo*	–		1.22, ip × 1	Suter (1975)
DLM, Dominant lethal mutation, mice *in vivo*	–		2.44, ip × 1	Ramaiya & Pomerantseva (1977)
DLM, Dominant lethal mutation, mice *in vivo*	–		2.44 ip × 1	Pomerantseva *et al.* (1980)
DLM, Dominant lethal mutation, mice *in vivo*	(+)		1.83, po × 5 days	Bleyl & Lewerenz (1980)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
DLR, Dominant lethal mutation, rats *in vivo*	–		6.10, po × 6 weeks	Sutou *et al.* (1980b)
MHT, Heritable translocation, mice *in vivo*	–		1.07, ip × 1	Gilliavod & Léonard (1975)
AVA, Aneuploidy, mouse oocytes *in vivo*	(+)		3.66, sc × 1	Shimada *et al.* (1976)
AVA, Aneuploidy, mouse oocytes *in vivo*	(+)		3.66, sc × 1	Watanabe *et al.* (1977)
AVA, Aneuploidy, mouse oocytes *in vivo*	–		3.66, ip × 1	Mailhes *et al.* (1988)
AVA, Aneuploidy, Syrian hamster oocytes *in vivo*	+		0.61, sc × 1	Watanabe *et al.* (1979)
AVA, Aneuploidy, mouse spermatocytes *in vivo*	(+)		3.66, ip × 1	Miller & Adler (1992)
SPM, Sperm morphology, mice *in vivo*	+		2.44, ip × 1	Pomerantseva *et al.* (1980)
SPM, Sperm morphology, mice *in vivo*	–		9, ip, × 5	Bruce & Heddle (1979)
SPM, Sperm morphology, mice *in vivo*	+		0.51, ip × 5	Mukherjee *et al.* (1988b)
SPM, Sperm morphology, mice *in vivo*	+		0.37, ip × 1	Han *et al.* (1992)
***, Inhibition of DNA synthesis, mouse testis *in vivo*	+		10, ip × 1	Friedman & Staub (1976)
***, Decreased chromosome length, human lymphocytes *in vitro*	+	0	1.12, 4 h	Andersen *et al.* (1983)
***, Stimulation of DNA synthesis in mouse liver and other organs *in vivo*	+		1, ip × 1	Hellman (1986)
Cadmium nitrate				
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	0	280	Nishioka (1975)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	28	Kanematsu *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium nitrate (contd)				
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
ECR, *Escherichia coli* DG1153, reverse mutation	–[d]	0	NR	Arlauskas *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster DON cells *in vitro*	–	0	0.18	Ohno *et al.* (1982)
DMM, *Drosophila melanogaster*, somatic mutation or recombination	–		132	Rasmuson (1985)
Cadmium sulfate				
ERD, *Escherichia coli* differential toxicity	+	+	67	De Flora *et al.* (1984a)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	28	Kanematsu *et al.* (1980)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA8, *Salmonella typhimurium* TA98, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA2, *Salmonella typhimurium* TA102, reverse mutation	(+)	(+)	7	De Flora *et al.* (1984b)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	0	0.03	Marzin & Phi (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SCG, *Saccharomyces cerevisiae*, gene conversion	+	0	54	Schiestl *et al.* (1989)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+	0	3.36	Sina *et al.* (1983)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	0	0.08	Oberly *et al.* (1982)
CIC, Chromosomal aberrations, Chinese hamster fibroblasts *in vitro*	+	0	11.2	Röhr & Bauchinger (1976)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium sulfate (contd)				
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.11	Armstrong *et al.* (1992)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.22	Bean *et al.* (1992)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	0	0.69	Bassendowska-Karska & Zawadzka-Kos (1987)
HMA, Chromosomal aberrations, mouse ascites tumour cells *in vivo*	–		0.02, parenterally × 1	Bishun & Pentecost (1981)
Cadmium sulfide				
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*[e]	+	0	8 × 24 h	Robison *et al.* (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*[e]	+	0	0.78	Costa *et al.* (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*[f]	–	0	3.90	Costa *et al.* (1982)
CHL, Chromosomal aberrations, human lymphocytes *in vitro* (unspecified)	+	0	0.05 × 4 h	Shiraishi *et al.* (1972)
Cadmium oxide				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	1466	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	0	147	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	0	147	Mortelmans *et al.* (1986)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium oxide (contd)				
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	1466	Mortelmans *et al.* (1986)
Cadmium carbonate				
PLI, *Vicia faba*, micronuclei	–[g]	0	0	De Marco *et al.* (1988)

+, 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; po, orally, by gavage; NR, not reported

[b]Exposed to lead and cadmium

[c]Positive at 12.5–25 μM in distilled deionized water

[d]Positive in fluctuation assay for *E. coli* DG1153 at 0.67 μg/ml

[e]Crystalline cadmium sulfide

[f]Amorphous cadmium sulfide

[g]Induced by 8×10^{-4} M in the presence of equimolar nitrilotriacetic acid 3Na salt

***Not displayed on profiles

reported non-disjunction of meiotic chromosomes in *D. melanogaster* after exposure to cadmium, suggesting damage to the mitotic apparatus. Lakkad *et al.* (1986) observed chromosomal damage after exposure of Chinese hamster ovary cells to very low concentrations of cadmium *in vitro*, which included micronuclei, lagging chromosomes, chromatid bridges and multinucleated cells, suggesting spindle damage. A project for the validation of tests for aneuploidy coordinated by the Commission of the European Communities included cadmium chloride among 10 known or presumed spindle poisons: Cadmium-induced spindle disturbances and aneuploidy were observed in test systems ranging from yeast to human cells and in mice *in vivo* (Table 14). Cadmium chloride also inhibited the assembly of purified *Drosophila* microtubules *in vitro* (Sehgal *et al.*, 1990).

The ionic charge and radius of Cd^{2+} are comparable to those of Ca^{2+} (Chao *et al.*, 1984). Thus, Cd^{2+} could conceivably replace Ca^{2+} at cellular Ca^{2+} binding sites and lead to disturbances in cellular calcium homeostasis. Verbost *et al.* (1989) observed inhibition of Ca^{2+}-ATPase-mediated Ca^{2+} extrusion in erythrocyte ghosts by Cd^{2+} at nanomolar concentrations, with involvement of thiol groups. [The Working Group noted that this effect occurred at very low concentrations and could have many consequences for cellular metabolism.]

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[1]

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)*.

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

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APPENDIX B

Eighth Report on Carcinogens Listing for Cadmium and Certain Cadmium Compounds (1998)

CADMIUM AND CERTAIN CADMIUM COMPOUNDS

First Listed in the *First Annual Report on Carcinogens*

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of cadmium (Cd) (CAS No. 7440-43-9) and the following cadmium compounds in experimental animals: cadmium chloride (10108-64-2), cadmium oxide (1306-19-0), cadmium sulfate (10124-36-4), and cadmium sulfide (1306-23-6) (IARC V.2, 1973; IARC V.11, 1976; IARC S.4, 1982; IARC S.7, 1987; ATSDR, 1993d). An IARC Working Group did not evaluate the carcinogenicity of cadmium carbonate (513-78-0), cadmium fluoborate (14486-19-2), or cadmium nitrate (10325-94-7). When administered by intramuscular injection, cadmium powder induced rhabdomyosarcomas and some fibrosarcomas in female rats. When administered by subcutaneous or intramuscular injection, cadmium sulfide induced local sarcomas in rats of both sexes. When administered by subcutaneous injection, cadmium sulfate induced local sarcomas and interstitial cell tumors of the testis in rats. When administered by subcutaneous injection, cadmium chloride induced interstitial cell tumors of the testis in rats, sarcomas and spindle cell sarcomas in male rats, and interstitial cell tumors of the testis in mice. When administered by injection into the ventral prostate, cadmium chloride induced a low incidence of prostatic carcinomas in rats. Male rats exposed continuously to cadmium chloride aerosols developed dose-related increases in adenocarcinomas, epidermoid (squamous cell) carcinomas, combined epidermoid carcinomas and adenocarcinomas, and mucoepidermoid carcinomas of the lung (Takenaka et al., 1983). When administered by subcutaneous injection, cadmium oxide induced local tumors in female rats (IARC V.11, 1976). When administered by intratracheal instillation, cadmium oxide induced an increased incidence of mammary tumors and an increase in tumors at multiple sites in male rats (ATSDR, 1993d).

An IARC Working Group reported that there is limited evidence for the carcinogenicity of cadmium and certain cadmium compounds in humans (IARC S.4, 1982; IARC S.7, 1987). Studies have suggested that human exposure to cadmium (primarily as the oxide) is associated with increased risks of prostatic, respiratory, and genitourinary cancers (IARC V.2, 1973; IARC V.11, 1976; IARC S.4, 1982; IARC S.7, 1987; ATSDR, 1993d). In one follow-up study of an investigation of cadmium-nickel battery workers and cadmium-copper alloy factory workers, additional cases of nasopharyngeal, colorectal, prostatic, and lung cancer were reported. In another study, the mortality of cadmium-copper alloy workers who were exposed to cadmium fume was compared with that of workers exposed indirectly to cadmium but also to arsenic. A third group of iron or brass founders was included, and the mortality rates were compared separately with statistics for the general population. Significantly increased mortality from prostatic, genitourinary and lung cancers was seen for people working in the vicinity but not for the cadmium workers themselves. In follow-up studies of four populations of cadmium-exposed workers, excess lung cancer was noted among male workers employed at 1 of 17 plants in a group that had had "ever medium" exposure for 10 years or more; an excess risk of prostatic cancer was seen in a group that had had "always low" exposures for 10 years or more. In a follow-up study of cadmium smelter workers, a significant trend was noted for cumulative cadmium exposure and lung cancer mortality. Potential confounding factors in these studies, such as smoking and exposure to nickel and arsenic, do not appear to account for the excess of lung cancer deaths.

PROPERTIES

Cadmium occurs as a soft, blue-white, malleable metal or grayish-white powder. It is soluble in acid, ammonium nitrate, and hot sulfuric acid and insoluble in cold and hot water. Cadmium carbonate occurs as a white amorphous powder that is soluble in acids, potassium cyanate, and ammonium salts and insoluble in ammonia and water, both cold and hot. Cadmium chloride occurs

as small, white-to-colorless, hexagonal crystals. It is soluble in water and acetone and insoluble in ethanol. Cadmium fluoborate is extremely hygroscopic and very soluble in water. When heated to decomposition, it emits toxic fumes of cadmium, hydrofluoric acid, and other fluorinated compounds. Cadmium nitrate occurs as white, amorphous pieces or hygroscopic needles. It is very soluble in acids and soluble in ethanol, acetone, water, and ammonia. Cadmium oxide occurs as a colorless amorphous powder or brown-red cubic crystals. It is soluble in acids, ammonium salts, and alkalies, but is insoluble in cold and hot water. When heated to decomposition, it emits toxic fumes of cadmium. Cadmium sulfate occurs as white rhombic crystals. It is soluble in water but insoluble in alcohol, acetate, and ammonia. Cadmium sulfide is a yellow-orange or brown powder. It forms a colloid in hot water; it is soluble in acids and ammonia and insoluble in cold water. When heated to decomposition, cadmium sulfate and cadmium sulfide emit toxic fumes of cadmium and sulfur oxides (SO_x).

Cadmium metal is available in purities ranging from 99.5%-99.999% in the following grades: technical, powder, pure sticks, ingots, slabs, and high-purity crystals with less than 10 ppm impurities. Cadmium carbonate is available in a commercial grade which has a purity of about 98% with lead, zinc, and iron as impurities. Reagent-grade cadmium carbonate, with purities ranging from 99.9%-99.995%, is also available. Commercial cadmium chloride is a mixture of hydrates that is similar to the dihydrate form of cadmium chloride. The commercial grade available in the United States typically contains about 51% cadmium and 0.005% each of iron and copper; higher purity grades (99.9%) are also available. Cadmium fluoborate is available commercially in a 50% aqueous solution. Cadmium nitrate is available in technical and reagent grades (purity > 99%) with typical impurities of chloride, sulfate, copper, iron, lead, zinc, and arsenic. Commercial-grade cadmium oxide is available in the United States with a purity of 99.7%; common contaminants are lead and thallium. Cadmium sulfate is available in technical and C.P. grades. Cadmium sulfide is available in technical, N.D., high-purity (single crystals), and commercial grades. Typically, cadmium sulfide is available in mixtures depending upon its use as either a pigment or a phosphor.

USE

In 1989, batteries (34%) were the primary market for cadmium, followed by coating and plating (27%), pigments (15%), plastic and synthetic products (14%), and alloys and miscellaneous uses (10%) (USDOI, 1990). In 1988, the use of cadmium in batteries surpassed coating and plating operations. The estimated consumption pattern for cadmium in 1987 was coating and plating, 30%; batteries, 30%; pigments, 20%; plastics and synthetic products, 15%; and alloys and other uses, 5% (USDOI, 1988). Cadmium (elemental) is used primarily as an electroplated coating on fabricated steel and cast iron parts for corrosion protection. It is also used in bearing, brazing, and low-melting alloys, in nickel-cadmium storage batteries, reactor control rods, and as a hardener for copper. The intermetallic compounds, including cadmium sulfide (CdS), cadmium selenide (CdSe), and cadmium telluride (CdTe), have been used as semiconductors for photoconductors, photovoltaic cells, and infrared windows (ACGIHa, 1986; Kirk-Othmer V.4, 1978). Cadmium carbonate is used as a catalyst in organic reactions and as a source of cadmium in other reactions. Cadmium chloride is used in photocopying, printing, dyeing, electroplating baths, and the manufacture of special mirrors and of cadmium yellow. A cadmium fluoborate bath is used for electrodeposition of cadmium on high-strength steels to avoid the problem of hydrogen embrittlement inherent in cyanide plating (Kirk-Othmer V.4, 1978). Cadmium nitrate and cadmium oxide are used in the production of cadmium salts, photographic emulsions, coloring glass and porcelain, and in the laboratory as reagents. Cadmium oxide also finds use in plating baths, in electrodes for storage batteries, in phosphors, as a nematocide, as a starting material for poly(vinyl chloride) (PVC) heat stabilizers, and as an additive in nitrite rubbers and plastics such as Teflon®. Cadmium sulfate and cadmium sulfide

are used in pigments, fluorescent screens, in photoelectric cells, and in electroplating. Cadmium sulfide is the most widely used cadmium compound and is used primarily as a pigment (Sax, 1987; Kirk-Othmer V.4, 1976).

PRODUCTION

Cadmium is recovered as a by-product of smelting domestic and imported zinc concentrates; as such, its production is dependent upon the demand for zinc. In 1989, four U.S. companies produced an estimated 3.9 million lb of cadmium (USDOI, 1990). Estimated U.S. cadmium imports almost reached 6 million lb in 1989. Estimated U.S. cadmium exports exceeded 1 million lb in 1989. Approximately 4.2 million lb of cadmium were produced domestically in 1988. U.S. imports for that year were almost 5.5 million lb. U.S. cadmium exports were nearly 1.4 million lb in 1988. In 1987, it was estimated that four companies produced 3.3 million lb of cadmium. Also in 1987, 6.6 million lb of cadmium metal were imported and 396,000 lb of cadmium were exported. Nearly 3.3 million lb of cadmium were produced in 1986, 7.0 million lb of cadmium metal were imported, and 83,600 lb of cadmium were exported. In 1985, 3.5 million lb of cadmium were produced, 4.4 million lb of cadmium metal were imported, and 189,200 lb of cadmium were exported. Production of cadmium in 1984 was 3.7 million lb, imports of cadmium metal were 4.2 million lb, and exports of cadmium were 233,200 lb. In 1983, 2.3 million lb of cadmium were produced domestically, 4.8 million lb of cadmium metal were imported, and 374,000 lb of cadmium were exported (USDOI, 1988; USDOI, 1987). In 1982, 2.2 million lb of cadmium were produced, 5.1 million lb of cadmium metal and 24,200 lb of cadmium flue dust were imported, and 24,200 lb of cadmium were exported. More than 3.5 million lb of cadmium were produced in 1981, 6.8 million lb of cadmium metal were imported, and 525,800 lb of cadmium were exported. In 1980, 3.5 million lb of cadmium were produced, 5.8 million lb of cadmium metal were imported, and 519,200 lb of cadmium were exported (USDOI, 1985). The 1979 TSCA Inventory reported that in 1977, there were 14 producers of cadmium producing 6.3 million lb and 18 importers importing 2.6 million lb (TSCA, 1979). Production for 1972 through 1977 ranged from 7.5 million to 4.1 million lb (Kirk-Othmer V.4, 1978).

The 1979 TSCA Inventory identified nine producers of cadmium carbonate refining 116,500 lb and two companies importing 1,000 lb in 1977. The TSCA Inventory also reported that in 1977, 116,000 lb of cadmium chloride were manufactured by eight producers and 2,000 lb were imported by two firms; four companies produced 5,500 lb of cadmium fluoborate; 561,000 lb of cadmium nitrate were produced by eight firms and 500 lb were imported by one company; 15.0 million lb of cadmium oxide were produced by 12 companies and 2,000 lb imported by four companies; 1.3 million lb of cadmium sulfate were manufactured by 14 producers and 1,000 lb were imported by three firms; and 12 firms produced 1.1 million lb of cadmium sulfide and nine companies imported 724,000 lb, with some site limitations. The CBI Aggregate was less than 1 million lb each for cadmium carbonate, cadmium chloride and cadmium fluoborate; and between 1 million and 100 million lb each for cadmium nitrate, cadmium oxide, cadmium sulfate and cadmium sulfide (TSCA, 1979).

EXPOSURE

The primary routes of potential human exposure to cadmium and certain cadmium compounds are inhalation, dermal contact, and ingestion. The four major sources of occupational exposure are smelting of zinc and lead ores; producing, processing, and handling of cadmium

powders; welding or remelting of cadmium-coated steel; and working with solders that contain cadmium (ATSDR, 1993d; NIOSH 42, 1984). The major route of occupational exposure to cadmium is inhalation. An estimated 213,000 workers were exposed to cadmium in the workplace at levels equal to or greater than 1 $\mu g/m^3$ (OSHA, 1987). Of these 213,000 workers, 65% were exposed to concentrations between 1 $\mu g/m^3$ and 39 $\mu g/m^3$; 21% were exposed to cadmium at concentrations between 40 $\mu g/m^3$ and 99 $\mu g/m^3$; and 14% were exposed to cadmium concentrations greater than 100 $\mu g/m^3$. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that approximately 1.5 million workers were possibly exposed to cadmium, of which 100,000 were identified with exposure to specific cadmium compounds or with industries that utilize cadmium (NIOSH, 1976). The National Occupational Exposure Survey (1981-1983) estimated that a total of 69,100 workers, including 15,400 women, potentially were exposed to cadmium compounds including cadmium, cadmium chloride, cadmium sulfate, cadmium nitrate, cadmium oxide, cadmium sulfide, and cadmium fluoborate (NIOSH, 1984).

Consumer exposure occurs through inhalation and ingestion. Small quantities of cadmium appear in the air, water, and soil. Food is the main source of human exposure (Merian, 1984; Nordberg et al., 1985). There is significant inhalation exposure in industrial areas where zinc, lead, or copper smelters are located. Ambient air concentrations in rural areas are usually less than 1 ng/m^3, and in industrial areas range from 5-40 ng/m^3. (ATSDR, 1993d). In the United States, about 2 million lb of cadmium are emitted during cadmium production and up to another 2 million lb are emitted from the use of cadmium (Merian, 1984). Cadmium is highly volatile and about two thirds of the cadmium produced is dissipated into the environment (Merian, 1984). Industry has increased cadmium recovery at primary smelters; release to the environment from industrial operations is expected to decrease (USDOI, 1990). The Toxic Chemical Release Inventory (EPA) listed 78 industrial facilities that produced, processed, or otherwise used cadmium in 1988 (TRI, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of cadmium to the environment which were estimated to total 668,000 lb in 1988. Burning of fossil fuels, such as coal or oil, and the incineration of municipal waste materials contributes to the cadmium emitted in the air (ATSDR, 1993d; Merian, 1984). In the United States, up to 2 million lb of cadmium annually are polluting the air from coal and fossil fuel burning. Atmospheric cadmium is mainly in the forms of cadmium oxide and cadmium chloride (Merian, 1984). Smoking may double an individual's intake of cadmium; tobacco smokers are exposed to an estimated 1.7 μg Cd/cigarette (IARC V.11, 1976; ATSDR, 1993d). Drinking water concentrations of cadmium have been estimated to be ≤ 1 $\mu g/l$. Cadmium can leach into ground water from pipes and solder used on pipes or from chemical/hazardous waste sites. It has been estimated that the ground water in New Jersey has a median level of 1 μg Cd/l with a high level of 405 $\mu g/l$ (ATSDR, 1993d). Nickel-cadmium batteries used in electronic equipment are primary sources of cadmium in municipal trash and garbage (Pollut. Eng., 1989). Cadmium released in solid waste totaled 542,000 lb in 1988. Contaminated topsoil may be indirectly responsible for the greatest human exposure to cadmium due to the uptake of cadmium in soil into edible plants and tobacco. Topsoil may be contaminated by the application of phosphate fertilizers or sewage sludge. It has been found that uncontaminated top soil in the Unites States may contain an average of 0.25 ppm cadmium (ATSDR, 1993d; Merian, 1984). Potential daily intake is 10-20 μg and may be assumed to increase in the future (Piscator, 1985). A decrease in soil pH due to acidic precipitation may increase dietary cadmium. CPSC has investigated the consumer hazard posed by inks used in printed products and by the products themselves but found no cadmium in the inks or in the final consumer products.

REGULATIONS

Under the Clean Water Act (CWA), the water quality criteria published by EPA for cadmium and its compounds for the protection of human health are identical to Safe Drinking Water Act (SDWA) standards of 10 μg/l. EPA's Carcinogen Assessment Group includes cadmium oxide, cadmium sulfide, and cadmium sulfate on its list of potential carcinogens. Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), reportable quantities (RQs) have been established for cadmium and cadmium chloride. EPA issued a Rebuttable Presumption Against Registration (RPAR) for cadmium-containing pesticides under FIFRA. Also under FIFRA, there are labeling and reporting requirements. Under the Food, Drug, and Cosmetic Act (FD&CA), cadmium compounds are regulated as toxic inert ingredients in pesticides. Cadmium and cadmium compounds are also regulated under the Resource Conservation and Recovery Act (RCRA) and Superfund Amendments and Reauthorization Act (SARA). Both RCRA and SARA subject cadmium and its compounds to reporting requirements. FDA, under FD&CA, has set a maximum concentration level of 0.005 mg Cd/L in bottled water and limits the amount of cadmium in color additives and direct food additives. In 1984, NIOSH recommended that exposure to cadmium be reduced to the lowest possible level (NIOSHc, 1996). OSHA adopted permissible exposure limits (PELs) for toxic effects other than cancer for cadmium: 0.1 mg/m^3 as an 8-hr time-weighted average (TWA) for fumes, 0.3 mg/m^3 as a ceiling for fumes, 0.2 mg/m^3 as an 8-hr TWA for dust, and 0.6 mg/m^3 as a ceiling for dust; the standards were adopted by OSHA. OSHA regulates cadmium and certain cadmium compounds under the Hazard Communication Standard and as chemical hazards in laboratories.

APPENDIX C

Description of Online Searches for Cadmium

DESCRIPTION OF ONLINE SEARCHES FOR CADMIUM

Searches were limited to 1992 [the year before the IARC Monograph (1993), which has an extensive literature review] through September 1997.

Online searches for cadmium [CASRN 7440-43-9] were performed in databases on the systems of STN International, DIALOG, NML'S TOXNET, and the Chemical Information System from 1980 to date. Toxicology information was sought in the EMIC, EMICBACK, TSCATS (epidemiology, chromosomal aberration, gene toxicity, mutagenicity), the Toxic Chemical Release Inventory 1995 (online availability 1997), RTECS, TOXLINE (reviews as well as MESH heading for all neoplasms). Occupational safety and health information was obtained from NIOSHTIC. Environmental hazard information was sought in IRIS (Integrated Risk Information System, URL = http://www.epa.gov/ngispgm3/iris/irisdat/0141.DAT). The Chemical Abstracts Service Registry file and SANSS provided chemical identification information.

Regulatory information was obtained from the in-house FESA CD-ROM containing the latest *Code of Federal Regulations* and the *Federal Register* pertaining to CFR titles 21 (FDA), 29 (OSHA), and 40 (EPA) regulations. Other government publications were sought from the GPO.

Also, the review of 1200 life sciences journals was accomplished using Current Contents on Diskette® for current awareness.

APPENDIX D

Report on Carcinogens (RoC), 9th Edition
Review Summary

Report on Carcinogens (RoC), 9th Edition
Review Summary

Cadmium and Cadmium Compounds

NOMINATION

Review for possible upgrading of current listing from *reasonably anticipated to be a human carcinogen* to *known to be human carcinogen* based on IARC reclassification of Cadmium and Cadmium Compounds as known human carcinogens (IARC Vol. 58, 1993).

DISCUSSION

Cadmium and Cadmium Compounds, used in batteries, coating and plating, plastic and synthetic products, and in alloys, is currently listed in the RoC as *reasonably anticipated to be a human carcinogen*. Cohort studies provide consistent evidence of elevated lung cancer risk in cadmium-exposed workers. Although confounding factors, such as co-exposure to arsenic, were present in several of these studies, it was concluded that the increase in lung cancer risk was unlikely to be explained by exposure to arsenic. Cadmium causes a variety of genetic damage including mutations, chromosomal damage, cell transformation, DNA strand breaks, disrupted DNA repair, effects on gene expression, and, in humans, chromosomal aberrations. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	upgrade and list as known human carcinogen	7 yes/1 no
NTP EC Working Group (RG2)	upgrade and list as known human carcinogen	8 yes/0 no
NTP Board RoC Subcommittee	upgrade and list as known human carcinogen	6 yes/0 no

Public Comments Received

A total of 3 public comments were received:

- 2 against upgrading current listing to a known to be human carcinogen
- 1 providing comments on the content of the background document prepared for the review of this nomination