CADMIUM AND CADMIUM COMPOUNDS

Cadmium and cadmium compounds were considered by previous IARC Working Groups in 1972, 1975, 1987, and 1993 (IARC, 1973, 1976, 1987, 1993a). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names and molecular formulae for cadmium, cadmium–copper alloy, and some cadmium compounds are presented in Table 1.1. 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.

1.2 Chemical and physical properties of the agents

Cadmium (atomic number, 48; relative atomic mass, 112.41) is a metal, which belongs 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. Selected chemical and physical properties of cadmium compounds are presented in the previous *IARC Monograph* (IARC, 1993a).

1.3 Use of the agents

Cadmium metal has specific properties that make it suitable for a wide variety of industrial applications. These include: excellent corrosion resistance, low melting temperature, high ductility, high thermal and electrical conductivity (National Resources Canada, 2007). It is used and traded globally as a metal and as a component in six classes of products, where it imparts distinct performance advantages. According to the US Geological Survey, the principal uses of cadmium in 2007 were: nickel–cadmium (Ni–Cd) batteries, 83%; pigments, 8%; coatings and plating, 7%; stabilizers for plastics, 1.2%; and other (includes non-ferrous alloys, semiconductors and photovoltaic devices), 0.8% (USGS, 2008).

Cadmium is also present as an impurity in non-ferrous metals (zinc, lead, and copper), iron and steel, fossil fuels (coal, oil, gas, peat, and wood), cement, and phosphate fertilizers. In these products, the presence of cadmium generally does not affect performance; rather, it is regarded as an environmental concern (International Cadmium Association, 2011). Cadmium is also produced from recycled materials (such as Ni–Cd batteries and manufacturing scrap) and some

Table 1.1 Chemical names, synonyms (CAS names are in italics), and molecular formulae of cadmium and cadmium compounds

Chemical name	CAS Reg. No.[a]	Synonyms	Formula
Cadmium	7440-43-9	Cadmium metal	Cd
Cadmium acetate	543-90-8 (24 558-49-4; 29 398-76-3)	*Acetic acid, cadmium salt*; bis(acetoxy)-cadmium; cadmium (II) acetate; cadmium diacetate; cadmium ethanoate	$Cd(CH_3COO)_2$
Cadmium carbonate	513-78-0 [93820-02-1]	*Carbonic acid, cadmium salt*; cadmium carbonate ($CdCo_3$); cadmium monocarbonate	$CdCO_3$
Cadmium chloride	10 108-64-2	Cadmium dichloride; dichlorocadmium	$CdCl_2$
Cadmium hydroxide	21 041-95-2 (1 306-13-4; 13 589-17-8)	*Cadmium hydroxide ($Cd(OH)_2$)*; cadmium dihydroxide	$Cd(OH)_2$
Cadmium nitrate	10 325-94-7 (14 177-24-3)	*Nitric acid, cadmium salt*; cadmium dinitrate; cadmium (II) nitrate	$Cd(NO_3)_2$
Cadmium stearate	2223-93-0	Cadmium distearate; cadmium octadecanoate; cadmium(II) stearate; octadecanoic acid, cadmium salt; *stearic acid, cadmium salt*	$Cd(C_{36}H_{72}O_4)$
Cadmium sulfate	10 124-36-4 (62 642-07-3) [31119-53-6]	Cadmium monosulfate; cadmium sulfate; *sulfuric acid, cadmium salt (1:1)*	$CdSO_4$
Cadmium sulfide	1306-23-6 (106 496-20-2)	Cadmium monosulfide; cadmium orange; cadmium yellow	CdS
Cadmium oxide	1306-19-0	Cadmium monoxide	CdO
Cadmium–copper alloy[b]	37 364-06-0	*Copper base, Cu, Cd*	Cd.Cu
	12 685-29-9 (52 863-93-1)	*Cadmium nonbase, Cd, Cu*	
	132 295-56-8	*Copper alloy, base, Cu 99.75–100, Cd 0.05–0.15*; UNS C14300	
	132 295-57-9	*Copper alloy, base, Cu 99.60–100, Cd 0.1–0.3*; UNS C14310	

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

residues (e.g. cadmium-containing dust from electric arc furnaces) or intermediate products. Recycling accounts for approximately 10–15% of the production of cadmium in developed countries (National Resources Canada, 2007).

The primary use of cadmium, in the form of cadmium hydroxide, is in electrodes for Ni–Cd batteries. Because of their performance characteristics (e.g. high cycle lives, excellent low- and high-temperature performance), Ni–Cd batteries are used extensively in the railroad and aircraft industry (for starting and emergency power), and in consumer products (e.g. cordless power tools, cellular telephones, camcorders, portable computers, portable household appliances and toys) (ATSDR, 2008; USGS, 2008).

Cadmium sulfide compounds (e.g. cadmium sulfide, cadmium sulfoselenide, and cadmium lithopone) are used as pigments in a wide variety of applications, including engineering plastics, glass, glazes, ceramics, rubber, enamels, artists colours, and fireworks. Ranging in colour from yellow to deep-red maroon, cadmium pigments have good covering power, and are highly resistant to a wide range of atmospheric and environmental conditions (e.g. the presence of hydrogen

sulfide or sulfur dioxide, light, high temperature and pressure) (Herron, 2001; ATSDR, 2008; International Cadmium Association, 2011).

Cadmium and cadmium alloys are used as engineered or electroplated coatings on iron, steel, aluminium, and other non-ferrous metals. They are particularly suitable for industrial applications requiring a high degree of safety or durability (e.g. aerospace industry, industrial fasteners, electrical parts, automotive systems, military equipment, and marine/offshore installations) because they demonstrate good corrosion resistance in alkaline or salt solutions, have a low coefficient of friction and good conductive properties, and are readily solderable (UNEP, 2008; International Cadmium Association, 2011).

Cadmium salts of organic acids (generally cadmium laurate or cadmium stearate, used in combination with barium sulfate) were widely used in the past as heat and light stabilizers for flexible polyvinyl chloride and other plastics (Herron, 2001; UNEP; 2008). Small quantities of cadmium are used in various alloys to improve their thermal and electrical conductivity, to increase the mechanical properties of the base alloy (e.g. strength, drawability, extrudability, hardness, wear resistance, tensile, and fatigue strength), or to lower the melting point. The metals most commonly alloyed with cadmium include copper, zinc, lead, tin, silver and other precious metals. Other minor uses of cadmium include cadmium telluride and cadmium sulfide in solar cells, and other semiconducting cadmium compounds in a variety of electronic applications (Morrow, 2001; UNEP, 2008; International Cadmium Association, 2011).

Traditionally, the most common end-use applications for cadmium were pigments, stabilizers, and coatings. However, in recent years, the use of cadmium for these purposes has declined, mainly due to concerns over the toxicity of cadmium, and the introduction of regulations, particularly in the European Union, restricting its use (National Resources Canada, 2007).

1.4 Environmental occurrence

Historical information on the occurrence of cadmium and cadmium compounds can be found in the previous *IARC Monograph* (IARC, 1993a).

Cadmium occurs naturally in the earth's crust and in ocean water. It is emitted to the environment as a result of both natural and anthropogenic activities. Natural sources of cadmium include volcanic activity, weathering of cadmium-containing rocks, sea spray, and mobilization of cadmium previously deposited in soils, sediments, landfills, etc. Anthropogenic sources of cadmium include the mining and smelting of zinc-bearing ores, the combustion of fossil fuels, waste incineration, and releases from tailings piles or municipal landfills (UNEP, 2008; ATSDR, 2008).

1.4.1 Natural occurrence

In the earth's crust, cadmium appears mainly in association with ores containing zinc, lead, and copper (in the form of complex oxides, sulfides, and carbonates). Elemental cadmium is a soft, silver-white metal, which is recovered as a by-product of zinc mining and refining. The average terrestrial abundance of cadmium is 0.1–0.2 mg/kg, although higher concentrations are found in zinc, lead, and copper ore deposits. Naturally occurring cadmium levels in ocean water range, on average, from < 5 to 110 ng/L. (National Resources Canada, 2007; ATSDR, 2008; UNEP, 2008)

1.4.2 Air

Particulate cadmium (as elemental cadmium and cadmium oxide, sulfide or chloride) is emitted to the atmosphere from both natural and anthropogenic sources. Weathering and erosion of cadmium-bearing rocks is the most important natural source of cadmium. Other natural sources include volcanoes, sea spray, and

forest fires. The principal anthropogenic sources are non-ferrous metal production and fossil fuel combustion, followed by ferrous metal production, waste incineration, and cement production (WHO, 2000; ATSDR, 2008; UNEP, 2008)

Cadmium does not break down in the environment. Atmospheric cadmium compounds are transported (sometimes for long distances) and deposited (onto surface soils and water) with minimal transformation in the atmosphere (ATSDR, 2008). There is uncertainty about the relative magnitude of natural emissions versus anthropogenic emissions. Total global anthropogenic emissions in the mid-1990s were estimated at approximately 3000 tonnes. During 1990–2003, anthropogenic emissions of cadmium reportedly decreased by about half in Europe, and by about two-thirds in Canada (UNEP, 2008).

Mean total cadmium concentrations in air vary according to proximity to industrial source, and to population density. Measurement data from northern Europe for the period 1980–88 were reported as being around 0.1 ng/m^3 in remote areas, 0.1–0.5 ng/m^3 in rural areas, 1–10 ng/m^3 in urban areas, and 1–20 ng/m^3 in industrial areas, with levels of up to 100 ng/m^3 being observed near emission sources (WHO, 2000). Similar variations were observed in the USA (UNEP, 2008).

1.4.3 Water

Cadmium enters the aquatic environment from numerous diffuse (e.g. agricultural and urban run-off, atmospheric fall-out) and point sources, both natural and anthropogenic. Weathering and erosion of cadmium-containing rocks result in the release of cadmium not only to the atmosphere, but also to the soil and the aquatic system (directly and through the deposition of airborne particles) (ATSDR, 2008; UNEP, 2008). Cadmium is released to the aquatic environment from a range of anthropogenic sources, including non-ferrous metal mining and smelting (from mine drainage water, waste water, tailing pond overflow, rainwater run-off from mine areas), plating operations, phosphate fertilizers, sewage-treatment plants, landfills, and hazardous waste sites (IARC, 1993a; ATSDR, 2008).

Weathering and erosion are estimated to contribute 15000 tonnes of cadmium annually to the global aquatic environment, while atmospheric fall-out (of anthropogenic and natural emissions) is estimated to contribute between 900 and 3600 tonnes (UNEP, 2008).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mine/smelter wastes, commercial fertilizers derived from phosphate ores or sewage sludge, municipal waste landfills) contribute to the levels of cadmium found in soil and sediments. Wet or dry deposition of atmospheric cadmium on plants and soil can lead to cadmium entering the food-chain through foliar absorption or root uptake. The rate of cadmium transfer depends on a variety of factors, including deposition rates, type of soil and plant, the pH of the soil, humus content, availability of organic matter, treatment of the soil with fertilizers, meteorology, and the presence of other elements, such as zinc (WHO, 2000; UNEP, 2008). Reported sediment concentrations of cadmium range from 0.03–1 mg/kg in marine sediments to as high as 5 mg/kg in river and lake sediments (Nordic Council of Ministers, 2003). Relatively high concentrations of cadmium (> 1 mg/kg) have been measured in the soil near smelters and other industrialized areas (WHO, 2000).

1.5 Human exposure

1.5.1 Exposure of the general population

The non-smoking general population is exposed to cadmium primarily via ingestion of food and, to a lesser extent, via inhalation of

ambient air, ingestion of drinking-water, contaminated soil or dust. For the US population, the geometric mean daily intake of cadmium in food is estimated to be 18.9 µg/day. In most countries, the average daily intake of cadmium in food is in the range of 0.1–0.4 µg/kg body weight (CDC, 2005; ATSDR, 2008; UNEP, 2008; EFSA, 2009)

Because tobacco leaves naturally accumulate large amounts of cadmium (Morrow, 2001), cigarettes are a significant source of cadmium exposure for the smoking general population. It has been estimated that tobacco smokers are exposed to 1.7 µg cadmium per cigarette, and about 10% is inhaled when smoked (Morrow, 2001; NTP, 2005). Data on blood and urine levels of smokers are found in Section 1.6.

1.5.2 Occupational exposure

The main route of cadmium exposure in the occupational setting is via the respiratory tract, although there may be incidental ingestion of dust from contaminated hands, and food (ATSDR, 2008). Occupations in which the highest potential exposures occur include cadmium production and refining, Ni–Cd battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, brazing with a silver–cadmium–silver alloy solder, and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased since the 1970s. For more details on historical occupational exposures to cadmium, see the previous *IARC Monograph* (IARC, 1993a).

Estimates of the number of workers potentially exposed to cadmium and cadmium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 207350 workers were exposed to cadmium and cadmium compounds in the European Union, with over 50% of workers employed in the construction (n = 32113), manufacture of fabricated metal products (n = 23541), non-ferrous base metal industries (n = 22290), manufacture of plastic products not elsewhere classified (n = 16493), personal and household services (n = 15004), and manufacture of machinery except electrical (n = 13266).

CAREX Canada estimates that 35000 Canadians (80% males) are exposed to cadmium in their workplaces (CAREX Canada, 2011). The largest exposed group are workers in polyvinyl chloride plastic product manufacturing (n = 12000), who are exposed to cadmium-bearing stabilizers. Other industries in which exposure occurs include: foundries, commercial and industrial machinery manufacturing, motor vehicle parts manufacture, architectural and structural metal manufacturing, non-ferrous metal (except aluminium) production and processing, metalworking machinery manufacturing, iron and steel mills and ferro-alloy manufacturing, alumina and aluminium production and processing, and other electrical equipment and component manufacture.

Data from studies published since the previous *IARC Monograph* on exposure to cadmium and cadmium compounds in different occupational situations are summarized below.

(a) Battery manufacture

Zhang *et al.* (2002) investigated the renal damage of cadmium-exposed workers in an Ni–Cd battery factory in the People's Republic of China between April and May 1998. Based on area sampling measurements collected during 1986–92, the geometric mean concentration of cadmium oxide dust was 2.17 mg/m^3, with a range of 0.1–32.8 mg/m^3. The overall geometric mean urinary cadmium concentration for the 214 workers was 12.8 µg/g creatinine (range of geometric means, 4.0–21.4 µg/g creatinine), and the overall geometric mean blood cadmium

concentration was 9.5 μg/L (range of geometric means, 3.8–17.4 μg/L).

Cumulative exposure to cadmium hydroxide in Ni–Cd battery workers in the United Kingdom (n = 926 male workers) was investigated during 1947–2000. Mean cadmium concentrations in air from personal samples were highest in the 1969–73 period (range, 0.88–3.99 mg/m^3), and were lowest in the 1989–92 period (range, 0.024–0.12 mg/m^3). Mean cadmium concentrations in air from static area samples were highest in the 1954–63 period (range, 0.35–1.29 mg/m^3), and were lowest in the 1989–92 period (range, 0.002–0.03 mg/m^3) (Sorahan & Esmen, 2004).

(b) Cadmium recovery

Occupational exposure to cadmium compounds (oxide, sulfide, and sulfate) was investigated in male production workers (n = 571) from a cadmium recovery facility in the USA during 1940–82. Estimates of airborne cadmium exposures in the production departments ranged from 0.2 (in the tankhouse) to 1.5 mg/m^3 (in the mixing, calcine and retort departments) before 1950, and from 0.02 (in the tankhouse) to 0.6 mg/m^3 (in the sampling and roaster departments) for the 1965–76 time period (Sorahan & Lancashire, 1997).

(c) Cadmium alloy production

Occupational exposure to cadmium oxide fumes was investigated in 347 copper–cadmium alloy workers, 624 workers employed in the vicinity of copper–cadmium alloy work, and 521 iron and brass foundry workers in England and Wales during 1922–80. Based on a review of 933 measurements of airborne cadmium made during 1951–83 (697 area samples, 236 personal samples), cumulative cadmium exposures were estimated to be 600 μg/m^3 for the 1926–30 time period, dropping to an estimated 56 μg/m^3 by the 1980s (Sorahan *et al.*, 1995).

(d) Smelting

Occupational exposure to cadmium was investigated in 1462 male employees in a tin smelter in the United Kingdom during 1972–91. Annual average exposures in the principal process areas were reported. Average air levels were negligible in the dry-refining and electro-refining areas, low in the raw materials handling and roasters and ball mill areas (range of averages, 0.005–0.008 mg/m^3), and moderate in the sintering and blast furnace areas (range of averages, 0.04–0.08 mg/m^3) (Jones *et al.*, 2007).

(e) Vehicle manufacture

Wang *et al.* (2006) evaluated the exposure to metals of 82 welders and 51 operators in two vehicle-manufacturing plants in China. The geometric mean concentration of cadmium in the blood of welders was 3.54 μg/L (range, 0.2–12.5 μg/L), and was significantly higher than the control group concentration of 0.79 μg/L (range, 0.1–4.8 μg/L).

(f) Population-based surveys

Yassin & Martonik (2004) calculated the prevalence and mean urinary cadmium levels for all US workers, based on data collected from 11228 US workers aged 18–64 years who participated in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–94). For all workers, urinary cadmium levels were in the range of 0.01–15.57 μg/L, with a geometric mean of 0.30 μg/L (0.28μg/g creatinine). The prevalence of elevated urinary cadmium levels was reported on the basis of the following ranges: ≥ 15 μg/L, ≥ 10 μg/L, ≥ 5 μg/L, and ≥ 3 μg/L. For all US workers aged 18–64 years, the prevalence of urinary cadmium levels ≥ 5 μg/L was 0.42% (n = 551000), for levels ≥ 10 μg/L, 0.06% (n = 78 471), and for levels ≥ 15 μg/L, 0.0028% (n = 3907). The proportion of workers with elevated urinary cadmium varied by occupation and industry. Within industry, urinary

cadmium levels ≥ 10 μg/L were twice as prevalent among workers in the metal industry compared to workers in the manufacturing industry (0.45% versus 0.26%). Within occupation, urinary cadmium levels ≥ 5 μg/L were 12 times as prevalent among vehicle mechanics than in transportation workers (1.71% versus 0.14%), and five times as prevalent in construction workers than in agriculture workers (0.73% versus 0.14%).

1.5.3 Dietary exposure

Low levels of cadmium have been measured in most foodstuffs (average concentrations are less than 0.02 μg/g). Factors influencing cadmium levels in food include: food type (e.g. seafood or leafy vegetables versus meat or dairy), growing conditions (e.g. soil type, water), agricultural and cultivation practices, meteorological conditions (i.e. rate of atmospheric deposition), and anthropogenic contamination of soil or aquatic system (UNEP, 2008; EFSA, 2009; WHO, 2011). Highly contaminated areas have higher cadmium concentrations in locally produced food, and the use of cadmium-containing fertilizers in agriculture increase cadmium concentrations in the crops, and derived products.

High concentrations of cadmium are found in leafy vegetables (e.g. lettuce, spinach), starchy roots (e.g. potatoes), cereals and grains, nuts and pulses (e.g. peanuts, soybeans, sunflower seeds). Lower concentrations of cadmium are found in meat and fish, with the exception of certain shellfish (e.g. oysters), and certain organ meats (e.g. kidney and liver), which concentrate cadmium. Weekly dietary intake estimates in the EU are in the range of 1.9–3.0 μg/kg body weight (mean, 2.3 μg/kg body weight) for non-vegetarians. Vegetarians, regular consumers of bivalve mollusks, and wild mushrooms are, respectively, estimated to have weekly dietary cadmium exposures of 5.4 μg, 4.6 μg, and 4.3 μg (per kg of body weight). On a body weight basis, estimated cadmium intakes are generally higher for infants and children than for adults (UNEP, 2008; EFSA, 2009).

1.5.4 Biomarkers of exposure

Several analytical procedures are available for measuring cadmium concentrations in biological samples. These include: atomic absorption spectroscopy (AAS), electrothermal atomic absorption spectroscopy (ET-AAS), flame atomic absorption, graphite furnace atomic absorption, inductively coupled plasma atomic emission spectroscopy (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS), neutron activation analysis, potentiometric stripping analysis, radiochemical neutron activation analysis, X-ray fluorescence, and treatment with methyl isobutyl ketone, ammonium pyrrolidenedithiocarbamate, or 13-bis[2-(pyridyl)ethylidene]thiocarbonhydride. The choice of analytical method is determined by several factors, including the sample matrix available (i.e. blood, plasma, serum, tissue, milk, hair, kidney, liver, muscle, urine, or teeth), and the detection limit required (ATSDR, 2008).

Cadmium in blood is used as an indicator of both recent and cumulative exposures, and urinary cadmium predominantly reflects cumulative exposure and the concentration of cadmium in the kidney (CDC, 2005). In the general population, normal blood cadmium concentrations are in the range of 0.4–1.0 μg/L for non-smokers and 1.4–4 μg/L for smokers, although much higher levels have been reported for environmental exposure (above 10 μg/L), and occupational exposure (up to 50 μg/L) (UNEP, 2008). Women typically have higher urinary cadmium concentrations than men, in part perhaps magnified by adjustment for creatinine excretion, which is lower in women (EFSA, 2009).

In a general population survey of approximately 4700 adults in Germany, Becker *et al.* (2002, 2003) found geometric mean cadmium levels of 0.44 μg/L in blood, and 0.23 μg/L in

urine. Smokers had a blood level of 1.1 µg/L, and non-smokers a level of 0.28 µg/L. Smokers had a urine level of 0.29 µg/L, former smokers 0.25 µg/L, and never-smokers 0.18 µg/L.

A study by the Centers for Disease Control and Prevention in the USA based on data from a random sample of people (National Health and Nutrition Examination Survey 1999–2002), found that the mean blood concentration of cadmium was 0.41 µg/L (n = 7970), and the 95th percentile blood concentration was 1.3 µg/L; the mean urine concentration of cadmium was 0.91 µg/L (n = 2257), and the 95th percentile blood concentration was 1.2 µg/L (CDC, 2005). NHANES data for workers in the period 1988–94 (urinary cadmium) are presented in Section 1.5.2 (Yassin & Martonik, 2004).

In an investigation of non-occupational cadmium exposure of 52 adult women in Bangkok, Thailand, Zhang *et al.* (1999) found a geometric mean level of cadmium in blood of 0.41 µg/L and 1.40 µg/g creatinine in urine. These were the lowest when compared to four neighbouring cities in South-eastern Asia (Kuala Lumpur, 0.74 µg/L and 1.51 µg/g; Manila, 0.47 µg/L and 1.21 µg/g; Nanning, 0.71 µg/L and 1.87 µg/g; and Tainan, 0.83 µg/L and 1.59 µg/g).

2. Cancer in Humans

The previous *IARC Monograph* on cadmium and cadmium compounds conclusion was based largely on evidence of increased lung cancer risk among workers exposed to cadmium (IARC, 1993b).

2.1 Cancer of the lung

In two small copper–cadmium alloy plants in the United Kingdom, the rate of mortality from lung cancer was increased in one but decreased in the other (Holden, 1980). The follow-up was extended by Sorahan *et al.* (1995) who documented increased risks of lung cancer in vicinity workers only, and an increased risk of non-malignant diseases of the respiratory system at higher cumulative cadmium exposures [Although an increased risk of lung cancer was not documented in this study, the Working Group noted that cases of lung cancer could potentially be misclassified as non-malignant disease. There was some population overlap between these studies.]

For cadmium-processing workers from 17 plants in the United Kingdom, mortality from lung cancer was significantly increased (standardized mortality ratio [SMR], 1.12; 95%CI: 1.00–1.24), with apparent positive trends with duration of employment and with intensity of exposure (Kazantzis & Blanks, 1992). The increase in lung cancer risk was stronger in the small proportion of workers with high cadmium exposure (SMR, 1.62; 95%CI: 0.89–2.73).

Follow-up of the United Kingdom Ni–Cd battery workers confirmed a slight increase in SMR for lung cancer associated with duration of employment in high-exposure jobs (Sorahan, 1987). Although not associated with cumulative exposure to cadmium, a significant increase in the SMR for cancers of the pharynx was also seen, and a non-significantly increased SMR for lung cancer was observed (Sorahan & Esmen, 2004).

An increase in mortality rates from lung cancer was detected in a small cohort of individuals who worked in the Ni–Cd battery-producing industry in Sweden, and who had the longest duration of employment and latency (Elinder *et al.*, 1985). Further follow-up showed an SMR for lung cancer in male battery workers of 1.76 (95%CI: 1.01–2.87), although without association with estimated total cadmium exposure (Järup *et al.*, 1998).

Excess mortality from lung cancer was reported among workers employed in a US cadmium recovery plant, which had been an arsenic smelter until 1925 (Lemen *et al.*, 1976),

and a dose–response relationship was demonstrated between the estimated cumulative exposure to cadmium and lung cancer risk (Stayner *et al.*, 1993). The dose–response relationship was unlikely to be due to confounding by cigarette smoking, and the relationship persisted among workers employed after 1940, when little arsenic was present in feedstock (Stayner *et al.*, 1993). The US Occupational Safety and Health Administration (OSHA) estimated that exposure to arsenic would have resulted in no more than one case of lung cancer death in this cohort. Using detailed job histories and dust measurements from the same US plant, Sorahan & Lancashire (1997) estimated total cadmium exposure, and identified workers with and without high potential for exposure to arsenic. Relative to the workers in the lowest cumulative exposure category, increased SMRs for lung cancer were found among the workers in higher exposure categories, especially after a lag time of 10 or 20 years. However, significant excess risks of lung cancer were found only for the early years of operation, when exposures to cadmium occurred in the presence of high arsenic exposures. For workers only employed in jobs with little or no exposure to arsenic, cumulative exposure to cadmium was weakly associated with lung cancer mortality. A subsequent analysis of the arsenic-exposed component of this cohort (Sorahan, 2009) showed a statistically significant reduction in risk of lung cancer SMRs in relation to time since leaving employment with arsenic exposure. This pattern was interpreted by the author as implying a late-stage action of arsenic, and a role for arsenic and not cadmium in the causation of lung cancer in this cohort. [The Working Group found this indirect argument against a role for cadmium not to be convincing. The Working Group noted that the population overlapped between these studies.]

In Belgium, Nawrot *et al.* (2006) studied subjects residing near three zinc smelters and also subjects from the area away from the cadmium pollution for the incidence of cancer from initial examinations in 1985–89 to 2004. Using urinary cadmium excretion and cadmium in garden soil as exposure indicators, the hazard ratio for lung cancer was 1.70 (95%CI: 1.13–2.57) for a doubling of the 24-hour urinary cadmium excretion, 4.17 (95%CI: 1.21–14.4) for residence in the high-exposure area versus the low-exposure area, and 1.57 (95%CI: 1.11–2.24) for a doubling of the cadmium concentration in soil. Overall cancer was also increased in the high-exposure group. Information on smoking was included in the adjustments. Data on urinary cadmium excretion adjusted for arsenic suggested that arsenic exposure alone could not explain the observed increases in risk.

See Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-03-Table2.1.pdf

2.2 Cancer of the prostate

Following a report of the occurrence of cancer of the prostate in a small group of workers employed in a plant manufacturing Ni–Cd batteries in the United Kingdom (Potts, 1965), a series of analyses of different occupational cohorts were undertaken, which did not confirm the excess (Kipling & Waterhouse, 1967; Kjellström *et al.*, 1979; Holden, 1980; Sorahan & Waterhouse, 1983; Elinder *et al.*, 1985; Thun *et al.*, 1985; Sorahan, 1987; Kazantzis & Blanks, 1992; Sorahan & Esmen, 2004). Some of these studies reported a non-significantly increased risk for cancer of the prostate among cadmium-exposed workers, but the results were inconsistent, and mostly based on small numbers of cases. Sahmoun *et al.* (2005) calculated a weighted SMR from four studies of Ni–Cd battery production workers who were highly exposed to cadmium. The summary SMR was 1.26 (95%CI: 0.83–1.84) based on 27 deaths. [The Working Group noted that these populations overlapped.] See Table 2.2

available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-03-Table2.2.pdf.

Slightly increased odds ratios for cancer of the prostate were also reported from a case–control study nested within occupational cohorts (Armstrong & Kazantzis, 1985). A hospital-based case–control study using cadmium measurements in toenails (Vinceti *et al.*, 2007) showed a significantly increased odds ratio at the highest concentrations. A case–control study nested within a cohort did not find this association, using the same biological sample collected at baseline as the exposure measure (Platz *et al.*, 2002). [The Working Group noted that the exposure in the second study was lower than in the first, and that the cadmium concentration in toenails may represent a prediagnostic retention level of unknown validity as a measure of long-term exposure.]

A descriptive study from cadmium-polluted areas in Japan reported an increased mortality from cancer of the prostate in two of four areas studied (Shigematsu *et al.*, 1982). Using increased urinary excretion of β_2-microglobulin as a marker of cadmium toxicity within the Nagasaki Prefecture, increased cancer mortality (relative risk [RR], 2.58; 95%CI: 1.25–5.36) and cancer incidence (RR, 1.79; 95%CI: 0.84–3.82) were found among the subjects with signs of cadmium toxicity (Arisawa *et al.*, 2001, 2007). Numbers for individual cancer sites were too low to allow for detailed analysis. [The Working Group noted that these populations overlapped.]

2.3 Other cancers

Other cancer sites, such as the pancreas, show a possible excess in SMRs, but only small numbers of cases have occurred in the occupational cohorts. In a small case–control study, the OR per ng/mL change in serum cadmium concentrations was estimated as 1.12 (95%CI: 1.04–1.23) for cancer of the pancreas (Kriegel *et al.*, 2006). [The Working Group noted that the serum concentration of cadmium is a less valid measure of cadmium exposure than concentrations in urine and whole blood.]

For cancer of the kidney, small numbers were reported in two of the cohort studies without any evidence of an association with cadmium exposure (Järup *et al.*, 1998; Sorahan & Esmen, 2004), but more recent data are available from case–control studies. A German multicentre study (Pesch *et al.*, 2000) included 935 cases of renal cell carcinoma and 4298 controls, and cadmium exposure was assessed by a national job–exposure matrix (JEM). In men and women, respectively, the OR was 1.4 (95%CI: 1.1–1.8) and 2.5 (95%CI: 1.2–5.3) for high exposure and 1.4 (95%CI: 0.9–2.1) and 2.2 (95%CI: 0.6–9.0) for very high exposure. In a Canadian study of 1279 cases of renal cell carcinoma and 5370 controls, self-reported cadmium exposure was a risk factor in males (OR, 1.7; 95%CI: 1.0–3.2) (Hu *et al.*, 2002). Most recently, a German hospital-based case–control study of 134 cases of renal cell carcinoma and 401 controls reported an OR for high exposure of 1.7 (95%CI: 0.7–4.2) (Brüning *et al.*, 2003).

A hypothesis-generating case–control study in the Montréal (Canada) metropolitan area showed that the bladder was the only one of 20 cancer sites to be associated with exposure to cadmium compounds (Siemiatycki, 1991). In a case–control study of transitional cell carcinoma of the bladder, the blood cadmium concentration was measured as an indicator of long-term cadmium exposure; the highest exposure tertile showed an OR of 5.7 (95%CI: 3.3–9.9); adjustments included smoking and occupational exposures to polyaromatic hydrocarbons and aromatic amines (Kellen *et al.*, 2007).

In another study, increased cadmium concentrations were found in breast tissue, but the mean cadmium concentration found in breast cancer patients was not significantly different from that of controls (Antila *et al.*, 1996). A larger case–control study of breast cancer used urinary cadmium excretion levels as a measure

of cumulated cadmium exposure; each increase by 1.0 µg/g creatinine was associated with an OR of 2.09 (95%CI: 1.2–3.8) (McElroy *et al.*, 2006).

On the basis of food frequency questionnaires in 1987–90 and 1997, Åkesson *et al.* (2008) calculated dietary cadmium intakes; the highest tertile of cadmium exposure had an OR of 1.39 [95%CI: 1.04–1.86] for endometrial cancer in postmenopausal women. The association was stronger in never-smokers, in women with normal body mass index, and in non-users of postmenopausal hormones.

2.4 Synthesis

The assessment of cancer risks in occupational cohorts exposed to cadmium is constrained by the small number of long-term, highly exposed workers, the lack of historical data on exposure to cadmium, particularly for the non-US plants, and the inability to define and examine a gradient of cumulative exposure across studies. Confounding by cigarette smoking in relation to the assessment of lung cancer risk among cadmium-exposed workers was addressed directly only in the study from the USA. Some other studies provided analyses based on internal comparisons, which are not likely to be affected by this problem of confounding. Few studies were able to control the confounding effect of co-exposure to other substances, particularly arsenic and nickel; however, the analyses of workers with low levels of exposure to arsenic still showed an increased lung cancer risk associated with cadmium exposure. Additional support for a cadmium-linked lung cancer risk comes from a prospective population-based study in environmentally polluted areas in Belgium.

The results of the studies on cadmium exposure and the risk of prostate cancer are suggestive of an association, but the results are inconsistent. In studies of occupational cohorts exposed to cadmium, studies of people residing in cadmium-contaminated areas and case–control studies of individuals with prostate cancer, some studies reported an increased risk for prostate cancer, while other studies did not indicate the same. The results from cohort studies are supported by a hospital-based case–control study that included highly exposed subjects.

Case–control studies suggest that other cancer sites, such as the kidney, and perhaps also the bladder, the breast, and the endometrium may show increased risks associated with dietary or respiratory cadmium exposure. [The Working Group noted that although case–control studies may be subject to bias from exposure misclassification, some studies considered have the strength of inclusion of blood or urine cadmium analyses that provide individual exposure data.]

3. Cancer in Experimental Animals

Cadmium compounds have been tested for carcinogenicity by subcutaneous administration to rats, mice, and hamsters, by intramuscular injection to rats, by oral exposure to rats and mice, by intraperitoneal exposure to mice, by inhalation exposure to rats, mice and hamsters, and by intratracheal administration to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* (IARC, 1993b) were reconsidered in this evaluation.

All cadmium compounds tested were not carcinogenic by all routes tested but most studies performed provided evidence for cadmium-induced carcinogenicity in animals.

3.1 Oral administration

Oral administration of cadmium chloride to rats increased the incidence of large granular lymphocytes, leukaemia, prostate tumours, and testis tumours in Wistar rats (Waalkes & Rehm, 1992). Noble rats exposed to oral cadmium chloride developed prostate hyperplasia (Waalkes *et al.*, 1999b).

See Table 3.1.

Table 3.1 Studies of cancer in experimental animals exposed to cadmium (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar WF/NCr (M) 77 wk Waalkes & Rehm (1992)	Cadmium chloride 0, 25, 50, 100 or 200 ppm in diet Also fed previous diets with zinc levels of 60 ppm (zinc adequate), 7 ppm (zinc deficient) for 2 wk 28/group 56 pooled controls	Prostate (tumours): 4/26 (15%) cadmium (50ppm) vs 1/54 (2%) pooled controls High-dose cadmium + zinc deficient: Testis (tumours)– 6/27 (22%) vs 1/28 (3%) controls Leukaemia (LGL): 7/25 (28%) vs pooled controls 3/55 (5%)	$P < 0.05$ $P < 0.05$	Age at start, 2 wk Prostate tumours not affected by zinc deficiency unless combined with prostate hyperplasias No increase in testis tumours with cadmium alone
Rat, Noble NBL/Cr (M) 102 wk Waalkes *et al.* (1999b)	Cadmium chloride 0, 25, 50, 100, 200 ppm in drinking-water 30/group	Prostate (dorsolateral and ventral; hyperplasias): 6 (21%), 12 (46%), 13 (50%), 6 (21%), 4 (15%) Testis (tumours): 2/29 (7%), 2/30 (7%), 3/30 (10%), 4/30 (13%), 5/28 (18%) Adrenal gland (pheochromocytomas): 2 (7%), 3 (10%), 8 (27%), 6 (20%), 3 (10%)	$P < 0.05$ vs control (Groups 2 & 3) NR $P < 0.05$ (mid-dose)	Age at start, 10 wk No dose response to induction of any tumour type

d, day or days; h, hour or hours; mo, month or months; LGL, large granular lymphocyte; NR, not reported; NS, not significant; vs, versus; wk, week or weeks

3.2 Inhalation and intratracheal administration

3.2.1 Rat

Inhalation exposure to cadmium chloride caused lung tumours in rats (Takenaka *et al.*, 1983; Glaser *et al.*, 1990). Cadmium sulfate, cadmium oxide, cadmium oxide fume and dust also caused lung tumours in rats (Glaser *et al.*, 1990).

Intratracheal administration of cadmium chloride and cadmium sulfide caused lung tumours in rats (Oberdörster & Cherian, 1992).

3.2.2 Hamster

Cadmium chloride, cadmium sulfate, cadmium sulfide, and cadmium oxide fume did not cause lung tumours in hamsters (Heinrich *et al.*, 1989; Heinrich, 1992).

See Table 3.2.

3.3 Subcutaneous administration

Many of the earliest carcinogenicity studies with cadmium compounds in rodents involved subcutaneous or intramuscular administration. In most studies, injection-site sarcomas developed in rats and mice. Mice were generally less susceptible than were rats. The earlier studies are reviewed in the previous *IARC Monograph*, and are not reviewed here, in part, because larger and better designed studies were published after 1993.

3.3.1 Mouse

Subcutaneous administration of cadmium chloride caused lymphomas, lung tumours (Waalkes & Rehm, 1994), and injection-site sarcomas (Waalkes *et al.*, 1991a; Waalkes & Rehm, 1994) in mice.

3.3.2 Rat

Subcutaneous administration of cadmium chloride caused injection-site sarcomas (Waalkes *et al.*, 1988, 1989, 1991b, 1997, 1999a, 2000; IARC, 1993b; Shirai *et al.*, 1993), and testis (interstitial cell) tumours in rats (Waalkes *et al.*, 1988, 1989, 1997, 1999b, 2000). Cadmium chloride caused prostate tumours and/or preneoplastic lesions in Wistar and Noble rats (Waalkes *et al.*, 1988, 1999b), but not in other studies in F344 or Wistar Furth rats (Waalkes *et al.*, 1991c, 2000; Shirai *et al.*, 1993).

3.3.3 Hamster

A single injection of cadmium chloride did not induce tumours in hamsters (Waalkes & Rehm, 1998).

A variety of cadmium compounds and metallic cadmium caused local sarcomas in rats or mice (IARC, 1993b).

See Table 3.3.

3.4 Administration with known carcinogens or other agents

The incidence of injection-site sarcomas in Wistar rats induced by cadmium chloride was significantly reduced by both the subcutaneous and oral administration of zinc (Waalkes *et al.*, 1989). Testicular tumours induced by subcutaneously administered cadmium chloride were inhibited by zinc, and were found to be associated with a reduction of the chronic degenerative testicular lesions induced by cadmium chloride (Waalkes *et al.*, 1989).

Testosterone implantation eliminated both cadmium-induced and spontaneous testis tumours in F344 rats but had no effect on cadmium-induced chronic testicular degeneration (Waalkes *et al.*, 1997).

Table 3.2 Studies of cancer in experimental animals exposed to cadmium (inhalation and intratracheal exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Inhalation				
Rat, Wistar, TNO/W75 (M) 31 mo Takenaka *et al.* (1983)	Cadmium chloride 12.5, 25 or 50 µg/m^3, 23 h/d, 7 d/wk for 18 mo 40/group	Lung (adenocarcinomas): 0/38, 6/39 (15%), 20/38 (52%), 25/35 (71%)	[$P < 0.0001$; Groups 3 & 4]	Age at start, 6 wk
Rat, Wistar, TNO/W75 > BOR-WISW (M, F) 31 mo Glaser *et al.* (1990)	0 to 900 µg/m^3 of cadmium chloride, cadmium sulfate, cadmium oxide, cadmium oxide fume, zinc oxide dust, and cadmium oxide dust, 40 h/wk for 18 mo Groups of 20–40 males, 20 females	All forms increased lung tumour incidence, 18/20 (90%) in cadmium sulfate females, 0/20 in controls from 31 experimental groups Controls, males 0/40, females 0/20 High doses > 75% incidences	[$P < 0.0001$]	Age at start, 9 wk Problem with concentration of cadmium in cadmium oxide fume Data from 31 experimental groups in Table 13, p.166, Volume 58 (IARC, 1993b)
Intratracheal				
Rat, Wistar (F) 124 wk Oberdörster & Cherian (1992)	Cadmium chloride or cadmium oxide 20 weekly 1 or 3 µg or 15 weekly 9 µg Cadmium sulfide 10 weekly 63, 250 or 1000 µg (purity 99%) Controls received 20x0.3ml saline	Lung (tumours): Cadmium chloride– Controls, 0/40; 20, 0/38; 60, 3/40 (7%); 135, 2/36 (6%) Cadmium oxide– 20, 2/37 (5%); 60, 2/40 (5%); 135, 0/39 Cadmium sulfide– 630, 2/39 (5%); 2500, 8/36 (22%); 10000, 7/36 (19%)	$P < 0.01$ trend test NS $P = 0.0005$ trend test	Cadmium chloride and cadmium sulfide purity, 99%

d, day or days; h, hour or hours; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to cadmium (subcutaneous or intramuscular exposure; for years < 1993, only selected references included)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar Crl WI BR (M) 104 wk Waalkes *et al.* (1988)	Cadmium chloride Single s.c. 0, 1, 2.5, 5, 10, 20, or 40 µmol/kg bw; 5 µmol/kg 4 × 5 and 10 µmol/kg 1 × each, 5 and 20 µmol/kg 1 × each (time 0 (low dose) and 48 h (high dose)) 30/group 45 pooled controls	Injection site (mostly sarcomas, also fibromas, epithelial tumours): 2/45 (4%), 1/30 (3%), 0/29, 1/30 (3%), 2/30 (7%), 1/29 (3%), *14/30 (47%) 0/30, 1/30 (3%), *8/30 (27%)	$P < 0.05$ from pooled control	Age at start, 6 wk High dose cadmium reduced testicular tumour responses Prostate tumour response is not strong or a dose response
		Testis (tumours): 8/45 (18%), 1/30 (3%), 3/29 (10%), 3/30 (10%), 4/30 (13%), *21/29 (72%), *24/29 (83%) 4/30 (13%), 2/30 (7%), 5/30 (17%)	$P < 0.05$	
		Prostate (ventral lobe; tumours): 5/44 (11%), 6/27 (22%), *8/26 (31%), 4/28 (14%), 4/23 (17%), 4/26 (15%), 3/29 (10%) 2/26 (8%), 5/28 (18%), 6/28 (21%)	$P < 0.05$ from pooled control	
		Preneoplastic foci: Positive trend with single dose (data in chart)	NR	
		Pancreas (acinar and islet cell): Negative trend with dose	NR	

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (M) 104 wk Waalkes *et al.* (1989)	Cadmium chloride Single injection s.c. 30 µmole/kg 3 × zinc acetate 0.1, 0.3, 1.0 mmol/kg i.m. 30 mmole/kg cadmium chloride + zinc chloride 1 mmol/kg + zinc acetate in water 30/group	Injection site (sarcomas): 12/30 (40%), pooled controls 0/84 1 × zinc reduced incidence Testis (tumours): Cd 1 × 25/30 (83%), controls 9/83 (11%) Zinc, dose-dependent decrease Prostate (adenoma): i.m. Cd 11/26 (42%), Cd+zinc 8/27 (30%), i.m. Cd+s.c. zinc 7/28 (25%), controls 8/83 (10%)	$P < 0.05$ $P < 0.05$ $P < 0.05$	
Rat, F344 (M) 104 wk Waalkes *et al.* (1997)	Cadmium chloride 20 µmole/kg s.c. once/wk for 5 wk Testosterone implants, 10 interim sacrifices 50/group	Testis (tumours): Controls 24/40 (60%) Testosterone only *0/40 Cd only *34/40 (98%) Testosterone+Cd *†0/37	*$P \leq 0.05$ from control †$P \leq 0.05$ from cadmium alone	Age at start, 10 wk
Rat, Noble, NBL/Cr (M) 72 wk Waalkes *et al.* (1999a)	Cadmium chloride Single injection s.c. 0, 1, 2, 4, 8, 16, 32 µmole/kg 30/group	Testis: 1/30 (3%), 0/30, 0/30, 1/30 (3%), 7/30 (23%), 29/30 (96%), 28/30 (93%) Injection site (sarcomas): 0/30, 0/30, 0/30, 0/30, 0/30, 0/30, 7/30 (22%), 11/30 (37%) Prostate (proliferative lesions): 9/25 (36%), 16/26 (62%), 19/29 (65%), 19/24 (79%), 17/27 (63%), 18/30 (60%), 15/29 (52%)	$P < 0.053$ (higher doses) $P < 0.05$ $P < 0.05$, three middle doses	Prostate hyperplasia only

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, WF/NCr, F344/NCr (M) 104 wk Waalkes *et al.* (2000)	Cadmium chloride Single injection, s.c. 0, 10, 20, 30 µmole/kg bw weekly for 18 wk, 3 µmole/kg 1 wk then weekly 17 × 30 µmole/kg 30/group	Injection site (sarcomas): WF–0/20, 1/29 (3%), 21/29 (72%), 23/28 (82%), 23/29 (79%) F344–0/30, 11/30 (37%), 17/30 (68%), 8/12 (67%), 18/30 (60%)	$P < 0.05$ WF, four highest doses; F344 all doses	No prostate tumours were reported
		Testis: WF–11/29 (38%), 27/29 (93%), 19/29 (65%), 15/28 (54%), 15/29 (52%) F344–29/30 (97%), 28/30 (93%), 14/25 (56%), 8/12 (67%), 12/30 (43%)	$P < 0.05$ WF, two lower doses; F344 reduction in three highest doses	Pituitary adenomas reduced in higher doses of WF rats
Mouse, DBA/2NCr, NFS/NCr 104 wk (Waalkes & Rehm, 1994)	Cadmium chloride 40 µmol/kg s.c. 1once or once/wk for 16 wk 30–40/group	Lymphomas: DBA–1X Cd, 11/23 (48%); 16 × Cd, *16/28 (57%) Controls, 7/27 (26%)	$P = 0.024$ trend test	Age, 8 wk Strain differences seen No testis tumours
		Injection site (sarcomas): NFS–1X Cd, 3/27 (11%); 16 × Cd, 3/32 (9%) Controls, 0/23	$P = 0.016$ trend test	
		Lung: NFS–1X Cd, *21/28 (75%); 16 × Cd, 9/35 (26%) Controls, 6/25 (24%)		

h, hour or hours; i.m., intramuscular; NR, not reported; s.c., subcutaneous; wk, week or weeks

3.5 Synthesis

By inhalation, various cadmium compounds induce lung tumours in rats (cadmium chloride, cadmium oxide, cadmium oxide dust, cadmium oxide fumes, cadmium sulfide). Intratracheal administration of cadmium chloride and cadmium sulfide induces lung tumours in rats. In one study, subcutaneous injection of cadmium chloride caused lung tumours in mice. A variety of cadmium compounds and metallic cadmium cause local sarcomas in rats or mice. Administration of various salts of cadmium causes testicular tumours in rats. Cadmium chloride induced prostatic proliferative lesions and testicular tumours in rats after subcutaneous or oral administration.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Inhalation is the major route of cadmium exposure in occupational settings, whereas most people in the general population are exposed to cadmium via the ingestion of both food and drinking-water. Exposure to cadmium particulates lead to cadmium absorption in animals and humans (IARC, 1993b).

In occupational settings, cadmium and cadmium compounds, being non-volatile, exist in air as fine particulates. Animal studies (Rusch *et al.*, 1986) have shown that lung retention may be up to 20%, especially after short-term exposure.

When ingested, most of the cadmium passes through the gastrointestinal tract without being absorbed. Estimates of the cadmium absorption rate in humans have been reported as 3–5% (Morgan & Sherlock, 1984) or 6.5% (Horiguchi *et al.*, 2004). Even lower rates have been reported for experimental animals, especially after long-term repeated exposures (Schäfer *et al.*, 1990).

When absorbed, cadmium will bind to metallothionein, forming a cadmium–metallothionein complex that is transferred (via blood) primarily to the liver and the kidney (Waalkes & Goering, 1990). Metallothionein is inducible in different tissues (e.g. liver, kidney, intestine, and lung) by exposure to various agents including cadmium (Waalkes & Goering, 1990). When transported to the kidney, cadmium–metallothionein is readily filtered at the glomerulus, and may be efficiently reabsorbed from the filtrate in the proximal tubules (Foulkes, 1978; Dorian *et al.*, 1992a). In the tubules, the protein portion is rapidly degraded to release cadmium (Dorian *et al.*, 1992b). Cadmium accumulates in kidney tubules, and causes damage to tubular cells, especially in the proximal tubules (Kasuya *et al.*, 1992).

Absorbed cadmium is excreted very slowly, and the amounts excreted into urine and faeces are approximately equal (Kjellström & Nordberg, 1978). In humans, half-life estimates are in the range of 7–16 years (Kjellström & Nordberg, 1978; Nordberg *et al.*, 2007).

4.2 Genetic and related effects

In rodent experiments, cadmium salts cause increased frequencies of micronuclei and chromosomal aberrations. In mammalian cells *in vitro*, cadmium compounds cause DNA strand breaks and chromosomal aberrations, and are weakly mutagenic, whereas in most bacterial assays, cadmium compounds are not mutagenic (Waalkes, 2003; DFG, 2006). Both soluble and insoluble cadmium compounds generally give comparable results in genotoxicity assays when tested in parallel.

Because cadmium salts do not cause DNA damage in cell extracts or with isolated DNA (Valverde *et al.*, 2001), the genotoxicity of cadmium has to be explained by indirect mechanisms. Frequently discussed mechanisms are related to oxidative stress, the inhibition of

DNA-repair systems, effects on cell proliferation, and on tumour-suppressor functions.

4.2.1 Induction of oxidative stress

Even though cadmium is not redox-active, it has been shown to induce oxidative stress, both *in vitro* and *in vivo*. Cadmium sulfide induced hydrogen peroxide formation in human polymorphonuclear leukocytes, and cadmium chloride enhanced the production of superoxide in rat and human phagocytes (Sugiyama, 1994). The induction of DNA strand breaks and chromosomal aberrations by cadmium in mammalian cells is suppressed by antioxidants and antioxidative enzymes (Ochi *et al.*, 1987; Stohs *et al.*, 2001; Valko *et al.*, 2006). Because cadmium does not undergo redox reactions under physiological conditions, the increased generation of reactive oxygen species levels and oxidative cellular damage may be due to the inhibitory effect of cadmium on antioxidant enzymes (Stohs *et al.*, 2001; Valko *et al.*, 2006) as well as on DNA-repair systems.

4.2.2 Inhibition of DNA repair

Cadmium is co-mutagenic and increases the mutagenicity of ultraviolet radiation, alkylation, and oxidation in mammalian cells. These effects are explained by the observation that cadmium inhibits several types of DNA-repair mechanisms, i.e. base excision, nucleotide excision, mismatch repair, and the elimination of the pre-mutagenic DNA precursor 7,8-dihydro-8-oxoguanine (Hartwig & Schwerdtle, 2002). In base-excision repair, low concentrations of cadmium that do not generate oxidative damage as such, very effectively inhibit the repair of oxidative DNA damage in mammalian cells (Dally & Hartwig, 1997; Fatur *et al.*, 2003). In nucleotide-excision repair, cadmium interferes with the removal of thymine dimers after UV irradiation by inhibiting the first step of this repair pathway, i.e. the incision at the DNA lesion (Hartwig & Schwerdtle, 2002; Fatur *et al.*, 2003). Furthermore, chronic exposure of yeast to very low cadmium concentrations results in hypermutability; and in human cell extracts, cadmium has been shown to inhibit DNA-mismatch repair (Jin *et al.*, 2003). Additionally, cadmium disturbs the removal of 8-oxo-dGTP from the nucleotide pool by inhibiting the 8-oxo-dGTPases of bacterial and human origin (Bialkowski & Kasprzak, 1998).

One molecular mechanism related to the inactivation of DNA-repair proteins involves the displacement by cadmium of zinc from zinc-finger structures in DNA-repair proteins such as xeroderma pigmentosum group A (XPA), which is required for nucleotide-excision repair, and formamidopyrimidine-DNA-glycosylase (Fpg), which is involved in base-excision repair in *E. coli* (Asmuss *et al.*, 2000). Cadmium also inhibits the function of human 8-oxoguanine-DNA-glycosylase (hOGG1), which is responsible for recognition and excision of the pre-mutagenic 7,8-dihydro-8-oxoguanine during base-excision repair in mammalian cells (Potts *et al.*, 2003). Even though hOGG1 contains no zinc-binding motif itself, the inhibition of its function is due to its downregulation as a result of diminished DNA-binding of the transcription factor SP1 that contains zinc-finger structures (Youn *et al.*, 2005). Finally, cadmium induces a conformational shift in the zinc-binding domain of the tumour-suppressor protein p53. Thus, in addition to inhibiting repair proteins directly, cadmium downregulates genes involved in DNA repair *in vivo* (Zhou *et al.*, 2004).

The impact of cadmium on DNA repair may be especially deleterious in cadmium-adapted cells. Cadmium induces several genes for cadmium and reactive oxygen species tolerance such as those coding for metallothionein, glutathione synthesis and function, catalase and superoxide dismutase (Stohs *et al.*, 2001). Hence, a condition for prolonged cell survival in the

presence of cadmium is established (Chubatsu *et al.*, 1992). Taking into account the impact of cadmium on DNA repair, tolerance to cadmium toxicity concurrently may constitute a greater opportunity for the induction of further critical mutations (Achanzar *et al.*, 2002).

4.2.3 Deregulation of cell proliferation and disturbance of tumour-suppressor functions

Cadmium interacts with a multitude of cellular signal transduction pathways, many of which associated with mitogenic signalling. Submicromolar concentrations of cadmium stimulated DNA synthesis, and the proliferation of rat myoblast cells (von Zglinicki *et al.*, 1992) and of rat macrophages (Misra *et al.*, 2002). In various cell types *in vitro*, cadmium induces the receptor-mediated release of the second messengers inositol-1,4,5-trisphosphate and calcium, activates various mitogenic protein kinases, transcription and translation factors, and induces the expression of cellular proto-oncogenes, *c-fos*, *c-myc*, and *c-jun* (Waisberg *et al.*, 2003). However, it should be noted that the activation of mitogen-activated protein kinases is not a sufficient condition for enhanced cell proliferation, because persistent low-dose exposure of cells to cadmium has been shown to result in sustained activation of protein kinase ERK, but also to caspase activation and apoptosis (Martin *et al.*, 2006). In addition to directly stimulating mitogenic signals, cadmium also inhibits the negative controls of cell proliferation. It inactivates the tumour-suppressor protein p53, and inhibits the p53 response to damaged DNA (Méplan *et al.*, 1999). This finding could be particularly important to explain the carcinogenicity of cadmium because p53 is required for cell-cycle control, DNA repair, and apoptosis; its inactivation would be expected to lead to genomic instability.

It was also reported that cadmium modulates steroid-hormone-dependent signalling in ovaries in rats, in a breast cancer cell line, and in cadmium-transformed prostate epithelial cells (Benbrahim-Tallaa *et al.*, 2007a; Brama *et al.*, 2007). Nevertheless, in in-vitro estrogenicity assays based on estrogen-receptor activity, no effect of cadmium was detected (Silva *et al.*, 2006). Whether or not cadmium promotes tumour growth by an estrogen-mediated mechanism is still unknown.

In addition to effects on genes and genetic stability, cadmium also exerts epigenetic effects, which may contribute to tumour development. During cadmium-induced cellular transformation, DNA–(cytosine-5) methyltransferase activity and global DNA methylation were reduced after 1 week of exposure to cadmium (Takiguchi *et al.*, 2003). Prolonged exposure to cadmium (~10 weeks) resulted in enhanced DNA–methyltransferase activity, and global DNA hypermethylation in these cells (Takiguchi *et al.*, 2003), and in human prostate epithelial cells (Benbrahim-Tallaa *et al.*, 2007b). Changes in DNA methylation is thought to have a tumour-promoting effect because a decrease in DNA methylation is associated with increased expression of cellular proto-oncogenes, and an increase of DNA methylation results in the silencing of tumour-suppressor genes.

4.3 Synthesis

Several mechanisms have been identified that potentially contribute to cadmium-induced carcinogenesis. Direct binding to DNA appears to be of minor importance, and mutagenic responses are weak. Convincing evidence exists on disturbances of DNA-repair and tumour-suppressor proteins, which lead to chromosomal damage and genomic instability. Further reported effects include changes in DNA-methylation patterns as well as interactions with signal-transduction processes, which may contribute to the deregulation of cell growth. However, it is not yet possible to assess the relative contributions of these latter mechanisms for cancer in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of cadmium and cadmium compounds. Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

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.

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

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