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)

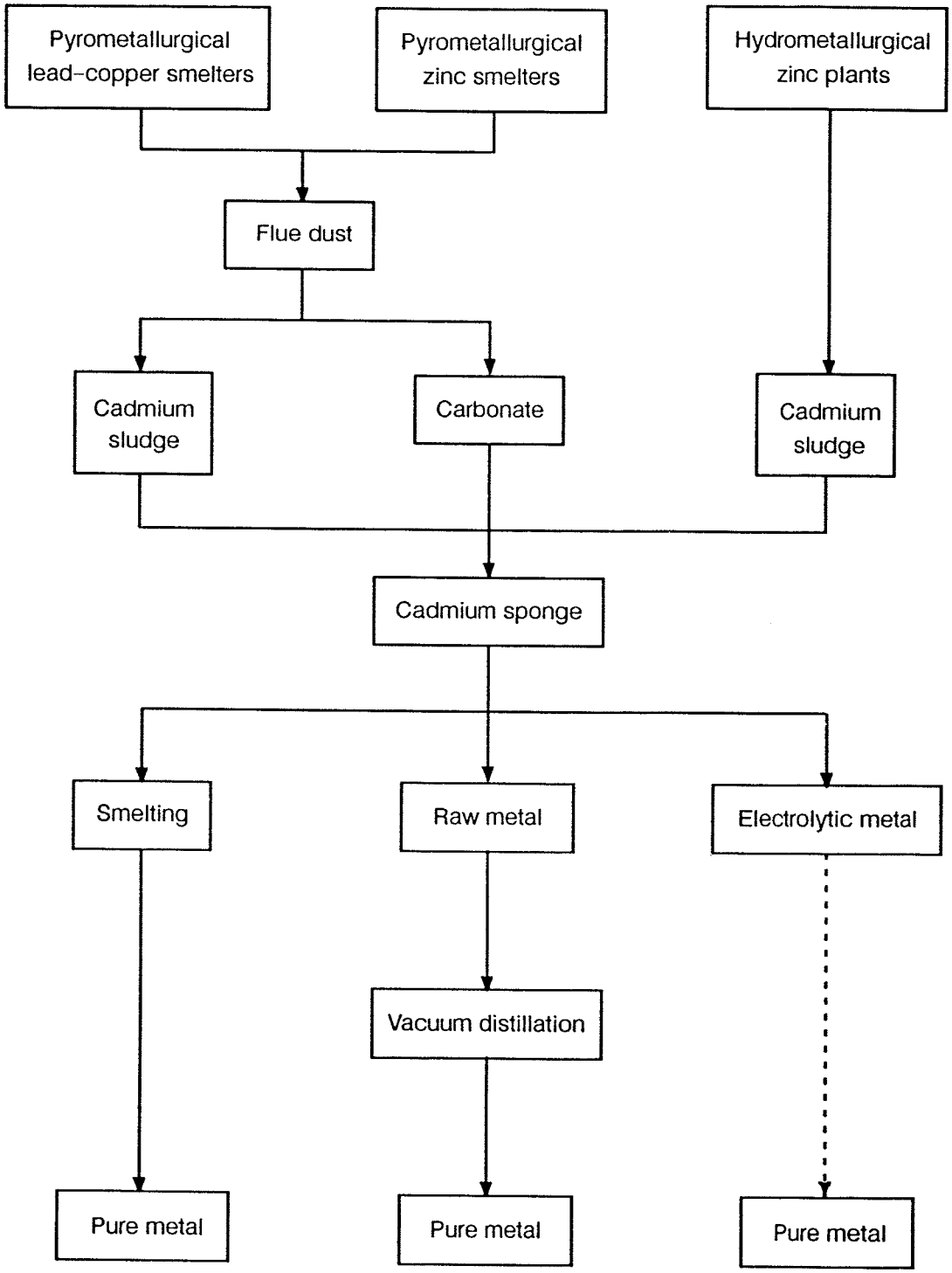
Country or region	1980	1981	1982	1983	1984	1987	1988	1989	1990	1991
Algeria	60	65	65	50	50	102	55	46	65	65
Argentina	18	NR	21	19	20	46	46	54	48	50
Australia	1 012	1 031	1 010	1 100	1 200	944	855	696	638	800
Austria	36	55	48	46	45	26	26	49	44	22
Belgium	1 524	1 176	996	800	850	1 308	1 836	1 761	1 956	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 ($\leq$ 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 ≤ 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			Relative risk (95% CI[a])	Comment
				Years	Estimated levels (mg/m^3)			
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	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		< 584 584–1460 1461–2920 > 2920			0.32 (1) 2.81 (6) 4.70 (5) 0 (0.6 exp.)	0.42 (1) 0 (0 exp.) 0.82 (1) 2.46 (2)
Cadmium processing							
United Kingdom Kazantzis *et al.* (1992); Kazantzis & Blanks (1992)	6910 men > 1 year	339/304.1 270 55 14	Overall Always low Ever medium Ever high			1.12 (1.00–1.24) 1.08 (0.96–1.22) 1.21 (0.91–1.57) 1.62 (0.89–2.73)	Mortality 1943–89; 17 plants; 3% of workers had ever high exposure.

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 Crl:[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 μg/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 μg/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 μg/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)*.

6. References

Abd Elghany, N., Schumacher, M.C., Slattery, M.L., West, D.W. & Lee, J.S. (1990) Occupation, cadmium exposure, and prostate cancer. *Epidemiology*, **1**, 107–115

Abe, H., Watanabe, T. & Ikeda, M. (1986) Cadmium levels in the urine of female farmers in non-polluted areas in Japan. *J. Toxicol. environ. Health*, **18**, 357–367

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

Abel, J., de Ruiter, N. & Kühn-Velten, W.N. (1991) Comparative study on metallothionein induction in whole testicular tissue and isolated Leydig cells. *Arch. Toxicol.*, **65**, 228–234

Abraham, R., Charles, A.K., Mankes, R., LeFevre, R., Renak, V. & Ashok, L. (1986) In vitro effects of cadmium chloride on preimplantation rat embryos. *Ecotoxicol. environ. Saf.*, **12**, 213–219

Adams, R.G. (1992) Manufacturing process, resultant risk profiles and their control in the production of nickel–cadmium (alkaline) batteries. *Occup. Med.*, **42**, 101–106

Adams, R.G., Harrison, J.F. & Scott, P. (1969) The development of cadmium-induced proteinuria, impaired renal function, and osteomalacia in alkaline battery workers. *Q. J. Med. New Ser.*, **38**, 425–443

Adamsson, E. (1979) Long-term sampling of airborne cadmium dust in an alkaline battery factory. *Scand. J. Work Environ. Health*, **5**, 178–187

Ades, A.E. & Kazantzis, G. (1988) Lung cancer in a non-ferrous smelter: the role of cadmium. *Br. J. ind. Med.*, **45**, 435–442

Adler, I.-D., Kliesch, U., van Hummelen, P. & Kirsch-Volders, M. (1991) Mouse micronucleus tests with known and suspect spindle poisons: results from two laboratories. *Mutagenesis*, **6**, 47–53

Agency for Toxic Substances and Disease Registry (1989) *Toxicological Profile for Cadmium* (ATSDR/TP-88/08; US NTIS PB89-194476), Atlanta, GA, US Public Health Service

Ahlgren, L. & Mattsson, S. (1981) Cadmium in man measured *in vivo* by X-ray fluorescence analysis. *Phys. Med. Biol.*, **26**, 19–26

Albertini, S. (1990) Analysis of nine known or suspected spindle poisons for mitotic chromosome malsegregation using *Saccharomyces cerevisiae* D61.M. *Mutagenesis*, **5**, 453–459

Aldrich Chemical Co. (1992) *Aldrich Catalog/Handbook of Fine Chemicals 1992–1993*, Milwaukee, WI, pp. 241–243

Alessio, L., Odone, P., Bertelli, G. & Foà, V. (1983) Cadmium. In: Alessio, L., Berlin, A., Roi, R. & Boni, M., eds, *Human Biological Monitoring of Industrial Chemical Series* (EUR 8476 EN), Luxembourg, Commission of the European Communities, pp. 23–44

Alessio, L., Apostoli, P. & Ferioli, A. (1990) Identification of reference values for metals in general population groups. The example of cadmium. *Toxicol. environ. Chem.*, **27**, 39–48

Alessio, L., Apostoli, P., Duca, P.G. & Braga, M. (1992) Definition of reference values for Cd-B and Cd-U: methodological aspects and preliminary results. In: Nordberg, G.F., Herber, R.F.M. & Alessio, L., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 93–99

Alfa Products (1990) *Alfa Catalog—Research Chemicals and Accessories*, Ward Hill, MA, pp. 78–81, 466–468

Ali, M.M., Murthy, R.C. & Chandra, S.V. (1986) Developmental and long-term neurobehavioral toxicity of low level in-utero cadmium exposure in rats. *Neurobehav. Toxicol. Teratol.*, **8**, 463-468

Amacher, D.E. & Paillet, S.C. (1980) Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK$^{+/-}$ cells. *Mutat. Res.*, **78**, 279-288

American Conference of Governmental Industrial Hygienists (1992) *1992–1993 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, pp. 14, 39, 63, 69

Andersen, O., Rønne, M. & Nordberg, G.F. (1983) Effects of inorganic metal salts on chromosome length in human lymphocytes. *Hereditas*, **98**, 65–70

Andersen, O., Nielsen, J.B. & Nordberg, G.F. (1992) Factors affecting the intestinal uptake of cadmium from the diet. In: Nordberg, G.F., Herber, R.F.M. & Alessio, L., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 173–187

Andersson, K., Elinder, C.-G., Hogstedt, C., Kjellström, T. & Spång, G. (1984) Mortality among cadmium and nickel-exposed workers in a Swedish battery factory. *Toxicol. environ. Chem.*, **9**, 53–62

Angerer, J. & Schaller, K.H., eds (1985) *Analyses of Hazardous Substances in Biological Materials*, Vol. 1, Weinheim, VCH Verlagsgesellschaft mbH, pp. 79–92

Angerer, J. & Schaller, K.H., eds (1988) *Analysis of Hazardous Substances in Biological Materials. Methods for Biological Monitoring*, Vol. 2, Weinheim, VCH Verlagsgesellschaft mbH, pp. 85–94

Anon. (1992) Occupational exposure limits. *BIBRA Bull.*, **31**, 287

Antoccia, A., Degrassi, F., Battistoni, A., Ciliutti, P. & Tanzarella, C. (1991) In vitro micronucleus test with kinetochore staining: evaluation of test performance. *Mutagenesis*, **6**, 319–324

Arbeidsinspectie [Labour Inspection] (1986) *De Nationale MAC-Lijst 1986* [National MAC List 1986], Voorburg, p. 9

Arbetarskyddsstyrelsens [National Board of Occupational Safety and Health] (1989) *Arbetarskyddsstyrelsens kungörelse om ändring i styrelsens kungörelse (AFS 1988:7) med föreskrifter om kadmium* [Notification by the National Board of Occupational Safety and Health of change in the notification of the Board (AFS 1988:7) with directives for cadmium and general advice of the Board on application of the directive] (AFS 1989:3), Stockholm

Arlauskas, A., Baker, R.S.U., Bonin, A.M., Tandon, R.K., Crisp, P.T. & Ellis, J. (1985) Mutagenicity of metal ions in bacteria. *Environ. Res.*, **36**, 379–388

Armstrong, B.G. & Kazantzis, G. (1983) The mortality of cadmium workers. *Lancet*, **i**, 1425–1427

Armstrong, M.J., Bean, C.L. & Galloway, S.M. (1992) A quantitative assessment of the cytotoxicity associated with chromosomal aberration detection in Chinese hamster ovary cells. *Mutat. Res.*, **265**, 45–60

Atomergic Chemetals Corp. (undated) *High Purity Metals Brochure*, Farmingdale, NY

Aufderheide, M., Mohr, U., Thiedemann, K.-U. & Heinrich, U. (1990) Quantification of hyperplastic areas in hamster lungs after chronic inhalation of different cadmium compounds. *Toxicol. environ. Chem.*, **27**, 173–180

Axelson, O. (1978) Aspects on confounding in occupational health epidemiology (Letter to the Editor). *Scand. J. Work Environ. Health*, **4**, 85–89

Axelsson, B. & Piscator, M. (1966) Renal damage after prolonged exposure to cadmium. An experimental study. *Arch. environ. Health*, **12**, 360–373

Baker, R.S.U. (1985) Evaluation of metals in in vitro assays, interpretation of data and possible mechanisms of action. In: Merian, E., ed., *Carcinogenic and Mutagenic Metal Compounds*, New York, Gordon & Breach, pp. 185–206

Bako, G., Smith, E.S.O., Hanson, J. & Dewar, R. (1982) The geographical distribution of high cadmium concentrations in the environment and prostate cancer in Alberta. *Can. J. Public Health*, **73**, 92–94

Banat, K., Förstner, U. & Müller, G. (1972) Heavy metals in sediments of the Danube, Rhine, Ems, Weser and Elbe in the Democratic Republic of Germany (Ger.). *Naturwissenschaften*, **59**, 525–528

Barański, B., Stetkiewicz, I., Trzcinka-Ochocka, M., Sitarek, K. & Szymczak, W. (1982) Teratogenicity, fetal toxicity and tissue concentration of cadmium administered to female rats during organogenesis. *J. appl. Toxicol.*, **2**, 255–259

Barański, B., Stetkiewicz, I., Sitarek, K. & Szymczak, W. (1983) Effects of oral, subchronic cadmium administration on fertility, prenatal and postnatal progeny developments in rats. *Arch. Toxicol.*, **54**, 297–302

Barlow, S.M. & Sullivan, F.M. (1982) *Reproductive Hazards of Industrial Chemicals. An Evaluation of Animal and Human Data*, London, Academic Press, pp. 136–177

Bassendowska-Karska, E. & Zawadzka-Kos, M. (1987) Cadmium sulfate does not induce sister chromatid exchanges in human lymphocytes *in vitro*. *Toxicol. Lett.*, **37**, 173–175

Bauchinger, M., Schmid, E., Einbrodt, H.J. & Dresp, J. (1976) Chromosome aberrations in lymphocytes after occupational exposure to lead and cadmium. *Mutat. Res.*, **40**, 57–62

Bean, C.L., Armstrong, M.J. & Galloway, S.M. (1992) Effect of sampling time on chromosome aberration yield for 7 chemicals in Chinese hamster ovary cells. *Mutat. Res.*, **265**, 31–44

Bernard, A. & Lauwerys, R. (1986) Cadmium in human population. *Experientia*, **50** (Suppl.), 114–123

Bhattacharyya, D., Boulden, A.M., Foote, R.S. & Mitra, S. (1988) Effects of polyvalent metal ions on the reactivity of human O^6-methylguanine-DNA methyltransferase. *Carcinogenesis*, **9**, 683–685

Bishun, N. & Pentecost, M. (1981) Cytogenetic effects of lead and cadmium compounds on ascitic tumour cells in the mouse. *Microbios Lett.*, **17**, 29–32

Blakley, B.R. (1986) The effect of cadmium on chemical- and viral-induced tumor production in mice. *J. appl. Toxicol.*, **6**, 425–429

Bleyl, D.W.R. & Lewerenz, H.J. (1980) Dominant lethal test in mice with repeated oral applications of cadmium chloride (Ger.). *Arch. exp. vet. Med.*, **34**, 399–404

Bomhard, E., Vogel, O. & Löser, E. (1987) Chronic effects of single and multiple oral and subcutaneous cadmium administrations on the testes of Wistar rats. *Cancer Lett.*, **36**, 307–315

Bonatti, S., Cavalieri, Z., Viaggi, S. & Abbondandolo, A. (1992) The analysis of 10 potential spindle poisons for their ability to induce CREST-positive micronuclei in human diploid fibroblasts. *Mutagenesis*, **7**, 111–114

Bonnell, J.A., Kazantzis, G. & King, E. (1959) A follow-up study of men exposed to cadmium oxide fume. *Br. J. ind. Med.*, **16**, 135–147

Borenfreund, E. & Babich, H. (1987) In vitro cytotoxicity of heavy metals, acrylamide, and organotin salts to neural cells and fibroblasts. *Cell Biol. Toxicol.*, **3**, 63–73

Bournias-Vardiabasis, N., Buzin, C. & Flores, J. (1990) Differential expression of heat shock proteins in *Drosophila* embryonic cells following metal ion exposure. *Exp. Cell Res.*, **189**, 177–182

Bowen, H.J.M. (1966) *Trace Elements in Biochemistry*, London, Academic Press

Brown, S.S. (1992) Quantitative analyses of cadmium: quality assured? In: Nordberg, G.F., Herber, R.F.M. & Alessio, L., *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 73–81

Bruaux, P., Claeys-Thoreau, F., Ducoffre, G., Lafontaine, A., Grech, A. & Vassallo, A. (1983) Exposure to lead and cadmium of the general population of Malta. *Int. Arch. occup. environ. Health*, **53**, 119–125

Bruce, W.R. & Heddle, J.A. (1979) The mutagenic activity of 61 agents as determined by the micronucleus, *Salmonella*, and sperm abnormality assays. *Can. J. Genet. Cytol.*, **21**, 319–334

Buchet, J.P., Lauwerys, R., Roels, H., Bernard, A., Bruaux, P., Claeys, F., Ducoffre, G., De Plaen, P., Staessen, J., Amery, A., Lijnen, P., Thijs, L., Rondia, D., Sartor, F., Saint Remy, A. & Nick, L. (1990) Renal effects of cadmium body burden of the general population. *Lancet*, **336**, 699–702

Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Rahway, NJ, Merck & Co., pp. 245–247

Bui, T.-H., Lindsten, J. & Nordberg, G.F. (1975) Chromosome analysis of lymphocytes from cadmium workers and itai-itai patients. *Environ. Res.*, **9**, 187–195

Cadmium Association/Cadmium Council (1991) *Technical Notes on Cadmium: Cadmium Production, Properties and Uses*, London/Greenwich, CT

Campbell, T.C., Chen, J., Liu, C., Li, J. & Parpia, B. (1990) Nonassociation of aflatoxin with primary liver cancer in a cross-sectional ecological survey in the People's Republic of China. *Cancer Res.*, **50**, 6882–6893

Carmichael, N.G., Backhouse, B.L., Winder, C. & Lewis, P.D. (1982) Teratogenicity, toxicity and perinatal effects of cadmium. *Hum. Toxicol.*, **1**, 159–186

Casto, B.C. (1983) Comparison of the sensitivity of rodent and human cells to chemical carcinogens using viral transformation, DNA damage, and cytotoxicity assays. *Basic Life Sci.*, **24**, 429–449

Casto, B.C., Meyers, J. & DiPaolo, J.A. (1979) Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. *Cancer Res.*, **39**, 193–198

CERAC, Inc. (1991) *Advanced Specialty Inorganics*, Milwaukee, WI, pp. 78–80

Chan, O.Y., Tan, K.T., Kwok, S.F. & Chio, L.F. (1982) Study on workers exposed to cadmium in alkaline storage battery manufacturing and PVC compounding. *Ann. Acad. Med.*, **11**, 122–130

Chao, S.-H., Suzuki, Y., Zysk, J.R. & Cheung, W.Y. (1984) Activation of calmodulin by various metal cations as a function of ionic radius. *Mol. Pharmacol.*, **26**, 75–82

Cherian, M.G., Goyer, R.A. & Valberg, L.S. (1978) Gastrointestinal absorption and organ distribution of oral cadmium chloride and cadmium-metallothionein in mice. *J. Toxicol. environ. Health*, **4**, 861–868

Chibber, R. & Ord, M. (1990) Cadmium-induced multistep transformation of cultured Indian muntjac skin fibroblasts. *Biol. Metals*, **3**, 213–221

Chopikashvili, L.V., Bobyleva, L.A. & Zolotareva, G.N. (1989) Genotoxic effects of heavy metals and their salts in an experiment on *Drosophila* and mammals (Russ.). *Tsitol. Genet.*, **23**, 35–38

Christley, J. & Webster, W.S. (1983) Cadmium uptake and distribution in mouse embryos following maternal exposure during the organogenic period: a scintillation and autoradiographic study. *Teratology*, **27**, 305–312

Christoffersson, J.O. & Mattsson, S. (1983) Polarised x-rays in XRF-analysis for improved in vivo detectability of cadmium in man. *Phys. Med. Biol.*, **28**, 1135–1144

Christoffersen, J., Christoffersen, M.R., Larsen, R., Rostrup, E., Tingsgaard, P., Andersen, O. & Grandjean, P. (1988) Interaction of cadmium ions with calcium hydroxyapatite crystals: a possible mechanism contributing to the pathogenesis of cadmium-induced diseases. *Calcif. Tissue Int.*, **42**, 331–339

Chung, Y.J. & Kim, S.H. (1982) The effects of heavy metal compounds on mutagenicity of *Drosophila melanogaster* (Korean). *J. Korean Res. Inst. Better Living*, **29**, 55–61

Cifone, M.G., Napolitano, T., Festuccia, C., Cantalini, M.G., De Nuntiis, G., Santoni, G., Marinelli, G. & Santoni, A. (1991) Effects of cadmium on cytotoxic functions of human natural killer cells. *Toxicol. in vitro*, **5**, 525–528

Clough, S.R., Welsh, M.J., Payne, A.H., Brown, C.D. & Brabec, M.J. (1990) Primary rat Sertoli and interstitial cells exhibit a different response to cadmium. *Cell Biol. Toxicol.*, **6**, 63–79

Commission of the European Communities (1983) Council Directive of 26 September 1983 on limit values and quality objectives for cadmium discharges (83/513/EEC). *Off. J. Eur. Comm.*, **L291**, 1–8

Commission of the European Communities (1990) Proposal for a Council Directive on the approximation of the laws of the Member States relating to cosmetic products. *Off. J. Eur. Comm.*, **C322**, 29–77

Commission of the European Communities (1991a) Cadmium sulphide. In: Berlin, A., Draper, M.H., Duffus, J.H. & van der Venne, M.T., eds, *The Toxicology of Chemicals*, Series One, *Carcinogenicity. Summary Reviews of the Scientific Evidence*, Vol. III (EUR13765 EN), Luxembourg, pp. 75–81

Commission of the European Communities (1991b) Cadmium sulphate. In: Berlin, A., Draper, M.H., Duffus, J.H. & van der Venne, M.T., eds, *The Toxicology of Chemicals*, Series One, *Carcinogenicity. Summary Reviews of the Scientific Evidence*, Vol. III (EUR13765 EN), Luxembourg, pp. 67–74

Commission of the European Communities (1991c) Thirteenth Commission Directive of 12 March 1991 adapting to technical progress Annexes II, III, IV, V, VI and VII to Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products (91/184/EEC). *Off J. Eur. Commun.*, **L91**, 59–62

Commission of the European Communities (1991d) Council Directive of 18 June 1991 amending for the 10th time Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (91/338/EEC). *Off J. Eur. Commun.*, **L186**, 59–63

Commission of the European Communities (1991e) Council Directive of 23 December 1991 standardizing and rationalizing reports on the implementation of certain Directives relating to the environment (91/692/EEC). *Off J. Eur. Commun.*, **L377**, 48–54

Coogan, T.P., Bare, R.M. & Waalkes, M.P. (1992) Cadmium-induced DNA strand damage in cultured liver cells: reduction in cadmium genotoxicity following zinc pretreatment. *Toxicol. appl. Pharmacol.*, **113**, 227–233

Cook, W.A., ed. (1987) *Occupational Exposure Limits—Worldwide*, Akron, OH, American Industrial Hygiene Association, pp. 118, 131, 168

Costa, M., Heck, J.D. & Robison, S.H. (1982) Selective phagocytosis of crystalline metal sulfide particles and DNA strand breaks as a mechanism for the induction of cellular transformation. *Cancer Res.*, **42**, 2757–2763

Crebelli, R., Conti, G., Conti, L. & Carere, A. (1991) In vitro studies with nine known or suspected spindle poisons: results in tests for chromosome malsegregation in *Aspergillus nidulans*. *Mutagenesis*, **6**, 131–136

Danielsson, B.R.G. & Dencker, L. (1984) Effects of cadmium on the placental uptake and transport to the fetus of nutrients. *Biol. Res. Pregn.*, **5**, 93–101

Daston, G.P. (1981a) Toxicity of minimal amounts of cadmium to the developing rat lung and pulmonary surfactant. *Toxicol. Lett.*, **9**, 125–130

Daston, G.P. (1981b) Effects of cadmium on the prenatal ultrastructural maturation of rat alveolar epithelium. *Teratology*, **23**, 75–84

Daston, G.P. (1982) Fetal zinc deficiency as a mechanism for cadmium induced toxicity to the developing rat lung and pulmonary surfactant. *Toxicology*, **24**, 55–63

Daston, G.P. & Grabowski, C.T. (1979) Toxic effects of cadmium on the developing rat lung. I. Altered pulmonary surfactant and the induction of respiratory distress syndrome. *J. Toxicol. environ. Health*, **5**, 973–983

Davison, A.G., Newman Taylor, A.J., Darbyshire, J., Chettle, D.R., Guthrie, C.J.G., O'Malley, D., Mason, H.J., Fayers, P.M., Venables, K.M., Pickering, C.A.C., Franklin, D., Scott, M.C., Holden, H. & Wright, A.L. (1988) Cadmium fume inhalation and emphysema. *Lancet*, **i**, 663–667

De, S.K., Dey, S.K. & Andrews, G.K. (1990) Cadmium teratogenicity and its relationship with metallothionein gene expression in midgestation mouse embryos. *Toxicology*, **64**, 89–104

Deaven, L.L. & Campbell, E.W. (1980) Factors affecting the induction of chromosomal aberrations by cadmium in Chinese hamster cells. *Cytogenet. Cell Genet.*, **26**, 251–260

De Flora, S., Zanacchi, P., Camoirano, A., Bennicelli, C. & Badolati, G.S. (1984a) Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test. *Mutat. Res.*, **133**, 161–198

De Flora, S., Camoirano, A., Zanacchi, P. & Bennicelli, C. (1984b) Mutagenicity testing with TA97 and TA102 of 30 DNA-damaging compounds, negative with other *Salmonella* strains. *Mutat. Res.*, **134**, 159–165

Degraeve, N. (1981) Carcinogenic, teratogenic and mutagenic effects of cadmium. *Mutat. Res.*, **86**, 115–135

Deknudt, G. & Deminatti, M. (1978) Chromosome studies in human lymphocytes after in vitro exposure to metal salts. *Toxicology*, **10**, 67–75

Deknudt, G. & Gerber, G.B. (1979) Chromosomal aberrations in bone-marrow cells of mice given a normal or a calcium-deficient diet supplemented with various heavy metals. *Mutat. Res.*, **68**, 163–168

Deknudt, G. & Léonard, A. (1975) Cytogenetic investigations on leucocytes of workers from a cadmium plant. *Environ. Physiol. Biochem.*, **5**, 319–327

De Marco, A., Paglialunga, S., Rizzoni, M., Testa, A. & Trinca, S. (1988) Induction of micronuclei in *Vicia faba* root tips treated with heavy metals (cadmium and chromium) in the presence of NTA. *Mutat. Res.*, **206**, 311–315

Dencker, L. (1975) Possible mechanisms of cadmium fetotoxicity in golden hamsters and mice: uptake by the embryo, placenta and ovary. *J. Reprod. Fertil.*, **44**, 461–471

De Silva, P.E. & Donnan, M.B. (1981) Chronic cadmium poisoning in a pigment manufacturing plant. *Br. J. ind. Med.*, **38**, 76–86

Deutsche Forschungsgemeinschaft (1992) *MAK- and BAT-Values 1992. Maximum Concentrations at the Workplace and Biological Tolerance Values for Working Materials* (Report No. 28), Weinheim, VCH Verlagsgesellschaft, p. 24

D.F. Goldsmith Chemical & Metal Corp. (undated) *High Purity Elements; Fine Inorganic Chemicals; Precious Metals; Mercury*, Evanston, IL, p. 7

Ding, G.Y., Sun, G.F., Fen, Z.L., Li, L.-X. & Li, C.Y. (1987) Epidemiologic research of cancer in exposed cadmium, lead, and arsenic workers (Chin.). *J. Chin. med. Univ.*, **16**, 368–371

DiPaolo, J.A. & Casto, B.C. (1979) Quantitative studies of in vitro morphological transformation of Syrian hamster cells by inorganic metal salts. *Cancer Res.*, **39**, 1008–1013

Doll, R. (1992) Is cadmium a human carcinogen? *Ann. Epidemiol.*, **2**, 336–337

Dudley, R.E., Svoboda, D.J. & Klaassen, C.D. (1982) Acute exposure to cadmium causes severe liver injury in rats. *Toxicol. appl. Pharmacol.*, **65**, 302–313

Dziekanowska, D. (1981) Studies on mutagenic effect of environmental factors in heavy metal plants (Pol.). *Pat. Pol.*, **32**, 263–268

Elinder, C.-G. (1992) Cadmium as an environmental hazard. In: Nordberg, G.F., Herber, R.F.M. & Alessio, L., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 123–132

Elinder, C.-G., Kjellström, T., Friberg, L., Lind, B. & Linnman, L. (1976) Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Estimation of biological half time in kidney cortex, considering calorie intake and smoking habits. *Arch. environ. Health*, **31**, 292–302

Elinder, C.-G., Friberg, L., Lind, B. & Jawaid, M. (1983) Lead and cadmium levels in blood samples from the general population of Sweden. *Environ. Res.*, **30**, 233–253

Elinder, C.-G., Kjellström, T., Hogstedt, C., Andersson, K. & Spång, G. (1985) Cancer mortality of cadmium workers. *Br. J. ind. Med.*, **42**, 651-655

Eller, P.M., ed. (1984a) Method 7300. In: *NIOSH Manual of Analytical Methods*, Vol. 1, 3rd Ed. (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 7300-1–7300-5

Eller, P.M., ed. (1984b) Method 8310. In: *NIOSH Manual of Analytical Methods*, Vol. 2, 3rd Ed. (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 8310-1–8310-6

Eller, P.M., ed. (1987) Method 7048. In: *NIOSH Manual of Analytical Methods*, Suppl. 2, 3rd Ed. (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 7048-1–7048-3

Ellis, K.J., Morgan, W.D., Zanzi, I., Yasumura, S., Vartsky, D. & Cohn, S.H. (1981) Critical concentrations of cadmium in human renal cortex: dose–effect studies in cadmium smelter workers. *J. Toxicol. environ. Health*, **7**, 691–703

Ellis, K.J., Cohn, S.H. & Smith, T.J. (1985) Cadmium inhalation exposure estimates: their significance with respect to kidney and liver cadmium burden. *J. Toxicol. environ. Health*, **15**, 173–187

Epstein, S.S., Arnold, E., Andrea, J., Bass, W. & Bishop, Y. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol. appl. Pharmacol.*, **23**, 288–325

Fairbridge, R.W. (1974) *The Encyclopedia of Geochemistry and Environmental Sciences*, Vol. IVA, *Encyclopedia of Earth Science Series*, New York, Van Nostrand Reinhold, pp. 99–100

FAO/WHO (1989) *Evaluation of Certain Food Additives and Contaminants. 33rd Report of the Joint FAO/WHO Expert Committee on Food Additives* (Technical Report Series 776), Geneva, pp. 28–31

Favino, A., Cavalleri, A., Nazari, G. & Tilli, M. (1968) Testosterone excretion in cadmium chloride induced testicular tumours in rats. *Med. Lav.*, **59**, 36–40

Feuston, M.H. & Scott, W.J., Jr (1985) Cadmium-induced forelimb ectrodactyly: a proposed mechanism of teratogenesis. *Teratology*, **32**, 407–419

Flanagan, P.R., McLellan, J.S., Haist, J., Cherian, M.G., Chamberlain, M.J. & Valberg, L.S. (1978) Increased dietary cadmium absorption in mice and human subjects with iron deficiency. *Gastroenterology*, **74**, 841–846

Fleig, I., Rieth, H., Stocker, W.G. & Thiess, A.M. (1983) Chromosome investigations of workers exposed to cadmium in the manufacturing of cadmium stabilizers and pigments. *Ecotoxicol. environ. Saf.*, **7**, 106–110

Forni, A., Toffoletto, F., Ortisi, E. & Alessio, L. (1990) Occupational exposure to cadmium: cytogenetic findings in relation to exposure levels. In: Seemayer, N.H. & Hadnagy, W., eds, *Environmental Hygiene II*, Berlin, Springer-Verlag, pp. 161–164

Förstner, U. (1984) Cadmium. In: Hutzingter, O., ed., *The Handbook of Environmental Chemistry*, Vol. 3, Part A, *Anthropogenic Compounds*, New York, Springer-Verlag, pp. 59–107

Friberg, L., Piscator, M. & Nordberg, G. (1971) *Cadmium in the Environment*, Cleveland, OH, CRC Press, pp. 19–26

Friberg, L., Piscator, M., Nordberg, G. & Kjellström, T., eds (1974) *Cadmium in the Environment*, 2nd Ed., Cleveland, OH, CRC Press

Friberg, L., Elinder, C.G., Kjellström, T. & Nordberg, G.F., eds (1985) *Cadmium and Health: A Toxicological and Epidemiological Appraisal*, Vol. I, *Exposure, Dose and Metabolism*, Cleveland, OH, CRC Press

Friberg, L., Kjellström, T. & Nordberg, G.F. (1986a) Cadmium. In: Friberg, L., Nordberg, G.F. & Vouk, V., eds, *Handbook on the Toxicology of Metals*, Vol. II, *Specific Metals*, 2nd Ed., Amsterdam, Elsevier, pp.130–184

Friberg, L., Elinder, C.-G., Kjellström, T. & Nordberg, G.F. (1986b) *Cadmium and Health: A Toxicological and Epidemiological Appraisal*, Vol. II, *Effects and Response*, Boca Raton, FL, CRC Press

Friedman, M.A. & Staub, J. (1976) Inhibition of mouse testicular DNA synthesis by mutagens and carcinogens as a potential simple mammalian assay for mutagenesis. *Mutat. Res.*, **37**, 67–76

Fukunaga, M., Kurachi, Y. & Mizuguchi, Y. (1982) Action of some metal ions on yeast chromosomes. *Chem. pharm. Bull.*, **30**, 3017–3019

Gale, T.F. (1979) Toxic effects of cadmium and amaranth on the developing hamster embryo. *Bull. environ. Contam. Toxicol.*, **22**, 175–181

Gasiorek, K. & Bauchinger, M. (1981) Chromosome changes in human lymphocytes after separate and combined treatment with divalent salts of lead, cadmium, and zinc. *Environ. Mutag.*, **3**, 513–518

Gerhardsson, L., Brune, D., Nordberg, G.F. & Wester, P.O. (1986) Distribution of cadmium, lead and zinc in lung, liver and kidney in long-term exposed smelter workers. *Sci. total Environ.*, **50**, 65–85

Ghess, M.-J., Wilbourn, J.D. & Vainio, H. (1992) *Directory of Agents Being Tested for Carcinogenicity* (No. 15), Lyon, IARC, p. 172

Ghezzi, I., Toffoletto, F., Sesana, G., Fagioli, M.G., Micheli, A., Di Silvestro, P., Zocchetti, C. & Alessio, L. (1985) Behaviour of biological indicators of cadmium in relation to occupational exposure. *Int. Arch. occup. environ. Health*, **55**, 133–140

Gilliavod, N. & Léonard, A. (1975) Mutagenicity tests with cadmium in the mouse. *Toxicology*, **5**, 43–47

Glaser, U., Klöppel, H. & Hochrainer, D. (1986) Bioavailability indicators of inhaled cadmium compounds. *Ecotoxicol. environ. Saf.*, **11**, 261–271

Glaser, U., Hochrainer, D., Otto, F.J. & Oldiges, H. (1990) Carcinogenicity and toxicity of four cadmium compounds inhaled by rats. *Toxicol. environ. Chem.*, **27**, 153–162

Glaser, U., Oldiges, H., Stoeppler, M. & Oberdörster, G. (1992) Cadmium solubility in suspension during long-term generation of CdS aerosols. In: Merian, E. & Haerdi, W., eds, *Metal Compounds in Environment and Life, 4*, Northwood/Wilmington, DE, Science and Technology Letters/Science Reviews, pp. 237–241

Greene, G.U. (1974) Cadmium compounds. In: Kirk, R.E. & Othmer, D.F., eds, *Encyclopedia of Chemical Technology*, 2nd Ed., Vol. 3, New York, John Wiley & Sons, pp. 899–911

Gunn, S.A., Gould, T.C. & Anderson, W.A.D. (1961) Zinc protection against cadmium injury to rat testis. *Arch. Pathol.*, **71**, 274–281

Gunn, S.A., Gould, T.C. & Anderson, W.A.D. (1963) Cadmium-induced interstitial-cell tumors in rats and mice and their prevention by zinc. *J. natl Cancer Inst.*, **31**, 745–759

Gunn, S.A., Gould, T.C. & Anderson, W.A.D. (1964) Effect of zinc on cancerogenesis by cadmium. *Proc. Soc. exp. Biol. Med.*, **115**, 653–657

Gunn, S.A., Gould, T.C. & Anderson, W.A.D. (1965) Comparative study of interstitial cell tumors of rat testis induced by cadmium injection and vascular ligation. *J. natl Cancer Inst.*, **35**, 329–337

Gunn, S.A., Gould, T.C. & Anderson, W.A.D. (1967) Specific response of mesenchymal tissue to cancerogenesis by cadmium. *Arch. Pathol.*, **83**, 493–499

Haddow, A., Dukes, C.E. & Mitchley, B.C.V. (1961) Carcinogenicity of iron preparations and metal–carbohydrate complexes. *Ann. Rep. Br. Emp. Cancer Campaign*, **39**, 74–76

Haddow, A., Roe, F.J.C., Dukes, C.E. & Mitchley, B.C.V. (1964) Cadmium neoplasia: sarcomata at the site of injection of cadmium sulphate in rats and mice. *Br. J. Cancer*, **18**, 667–673

Hamilton-Koch, W., Snyder, R.D. & Lavelle, J.M. (1986) Metal-induced DNA damage and repair in human diploid fibroblasts and Chinese hamster ovary cells. *Chem.-biol. Interactions*, **59**, 17–28

Han, C., Wu, G., Yin, Y. & Shen, M. (1992) Inhibition by germanium oxide of the mutagenicity of cadmium chloride in various genotoxicity assays. *Food chem. Toxicol.*, **30**, 521–524

Hansen, K. & Stern, R.M. (1984) A survey of metal-induced mutagenicity *in vitro* and *in vivo*. *J. Am. Coll. Toxicol.*, **3**, 381–430

Harrison, P.T.C. & Heath, J.C. (1986) Apparent synergy in lung carcinogenesis: interactions between *N*-nitrosoheptamethyleneimine, particulate cadmium and crocidolite asbestos fibres in rats. *Carcinogenesis*, **7**, 1903–1908

Hartwig, A. & Beyersmann, D. (1989) Comutagenicity and inhibition of DNA repair by metal ions in mammalian cells. *Biol. Trace Elem. Res.*, **21**, 359–365

Hassler, E., Lind, B. & Piscator, M. (1983) Cadmium in blood and urine related to present and past exposure. A study of workers in an alkaline battery factory. *Br. J. ind. Med.*, **40**, 420–425

Health and Safety Executive (1992) *EH40/92. Occupational Exposure Limits 1992*, London, Her Majesty's Stationary Office, p. 11

Heath, J.C. & Daniel, M.R. (1964) The production of malignant tumours by cadmium in the rat. *Br. J. Cancer*, **18**, 124–129

Heath, J.C., Daniel, M.R., Dingle, J.T. & Webb, M. (1962) Cadmium as a carcinogen. *Nature*, **193**, 592–593

Heinrich, U. (1992) Pulmonary carcinogenicity of cadmium by inhalation in animals. In: Nordberg, G.F., Herber, R.F.M. & Alessio, L., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 405–413

Heinrich, U., Peters, L., Ernst, H., Rittinghausen, S., Dasenbrock, C. & König, H. (1989) Investigation of the carcinogenic effects of various cadmium compounds after inhalation exposure in hamsters and mice. *Exp. Pathol.*, **37**, 253–258

Hellman, B. (1986) Evidence for stimulatory and inhibitory effects of cadmium on the [^{3}H]-thymidine incorporation into various organs of the mouse. *Toxicology*, **40**, 13–23

Herber, R.F.M., Stoeppler, M. & Tonks, D.B. (1990a) Cooperative interlaboratory surveys of the determination of cadmium in whole blood. *Fresenius' J. anal. Chem.*, **338**, 269–278

Herber, R.F.M., Stoeppler, M. & Tonks, D.B. (1990b) Cooperative interlaboratory surveys of cadmium analysis in urine. *Fresenius' J. anal. Chem.*, **338**, 279–286

Hoffmann, L., Putzke, H.-P., Simonn, C., Gase, P., Russbült, R., Kampehl, H.-J., Serfling, D., Erdmann, T. & Huckstorf, C. (1985a) Does cadmium play a role in the aetiology and pathogenesis of prostate carcinoma? (Ger.) *Z. ges. Hyg.*, **31**, 224–227

Hoffmann, L., Putzke, H.-P., Kampehl, H.-J., Russbült, R., Gase, P., Simonn, C., Erdmann, T. & Huckstorf, C. (1985b) Carcinogenic effects of cadmium on the prostate of the rat. *J. Cancer Res. clin. Oncol.*, **109**, 193–199

Hoffmann, L., Putzke, H.-P., Bendel, L., Erdmann, T. & Huckstorf, C. (1988) Electron microscopic results on the ventral prostate of the rat after $CdCl_2$ administration. A contribution towards etiology of the cancer of the prostate. *J. Cancer Res. clin. Oncol.*, **114**, 273–278

Holden, H. (1980a) Further mortality studies on workers exposed to cadmium fume. In: *Proceedings of the Seminar on Occupational Exposure to Cadmium, London, 20 March 1980*, London, Cadmium Association, pp. 23–24

Holden, H. (1980b) A mortality study of workers exposed to cadmium fumes. In: *Edited Proceedings of the Second International Cadmium Conference, Cannes, 6–8 February 1979*, London, Metal Bulletin Ltd, p. 211–215

Holden, H.A. (1982) Manufacture of cadmium–copper alloy. In: Wilson, D. & Volpe, R.A., eds, *Edited Proceedings of the Third International Cadmium Conference, Miami, FL, 3–5 February 1981*, London/New York, Cadmium Association/Cadmium Council, pp. 49–50

Hollander, M.L. & Carapella, S.C., Jr (1978) Cadmium and cadmium alloys. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 4, New York, John Wiley & Sons, pp. 387–396

Holt, D. & Webb, M. (1987) Teratogenicity of ionic cadmium in the Wistar rat. *Arch. Toxicol.*, **59**, 443–447

Howard, W., Leonard, B., Moody, W. & Kochhar, T.S. (1991) Induction of chromosome changes by metal compounds in cultured CHO cells. *Toxicol. Lett.*, **56**, 179–186

Hubermont, G., Buchet, J.P., Roels, H. & Lauwerys, R. (1978) Placental transfer of lead, mercury and cadmium in women living in a rural area. Importance of drinking water in lead exposure. *Int. Arch. occup. environ. Health*, **41**, 117–124

IARC (1973) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 2, *Some Inorganic and Organometallic Compounds*, Lyon, pp. 74–99

IARC (1976) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 11, *Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics*, Lyon, pp. 39–74

IARC (1986a) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon

IARC (1986b) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 40, *Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation*, Lyon, pp. 161–206

IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 139–142

IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 230–232

IARC (1987c) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 6, *Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42*, Lyon, pp. 100–106

IARC (1987d) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 6, *Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42*, Lyon, pp. 252–254

IARC (1989) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*, Lyon, pp. 329–442

IARC (1990a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 49, *Chromium, Nickel and Welding*, Lyon, pp. 257–445

IARC (1990b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 49, *Chromium, Nickel and Welding*, Lyon, pp. 447–525

IARC (1990c) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 49, *Chromium, Nickel and Welding*, Lyon, pp. 49–256

IARC (1992) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 54, *Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals*, Lyon, pp. 189–211

Impens, R.A., Delcarte, E. & Fagot, J. (1989) Sources, pathways, and transfer of cadmium in the environment: practical possibilities of controlling its dispersion. In: Hiscock, S.A. & Volpe, R.A., eds, *Edited Proceedings of the Sixth International Cadmium Conference, Paris, 19–21 April 1989*, London/Greenwich, CT, Cadmium Association/Cadmium Council, pp.20–23

Inoue, Y. & Watanabe, T.K. (1978) Toxicity and mutagenicity of cadmium and furylfuramide in *Drosophila melanogaster*. *Jpn. J. Genet.*, **53**, 183–189

International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva, pp. 68–71

Järup, L., Rogenfelt, A., Elinder, C.-G., Nogawa, K. & Kjellström, T. (1983) Biological half-time of cadmium in the blood of workers after cessation of exposure. *Scand. J. Work Environ. Health*, **9**, 327–331

Jin, P. & Ringertz, N.R. (1990) Cadmium induces transcription of proto-oncogenes c-*jun* and c-*myc* in rat L6 myoblasts. *J. biol. Chem.*, **265**, 14061–14064

J.T. Baker (1989) *1989/90 Catalog—Laboratory Reagents and Chromatography Products*, Phillipsburg, NJ, pp. 31–32

Kanematsu, N., Hara, M. & Kada, T. (1980) *rec* Assay and mutagenicity studies on metal compounds. *Mutat. Res.*, **77**, 109–116

Kanematsu, N., Nakamine, H., Fukuta, Y., Yasuda, J.-I., Kurenuma, S. & Shibata, K.-I. (1990) Mutagenicity of cadmium, platinum and rhodium compounds in cultured mammalian cells. *J. Gifu dent. Soc.*, **17**, 575–582

Kanisawa, M. & Schroeder, H.A. (1969) Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. *Cancer Res.*, **29**, 892–895

Kasuya, M., Teranishi, H., Kubota, M., Katoh, T., Aoshima, K., Saijo, Y., Iwata, K. & Kanai, M. (1986) Low molecular weight protein in blood and urine of itai-itai disease patients and their family members (Jpn). *Kankyo Hoken Rep.*, **52**, 176–180

Kasuya, M., Aoshima, K., Katoh, T., Teranishi, H., Horiguchi, H., Kitagawa, M. & Hagino, S. (1992) Natural history of itai-itai disease: a long-term observation on the clinical and laboratory findings in patients with itai-itai disease. In: Cook, M.E., Hiscock, S.A., Morrow, H. & Volpe, R.A., eds, *Edited Proceedings of the Seventh International Cadmium Conference, New Orleans, LA, 6–8 April 1992*, London/Reston, VA, Cadmium Association/Cadmium Council, pp. 180–192

Kawada, T., Koyama, H. & Suzuki, S. (1989) Cadmium, NAG activity and β_2-microglobulin in the urine of cadmium pigment workers. *Br. J. ind. Med.*, **46**, 52–55

Kawada, T., Shinmyo, R.R. & Suzuki, S. (1992) Urinary cadmium and *N*-acetyl-β-D-glucosaminidase excretion of inhabitants living in a cadmium-polluted area. *Int. Arch. occup. environ. Health*, **63**, 541–546

Kazantzis, G. (1963) Induction of sarcoma in the rat by cadmium sulphide pigment. *Nature*, **198**, 1213–1214

Kazantzis, G. (1987) Cadmium. In: Fishbein, L., Furst, A. & Mehlman, M.A., eds, *Advances in Modern Environmental Toxicology*, Vol. 11, *Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure*, Princeton, NJ, Princeton Scientific Publishing, pp. 127–143

Kazantzis, G. & Armstrong, B.G. (1983) A mortality study of cadmium workers from seventeen plants in England. In: Wilson, D. & Volpe, R.A., eds, *Edited Proceedings of the Fourth International Cadmium Conference, Munich, 2–4 March 1983*, London/New York, Cadmium Association/Cadmium Council, pp. 139–142

Kazantzis, G. & Blanks, R.G. (1992) A mortality study of cadmium exposed workers. In: Cook, M.E., Hiscock, S.A., Morrow, H. & Volpe, R.A., eds, *Edited Proceedings of the Seventh International Cadmium Conference, New Orleans, LA, 6-8 April 1992*, London/Reston, VA, Cadmium Association/Cadmium Council, pp. 150–157

Kazantzis, G. & Hanbury, W.J. (1966) The induction of sarcoma in the rat by cadmium sulphide and by cadmium oxide. *Br. J. Cancer*, **20**, 190–199

Kazantzis, G., Lam, T.-H. & Sullivan, K.R. (1988) Mortality of cadmium-exposed workers. A five-year update. *Scand. J. Work Environ. Health*, **14**, 220–223

Kazantzis, G., Blanks, R. & Teather, S. (1989) The mortality of cadmium exposed workers. In: Vernet, J.-P., ed., *Proceedings of the International Conference on Heavy Metals in the Environment, Geneva, September 1989*, Vol. 1, Edinburgh, CEP Consultants Ltd, pp. 304–307

Kazantzis, G., Blanks, R.G. & Sullivan, K.R. (1992) Is cadmium a human carcinogen? In: Nordberg, G.F., Herber, R.F.M. & Alessio, L., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 435–446

Kershaw, W.C. & Klaassen, C.D. (1991) Cadmium-induced elevation of hepatic isometallothionein concentrations in inbred strains of mice. *Chem.-biol. Interactions*, **78**, 269–282

Keyse, S.M. & Tyrrell, R.M. (1989) Heme oxygenase is the major 32-kDa stress protein induced in human skin fibroblasts by UVA radiation, hydrogen peroxide, and sodium arsenite. *Proc. natl Acad. Sci USA*, **86**, 99–103

Kido, T., Honda, R., Tsuritani, I., Yamaya, H., Ishizaki, M., Yamada, Y. & Nogawa, K. (1988) Progress of renal dysfunction in inhabitants environmentally exposed to cadmium. *Arch. environ. Health*, **43**, 213–217

Kimura, M., Nomura, T., Tanioka, Y., Tanimoto, Y., Suda, T., Yashiki, S., Tazaki, H., Tata, R., Deguchi, N., Kotako, N. & Salgusa, J. (1988) Effects of nutritional factors in monkeys given cadmium: an overall view (Jpn). *Kankyo Hoken Rep.*, **54**, 116–122

King, E. (1955) An environmental study of casting copper–cadmium alloys. *Br. J. ind. Med.*, **12**, 198–205

Kipling, M.D. & Waterhouse, J.A.H. (1967) Cadmium and prostatic carcinoma (Letter to the Editor). *Lancet*, **i**, 730–731

Kjellström, T. & Nordberg, G.F. (1978) A kinetic model of cadmium metabolism in the human being. *Environ. Res.*, **16**, 248–269

Kjellström, T., Evrin, P.-E. & Rahnster, B. (1977) Dose–response analysis of cadmium-induced tubular proteinuria. A study of urinary β_2-microglobulin excretion among workers in a battery factory. *Environ. Res.*, **13**, 303–317

Kjellström, T., Friberg, L. & Rahnster, B. (1979) Mortality and cancer morbidity among cadmium-exposed workers. *Environ. Health Perspectives*, **28**, 199–204

Kleinman, M.T., Rhodes, J.R., Guinn, V.P. & Thompson, R.J. (1989a) General atomic absorption procedure for trace metals in airborne material collected on filters. In: Lodge, J.P., Jr, ed., *Methods of Air Sampling and Analysis*, 3rd Ed., Chelsea, MI, Lewis Publishers, pp. 608–618

Kleinman, M.T., Courtney, W.J., Guinn, V.P., Rains, T.C., Rhodes, J.R. & Thompson, R.J. (1989b) General method for preparation of tissue samples for analysis for trace metals. In: Lodge, J.P., Jr, ed., *Methods of Air Sampling and Analysis*, 3rd Ed., Chelsea, MI, Lewis Publishers, pp. 619–622

Knorre, D. (1970a) Induction of skin sarcomas in albino rats by cadmium chloride (Ger.). *Arch. Geschwulstforsch.*, **36**, 119–126

Knorre, D. (1970b) Local skin damage in albino rats during the latent period of sarcoma formation after cadmium chloride injection (Ger.). *Zbl. allgemein. Pathol.*, **113**, 192–197

Knorre, D. (1971) Induction of interstitial tumours of the testis in albino rats by cadmium chloride (Ger.). *Arch. Geschwulstforsch.*, **38**, 257–263

Kogan, I.G., Grozdova, T.Y. & Kholikova, T.A. (1978) Mutagenic action of cadmium chloride on the germ cells of *Drosophila melanogaster*. *Sov. Genet.*, **14**, 1484–1488

Koizumi, T., Li, Z.G. & Tatsumoto, H. (1992) DNA Damaging activity of cadmium in Leydig cells, a target cell population for cadmium carcinogenesis in the rat testis. *Toxicol. Lett.*, **63**, 211–220

Kojima, S., Furukawa, A., Kiyozumi, M. & Shimada, H. (1991) Comparative renal toxicity of metallothineins with different cadmium/zinc ratios in rats. *Toxicol. Lett.*, **56**, 197–205

Kollmeier, H., Seemann, J., Wittig, P., Rothe, G. & Müller, K.-M. (1990) Cadmium in human lung tissue. *Int. Arch. occup. environ. Health*, **62**, 373–377

König, H.P., Heinrich, U., Koch, H. & Peters, L. (1992) Effect of photocorrosion on cadmium sulfide suspensions applied in animal inhalation studies with CdS particles. *Arch. environ. Contam. Toxicol.*, **22**, 30–35

Konishi, N., Ward, J.M. & Waalkes, M.P. (1990) Pancreatic hepatocytes in Fischer and Wistar rats induced by repeated injections of cadmium chloride. *Toxicol. appl. Pharmacol.*, **104**, 149–156

Kowal, N.E., Johnson, D.E., Kraemer, D.F. & Pahren, H.R. (1979) Normal levels of cadmium in diet, urine, blood, and tissues of inhabitants of the United States. *J. Toxicol. environ. Health*, **5**, 995–1014

Kozachenko, V.I., Pashin, Y. V., Soboleva, L.S. & Salnikova, L.E. (1987) Study of the mutagenic effect of cadmium chloride on mammals (Russ.). *Biol. Nauk.*, **11**, 102–105

Kuhnert, P.M., Kuhnert, B.R., Bottoms, S.F. & Erhard, P. (1982) Cadmium levels in maternal blood, fetal cord blood, and placental tissues of pregnant women who smoke. *Am. J. Obstet. Gynecol.*, **142**, 1021–1029

Kuhnert, B.R., Kuhnert, P.M., Debanne, S. & Williams, T.G. (1987) The relationship between cadmium, zinc, and birth weight in pregnant women who smoke. *Am. J. Obstet. Gynecol.*, **157**, 1247–1251

Kurokawa, Y., Matsushima, M., Imazawa, T., Takamura, N., Takahashi, M. & Hayashi, Y. (1985) Promoting effect of metal compounds on rat renal tumorigenesis. *J. Am. Coll. Toxicol.*, **4**, 321–330

Kurokawa, Y., Takahashi, M., Maekawa, A. & Hayashi, Y. (1989) Promoting effect of metal compounds on liver, stomach, kidney, pancreas, and skin carcinogenesis. *J. Am. Coll. Toxicol.*, **8**, 1235–1239

Lakkad, B.C., Nigam, S.K., Karnik, A.B., Thakore, K.N. & Chatterjee, B.B. (1986) Effect of cadmium chloride on cell division and chromosomes in Chinese hamster ovary cells. *Bull. environ. Contam. Toxicol.*, **36**, 342–349

Lamm, S.H., Parkinson, M., Anderson, M. & Taylor, W. (1992) Determinants of lung cancer risk among cadmium-exposed workers. *Ann. Epidemiol.*, **2**, 195–211

Laskey, J.W. & Phelps, P.V. (1991) Effect of cadmium and other metal cations on in vitro Leydig cell testosterone production. *Toxicol. appl. Pharmacol.*, **108**, 296–306

Laskey, J.W., Rehnberg, G.L., Favor, M.J., Cahill, D.F. & Pietrzak-Flis, Z. (1980) Chronic ingestion of cadmium and/or tritium. II. Effects on growth, development, and reproductive function. *Environ. Res.*, **22**, 466–475

Laskey, J.W., Rehnberg, G.L., Laws, S.C. & Hein, J.F. (1984) Reproductive effects of low acute doses of cadmium chloride in adult male rats. *Toxicol. appl. Pharmacol.*, **73**, 250–255

Laskey, J.W., Rehnberg, G.L., Laws, S.C. & Hein, J.F. (1986) Age-related dose response of selected reproductive parameters to acute cadmium chloride exposure in the male Long-Evans rat. *J. Toxicol. environ. Health*, **19**, 393–401

Lauwerys, R.R., Buchet, J.P. & Roels, H. (1976) The relationship between cadmium exposure or body burden and the concentration of cadmium in blood and urine in man. *Int. Arch. occup. environ. Health*, **36**, 275–285

Lauwerys, R., Buchet, J.P., Roels, H., Bernard, A., Chettle, D.R., Harvey, T.C. & Al Haddad, I.K. (1980) Biological significance of cadmium concentration in blood and urine and their application in monitoring workers exposed to cadmium. In: *Edited Proceedings of the Second International Cadmium Conference, Cannes, 6–8 February 1979*, London, Metal Bulletin Ltd, pp. 164–167

Layton, W.M., Jr & Layton, M.W. (1979) Cadmium induced limb defects in mice: strain associated differences in sensitivity. *Teratology*, **19**, 229–236

Lehman, L.D. & Klaassen, C.D. (1986) Dosage-dependent disposition of cadmium administered orally to rats. *Toxicol. appl. Pharmacol.*, **84**, 159–167

Lehotzky, K., Ungváry, G., Polinák, D. & Kiss, A. (1990) Behavioral deficits due to prenatal exposure to cadmium chloride in CFY rat pups. *Neurotoxicol. Teratol.*, **12**, 169–172

Lemen, R.A., Lee, J.S., Wagoner, J.K. & Blejer, H.P. (1976) Cancer mortality among cadmium production workers. *Ann. N.Y. Acad. Sci.*, **271**, 273–279

Léonard, A. (1988) Mechanisms in metal genotoxicity: the significance of in vitro approaches. *Mutat. Res.*, **198**, 321–326

Levin, A.A. & Miller, R.K. (1980) Fetal toxicity of cadmium in the rat: maternal *vs* fetal injections. *Teratology*, **22**, 1–5

Levin, A.A. & Miller, R.K. (1981) Fetal toxicity of cadmium in the rat: decreased utero-placental blood flow. *Toxicol. appl. Pharmacol.*, **58**, 297–203

Levin, A.A., Kilpper, R.W. & Miller, R.K. (1987) Fetal toxicity of cadmium chloride: the pharmacokinetics in the pregnant Wistar rat. *Teratology*, **36**, 163–170

Levy, L.S. & Clack, J. (1975) Further studies on the effect of cadmium on the prostate gland. I. Absence of prostatic changes in rats given oral cadmium sulphate for two years. *Ann. occup. Hyg.*, **17**, 205–211

Levy, L.S., Roe, F.J.C., Malcolm, D., Kazantzis, G., Clack, J. & Platt, H.S. (1973) Absence of prostatic changes in rats exposed to cadmium. *Ann. occup. Hyg.*, **16**, 111–118

Levy, L.S., Clack, J. & Roe, F.J.C. (1975) Further studies on the effect of cadmium on the prostate gland. II. Absence of prostatic changes in mice given oral cadmium sulphate for eighteen months. *Ann. occup. Hyg.*, **17**, 213–220

Lewis, G.P., Jusko, W.J., Coughlin, L.L. & Hartz, S. (1972) Contribution of cigarette smoking to cadmium accumulation in man (Preliminary communication). *Lancet*, **i**, 291–292

Lide, D.R., ed. (1991) *CRC Handbook of Chemistry and Physics*, 72nd Ed., Boca Raton, FL, CRC Press, pp. 4-46–4-47

Lindegaard, P.M., Hansen, S.O., Christensen, J.E.J., Andersen, B.B. & Andersen, O. (1990) The distribution of cadmium within the human prostate. *Biol. Trace Elem. Res.*, **25**, 97–104

Litvinov, N.N., Voronin, V.M. & Kazatchkov, V.I. (1986) Evaluation of carcinogenicity of nitrosodimethylamine used in combination with benzene, cadmium, boron or ethanol (Russ.). *Vopr. Onkol.*, **32**, 80–84

Llewellyn, T.O. (1992) *Annual Review: Cadmium in 1991*, Washington DC, Bureau of Mines, US Department of the Interior

Loiacono, N.J., Graziano, J.H., Kline, J.K., Popovac, D., Ahmedi, X., Gashi, E., Mehmeti, A. & Rajovic, B. (1992) Placental cadmium and birthweight in women living near a lead smelter. *Arch. environ. Health*, **47**, 250–255

Lorke, D. (1978) New studies on cadmium toxicology. In: *Edited Proceedings of the First International Cadmium Conference, San Francisco, 31 January–2 February 1977*, London, Metal Bulletin Ltd, pp. 175–179

Löser, E. (1980a) A 2-year oral carcinogenicity study with cadmium on rats. *Cancer Lett.*, **9**, 191–198

Löser, E. (1980b) Chronic toxicity and multigeneration studies on rats with cadmium. In: *Edited Proceedings of the Second International Cadmium Conference, Cannes, 6–8 February 1979*, London, Metal Bulletin Ltd, pp. 131–134

Louekari, K., Valkonen, S., Pousi, S. & Virtanen, L. (1991) Estimated dietary intake of lead and cadmium and their concentration in blood. *Sci. total Environ.*, **105**, 87–99

Lucas, P.A., Jariwalla, A.G., Jones, J.H., Gough, J. & Vale, P.T. (1980) Fatal cadmium fume inhalation (Letter to the Editor). *Lancet*, **ii**, 205

Lucis, O.J., Lucis, R. & Aterman, K. (1972) Tumorigenesis by cadmium. *Oncology*, **26**, 53–67

Machemer, L. & Lorke, D. (1981) Embryotoxic effect of cadmium on rats upon oral administration. *Toxicol. appl. Pharmacol.*, **58**, 438–443

Magos, L. (1991) Epidemiological and experimental aspects of metal carcinogenesis: physicochemical properties, kinetics, and the active species. *Environ. Health Perspectives*, **95**, 157–189

Mailhes, J.B., Preston, R.J., Yuan, Z.P. & Payne, H.S. (1988) Analysis of mouse metaphase II oocytes as an assay for chemically induced aneuploidy. *Mutat. Res.*, **198**, 145–152

Maitani, T., Waalkes, M.P. & Klaassen, C.D. (1984) Distribution of cadmium after oral administration of cadmium-thionein to mice. *Toxicol. appl. Pharmacol.*, **74**, 237–243

Malcolm, D. (1983) *Batteries, secondary or rechargeable, or accumulator.* In: Parmeggiani, L., ed., *Encyclopaedia of Occupational Health and Safety*, 3rd rev. Ed., Vol. 1, Geneva, International Labour Office, pp. 249–253

Mandel, R. & Ryser, H.J.-P. (1984) Mutagenicity of cadmium in *Salmonella typhimurium* and its synergism with two nitrosamines. *Mutat. Res.*, **138**, 9–16

Marzin, D.R. & Phi, H.V. (1985) Study of the mutagenicity of metal derivatives with *Salmonella typhimurium* TA102. *Mutat. Res.*, **155**, 49–51

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C. & Caspary, W.J. (1988) Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. *Environ. mol. Mutag.*, **12**, 85–154

McLean, J.R., McWilliams, R.S., Kaplan, J.G. & Birnboim, H.C. (1982) Rapid detection of DNA strand breaks in human peripheral blood cells and animal organs following treatment with physical and chemical agents. *Prog. Mutat. Res.*, **3**, 137–141

McLellan, J.S., Flanagan, P.R., Chamberlain, M.J. & Valberg, L.S. (1978) Measurement of dietary cadmium absorption in humans. *J. Toxicol. environ. Health*, **4**, 131–138

Messerle, K. & Webster, W.S. (1982) The classification and development of cadmium-induced limb defects in mice. *Teratology*, **25**, 61–70

Miller, B.M. & Adler, I.-D. (1992) Aneuploidy induction in mouse spermatocytes. *Mutagenesis*, **7**, 69–76

Min, K.-S., Fujita, Y., Onosaka, S. & Tanaka, K. (1991) Role of intestinal metallothionein in absorption and distribution of orally administered cadmium. *Toxicol. appl. Pharmacol.*, **109**, 7–16

Mitra, R.S. & Bernstein, I.A. (1978) Single-strand breakage in DNA of *Escherichia coli* exposed to Cd^{2+}. *J. Bacteriol.*, **133**, 75–80

Morselt, A.F.W., Leene, W., De Groot, C., Kipp, J.B.A., Evers, M., Roelofsen, A.M. & Bosch, K.S. (1988) Differences in immunological susceptibility to cadmium toxicity between two rat strains as demonstrated with cell biological methods. Effect of cadmium on DNA synthesis of thymus lymphocytes. *Toxicology*, **48**, 127–139

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. & Zeiger, E. (1986) *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. Mutag.*, **8** (Suppl. 7)

Mukherjee, A., Sharma, A. & Talukder, G. (1988a) Effect of selenium on cadmium-induced chromosomal aberrations in bone marrow cells of mice. *Toxicol. Lett.*, **41**, 23–29

Mukherjee, A., Giri, A.K., Sharma, A. & Talukder, G. (1988b) Relative efficacy of short-term tests in detecting genotoxic effects of cadmium chloride in mice *in vivo*. *Mutat. Res.*, **206**, 285–295

Müller, W.-U., Streffer, C. & Joos, A.L. (1990) Toxicity of cadmium sulphate and methylmercuric chloride applied singly or in combination to early mouse embryos *in vitro*. *Toxicol. in vitro*, **4**, 57–61

Müller, T., Schuckelt, R. & Jaenicke, L. (1991) Cadmium/zinc-metallothionein induces DNA strand breaks *in vitro*. *Arch. Toxicol.*, **65**, 20–26

Muntau, H. & Baudo, R. (1992) Sources of cadmium, its distribution and turnover in the freshwater environment. In: Nordberg, G., Herber, R.F.M. & Alessio, L., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 133–148

Murdoch, R.N. & Cowen, N.L. (1981) Foetotoxicity of cadmium in Quackenbush strain mice and the effects of the metal on uterine alkaline phosphatase during pseudopregnancy. *Aust. J. biol. Sci.*, **34**, 305–312

Nakagawa, H., Kawano, S., Okumura, Y., Fujita, T. & Nishi, M. (1987) Mortality study of inhabitants in a cadmium-polluted area. *Bull. environ. Contam. Toxicol.*, **38**, 553–560

Nakao, M. (1986) Studies on the effect of manganese and cadmium on carcinogenesis of prostatic cancer in rats (Jpn). *J. Kyoto Prefect. Univ. Med.*, **95**, 1681–1692

Naruse, I. & Hayashi, Y. (1989) Amelioration of the teratogenicity of cadmium by the metallothionein induced by bismuth nitrate. *Teratology*, **40**, 459–465

Nayak, B.N., Ray, M., Persaud, T.V.N. & Nigli, M. (1989) Embryotoxicity and in vivo cytogenetic changes following maternal exposure to cadmium chloride in mice. *Exp. Pathol.*, **36**, 75–80

Nishioka, H. (1975) Mutagenic activities of metal compounds in bacteria. *Mutat. Res.*, **31**, 185-189

Nogawa, K., Tsuritani, I., Yamada, Y., Kido, T., Honda, R., Ishizaki, M. & Kurihara, T. (1986) Sister chromatid exchanges in the lymphocytes of people exposed to environmental cadmium. *Toxicol. Lett.*, **32**, 283–288

Nogawa, K., Tsuritani, I., Kido, T., Honda, R., Ishizaki, M. & Yamada, Y. (1990) Serum vitamin D metabolites in cadmium-exposed persons with renal damage. *Int. Arch. occup. environ. Health*, **62**, 189–193

Nomiyama, K. & Nomiyama, H. (1984) Reversibility of cadmium-induced health effects in rabbits. *Environ. Health Perspectives*, **54**, 201–211

Nomiyama, K., Liu, S.-J. & Nomiyama, H. (1992) Critical levels of blood and urinary cadmium, urinary β_2-microglobulin and retinol-binding protein for monitoring cadmium health effects. In: Nordberg, G.F., Herber, R.F.M. & Alessio, G., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientification Publications No. 118), Lyon, IARC, pp. 325–340

Nordberg, G.F. (1972) Cadmium metabolism and toxicity. Experimental studies on mice with special reference to the use of biological materials as indices of retention and the possible role of metallothionein in transport and detoxification of cadmium. *Environ. Physiol. Biochem.*, **2**, 7–36

Nordberg, G.F. & Nordberg, M. (1988) Biological monitoring of cadmium. In: Clarkson, T.W., Friberg L., Nordberg, G.F. & Sager, P.R., eds, *Biological Monitoring of Toxic Metals*, New York, Plenum Press, pp. 151–168

Nordberg, G.F., Piscator, M. & Lind, B. (1971) Distribution of cadmium among protein fractions of mouse liver. *Acta pharmacol. toxicol.*, **29**, 456–470

Nordberg, G.F., Goyer, R.A. & Nordberg, M. (1975) Comparative toxicity of cadmium-metallothionein and cadmium chloride on mouse kidney. *Arch. Pathol.*, **99**, 192–197

Nordberg, G.F., Herber, R.F.M. & Alessio, L., eds (1992) *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC

Nriagu, J.O. & Pacyna, J.M. (1988) Quantitative assessment of worldwide contamination of air, water and soils by trace metals. *Nature*, **333**, 134–139

Oberdörster, G. (1986) Update on animal carcinogenicity studies with cadmium: extrapolation to humans and future research needs. In: Wilson, D. & Volpe, R.A., eds, *Edited Proceedings of the Fifth International Cadmium Conference, San Francisco, CA, 4–6 February 1986*, London/New York, Cadmium Association/Cadmium Council, pp. 108–111

Oberdörster, G. (1989) Pulmonary toxicity and carcinogenicity of cadmium. *J. Am. Coll. Toxicol.*, **8**, 1251–1263

Oberdörster, G. & Cherian, M.G. (1992) Cadmium and the lung: current perspectives of carcinogenicity. In: Cook, M.F., Hiscock, S.A., Morrow, H. & Volpe, R.A., eds, *Edited Proceedings of the Seventh International Cadmium Conference, New Orleans, LA, 6–8 April 1992*, London/Reston VA, Cadmium Association/Cadmium Council, pp. 130–134

Oberdörster, G. & Cox, C. (1989) Kinetics of inhaled $CdCl_2$, CdO and CdS in rats and monkeys. In: Hiscock, S.A. & Volpe, R.A., eds, *Edited Proceedings of the Sixth International Cadmium Conference, Paris, 19–21 April 1989*, London/New York, Cadmium Association/Cadmium Council, pp. 147–154

Oberdörster, G. & Cox, C. (1990) Carcinogenicity of cadmium in animals: What is the significance for man? *Toxicol. environ. Chem.*, **27**, 181–195

Oberdörster, G., Cherian, M.G. & Baggs, R.B. (1993) Correlation between cadmium-induced pulmonary carcinogenicity, metallothionein expression and inflammatory processes: a species comparison. *Environ. Health Perspectives* (in press)

Oberly, T.J., Piper, C.E. & McDonald, D.S. (1982) Mutagenicity of metal salts in the L5178Y mouse lymphoma assay. *J. Toxicol. environ. Health*, **9**, 367–376

Ochi, T. (1991) Cadmium-resistant Chinese hamster V79 cells with decreased accumulation of cadmium. *Chem.-biol. Interactions*, **78**, 207–221

Ochi, T. & Ohsawa, M. (1983) Induction of 6-thioguanine-resistant mutants and single-strand scission of DNA by cadmium chloride in cultured Chinese hamster cells. *Mutat. Res.*, **111**, 69–78

Ochi, T. & Ohsawa, M. (1985) Participation of active oxygen species in the induction of chromosomal aberrations by cadmium chloride in cultured Chinese hamster cells. *Mutat. Res.*, **143**, 137–142

Ochi, T., Ishiguro, T. & Ohsawa, M. (1983) Participation of active oxygen species in the induction of DNA single-strand scissions by cadmium chloride in cultured Chinese hamster cells. *Mutat. Res.*, **122**, 169–175

Ochi, T., Mogi, M., Watanabe, M. & Ohsawa, M. (1984) Induction of chromosomal aberrations in cultured Chinese hamster cells by short-term treatment with cadmium chloride. *Mutat. Res.*, **137**, 103–109

Ochi, T., Takahashi, K. & Ohsawa, M. (1987) Indirect evidence for the induction of a prooxidant state by cadmium chloride in cultured mammalian cells and a possible mechanism for the induction. *Mutat. Res.*, **180**, 257–266

Odone, P., Bertelli, G., Dell'Orto, A., Castoldi, M.R. & Alessio, L. (1983) Biological monitoring of cadmium-exposed workers (Ital.). *Med. Lav.*, **74**, 182–190

Ohno, H., Hanaoka, F. & Yamada, M.-A. (1982) Inducibility of sister-chromatid exchanges by heavy-metal ions. *Mutat. Res.*, **104**, 141–145

Ohta, H., Seki, Y. & Imamiya, S. (1988) Metallothionein-like cadmium binding protein in rat testes administered with cadmium and selenium. *Bull. environ. Contam. Toxicol.*, **41**, 195–200

O'Riordan, M.L., Hughes, E.G. & Evans, H.J. (1978) Chromosome studies on blood lymphocytes of men occupationally exposed to cadmium. *Mutat. Res.*, **58**, 305–311

Osgood, C., Zimmering, S. & Mason, J.M. (1991) Aneuploidy in Drosophila, II. Further validation of the FIX and ZESTE genetic test systems employing female *Drosophila melanogaster*. *Mutat. Res.*, **259**, 147–163

Otsuka, F. & Ohsawa, M. (1991) Differential susceptibility of T- and B-lymphocyte proliferation to cadmium: relevance to zinc requirement in T-lymphocyte proliferation. *Chem.-biol. Interactions*, **78**, 193–205

Pääkkö, P., Kokkonen, P., Anttila, S. & Kalliomäki, P.-L. (1989) Cadmium and chromium as markers of smoking in human lung tissue. *Environ. Res.*, **49**, 197–207

Padmanabhan, R. & Hameed, M.S. (1990) Characteristics of the limb malformations induced by maternal exposure to cadmium in the mouse. *Reprod. Toxicol.*, **4**, 291–304

Pagano, D.A & Zeiger, E. (1992) Conditions for detecting the mutagenicity of divalent metals in *Salmonella typhimurium*. *Environ. mol. Mutag.*, **19**, 139–146

Parizek, J. (1960) Sterilization of the male by cadmium salts. *J. Reprod. Fertil.*, **1**, 294–309

Parízek, J. (1983) Cadmium and reproduction: a perspective after 25 years. In: Clarkson, T.W., Nordberg, G.F. & Sager, P.R., eds, *Reproductive and Developmental Toxicity of Metals*, New York, Plenum Press, pp. 301–313

Parker, P.D. (1978) Cadmium compounds. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 4, New York, John Wiley & Sons, pp. 397–411

Parzyck, D.C., Shaw, S.M., Kessler, W.V., Vetter, R.J., Van Sickle, D.C. & Mayes, R.A. (1978) Fetal effects of cadmium in pregnant rats on normal and zinc deficient diets. *Bull. environ. Contam. Toxicol.*, **19**, 206–214

Peters, J.M., Thomas, D., Falk, H., Oberdörster, G. & Smith, T.J. (1986) Contribution of metals to respiratory cancer. *Environ. Health Perspectives*, **70**, 71–83

Plunkert, P.A. (1985) Cadmium. In: *Minerals Yearbook*, Vol. 1, *Metals and Minerals*, Washington DC, Bureau of Mines, US Department of the Interior, pp. 181–186

Pocock, S.J., Delves, H.T., Ashby, D., Shaper, A.G. & Clayton, B.E. (1988) Blood cadmium concentrations in the general population of British middle-aged men. *Hum. Toxicol.*, **7**, 95–103

Poirier, L.A., Kasprzak, K.S., Hoover, K.L. & Wenk, M.L. (1983) Effects of calcium and magnesium acetates on the carcinogenicity of cadmium chloride in Wistar rats. *Cancer Res.*, **43**, 4575–4581

Pomerantseva, M.D., Ramaiya, L.K. & Vilkina, G.A. (1980) Comparative efficiency of three different tests for estimation of mutagenicity of some factors in mammals (Russ.). *Genetika*, **8**, 1398–1403

Popenoe, E.A. & Schmaeler, M.A. (1979) Interaction of human DNA polymerase β with ions of copper, lead, and cadmium. *Arch. Biochem. Biophys.*, **196**, 109–120

Pott, F., Ziem, U., Reiffer, F.-J., Huth, F., Ernst, H. & Mohr, U. (1987) Carcinogenicity studies on fibres, metal compounds and some other dusts in rats. *Exp. Pathol.*, **32**, 129–152

Potts, C.L. (1965) Cadmium proteinuria. The health of battery workers exposed to cadmium oxide dust. *Ann. occup. Hyg.*, **8**, 55–61

Prigge, E. (1978) Inhalative cadmium effects in pregnant and fetal rats. *Toxicology*, **10**, 297–309

Princi, F. (1947) A study of industrial exposures to cadmium. *J. ind. Hyg. Toxicol.*, **29**, 315–320

Ramaiya, L.K. & Pomerantseva, M.D. (1977) A study of the mutagenic effect of cadmium on the germ cells of male mice. *Sov. Genet.*, **13**, 43–46

Ramel, C. & Magnusson, J. (1979) Chemical induction of nondisjunction in *Drosophila*. *Environ. Health Perspectives*, **31**, 59–66

Rasmuson, Å. (1985) Mutagenic effects of some water-soluble metal compounds in a somatic eye-color test system in *Drosophila melanogaster*. *Mutat. Res.*, **157**, 157–162

Reddy, J., Svoboda, D., Azarnoff, D. & Dawar, R. (1973) Cadmium-induced Leydig cell tumors of rat testis: morphologic and cytochemical study. *J. natl Cancer Inst.*, **51**, 891–903

Rehm, S. & Waalkes, M.P. (1988) Cadmium-induced ovarian toxicity in hamsters, mice, and rats. *Fundam. appl. Toxicol.*, **10**, 635–647

Richards, F.M., Watson, A. & Hickman, J.A. (1988) Investigation of the effects of heat shock and agents which induce a heat shock response on the induction of differentiation of HL-60 cells. *Cancer Res.*, **48**, 6715–6720

Ricksecker, R.E. (1979) Copper alloys. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 7, New York, John Wiley & Sons, pp. 1–68

Rivai, I.F., Koyama, H. & Suzuki, S. (1990) Cadmium content in rice and its daily intake in various countries. *Bull. environ. Contam. Toxicol.*, **44**, 910–916

Rivedal, E. & Sanner, T. (1981) Metal salts as promoters of in vitro morphological transformation of hamster embryo cells initiated by benzo(*a*)pyrene. *Cancer Res.*, **41**, 2950–2953

Robison, S.H., Cantoni, O. & Costa, M. (1982) Strand breakage and decreased molecular weight of DNA induced by specific metal compounds. *Carcinogenesis*, **3**, 657–662

Roe, F.J.C., Dukes, C.E., Cameron, K.M., Pugh, R.C.B. & Mitchley, B.C.V. (1964) Cadmium neoplasia: testicular atrophy and Leydig cell hyperplasia and neoplasia in rats and mice following subcutaneous injection of cadmium salts. *Br. J. Cancer*, **18**, 674–681

Roe, F.J.C., Carter, R.L., Dukes, C.E. & Mitchley, B.C.V. (1968) Non-carcinogenicity of cadmium-free ferritin. *Br. J. Cancer*, **22**, 517–520

Roeleveld, N., Zielhuis, G.A. & Gabreëls, F. (1990) Occupational exposure and defects of the central nervous system in offspring: a review. *Br. J. ind. Med.*, **47**, 580–588

Roels, H.A., Lauwerys, R.R., Buchet, J.-P., Bernard, A., Chettle, D.R., Harvey, T.C. & Al-Haddad, I.K. (1981) In vivo measurement of liver and kidney cadmium in workers exposed to this metal: its significance with respect to cadmium in blood and urine. *Environ. Res.*, **26**, 217–240

Roels, H.A., Lauwerys, R.R., Buchet, J.-P., Bernard, A., Vos, A. & Oversteyns, M. (1989) Health significance of cadmium induced renal dysfunction: a five year follow up. *Br. J. ind. Med.*, **46**, 755–764

Röhr, G & Bauchinger, M. (1976) Chromosome analyses in cell cultures of the Chinese hamster after application of cadmium sulphate. *Mutat. Res.*, **40**, 125–130

Rosas, I., Carbajal, M.E., Gómez-Arroyo, S., Belmont, R. & Villalobos-Pietrini, R. (1984) Cytogenetic effects of cadmium accumulation on water hyacinth (*Eichhornia crassipes*). *Environ. Res.*, **33**, 386–395

Rosenberg, D.W. & Kappas, A. (1991) Induction of heme oxygenase in the small intestinal epithelium: a response to oral cadmium exposure. *Toxicology*, **67**, 199–210

Rossman, T.G. & Molina, M. (1986) The genetic toxicology of metal compounds: II. Enhancement of ultraviolet light-induced mutagenesis in *Escherichia coli* WP2. *Environ. Mutag.*, **8**, 263–271

Rossman, T.G., Molina, M. & Meyer, L.W. (1984) The genetic toxicology of metal compounds: I. Induction of λ prophage in *E. coli* $WP2_s$ (λ). *Environ. Mutag.*, **6**, 59–69

Rossman, T.G., Roy, N.K. & Lin, W.-C. (1992) Is cadmium genotoxic? In: Nordberg, G.F., Herber, R.F.M. & Alessio, L., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 367–375

Saffiotti, U. & Bertolero, F. (1989) Neoplastic transformation of BALB/3T3 cells by metals and the quest for induction of a metastatic phenotype. *Biol. Trace Elem. Res.*, **21**, 475–482

Saillenfait, A.M., Payan, J.P., Brondeau, M.T., Zissu, D. & de Ceaurriz, J. (1991) Changes in urinary proximal tubule parameters in neonatal rats exposed to cadmium chloride during pregnancy. *J. appl. Toxicol.*, **11**, 23–27

Saito, H. (1987) Health of the inhabitants after removal of cadmium-polluted surface soil (Jpn.). *Kankyo Hoken Rep.*, **53**, 215–216

Saltzman, R.A., Miller, R.K. & di Sant'Agnese, P.A. (1989) Cadmium exposure on day 12 of gestation in the Wistar rat: distribution, uteroplacental blood flow, and fetal viability. *Teratology*, **39**, 19–30

Samarawickrama, G.P. & Webb, M. (1979) Acute effects of cadmium on the pregnant rat and embryo-fetal development. *Environ. Health Perspectives*, **28**, 245–249

Samarawickrama, G.P. & Webb, M. (1981) The acute toxicity and teratogenicity of cadmium in the pregnant rat. *J. appl. Toxicol.*, **1**, 264–269

Sanders, C.L. & Mahaffey, J.A. (1984) Carcinogenicity of single and multiple intratracheal instillations of cadmium oxide in the rat. *Environ. Res.*, **33**, 227–233

Sandhu, S.S., Dhesi, J.S., Gill, B.S. & Svendsgaard, D. (1991) Evaluation of 10 chemicals for aneuploidy induction in the hexaploid wheat assay. *Mutagenesis*, **6**, 369–373

Savitz, D. (1986) Changes in Spanish surname cancer rates relative to other whites, Denver area, 1969–71 to 1979–81. *Am. J. public Health*, **76**, 1210–1215

Sax, N.I. & Lewis, R.J. (1987) *Hawley's Condensed Chemical Dictionary*, 11th Ed., New York, Van Nostrand Reinhold, pp. 195–198

Saxena, D.K., Murthy, R.C. & Chandra, S.V. (1986) Embryotoxic and teratogenic effects of interaction of cadmium and lindane in rats. *Acta pharmacol. toxicol.*, **59**, 175–178

Schaller, K.H., Angerer, J. & Lehnert, G. (1991) Internal and external quality control in the toxicological analysis of blood and urine samples in the Federal Republic of Germany. *Int. Arch. occup. environ. Health*, **62**, 537–542

Schiestl, R.H., Gietz, R.D., Mehta, R.D. & Hastings, P.J. (1989) Carcinogens induce intrachromosomal recombination in yeast. *Carcinogenesis*, **10**, 1445–1455

Schmid, B.P., Hall, J.L., Goulding, E., Fabro, S. & Dixon, R. (1983) In vitro exposure of male and female mice gametes to cadmium chloride during the fertilization process, and its effects on pregnancy outcome. *Toxicol. appl. Pharmacol.*, **69**, 326–332

Schroeder, H.A., Vinton, W.H., Jr & Balassa, J.J. (1963) Effects of chromium, cadmium and lead on the growth and survival of rats. *J. Nutr.*, **80**, 48–54

Schroeder, H.A., Balassa, J.J. & Vinton, W.H., Jr (1964) Chromium, lead, cadmium, nickel and titanium in mice: effect on mortality, tumors and tissue levels. *J. Nutr.*, **83**, 239–250

Schroeder, H.A., Balassa, J.J. & Vinton, W.H., Jr (1965) Chromium, cadmium and lead in rats: effects on life span, tumors and tissue levels. *J. Nutr.*, **86**, 51–66

Schulte-Schrepping, K.-H. & Piscator, M. (1985) Cadmium and cadmium compounds. In: Gerhartz, W., Yamamoto, Y.S., Campbell, F.T., Pfefferkorn, R. & Rounsaville, J.F., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th Ed., Vol. A4, Deerfield Beach, FL, VCH Publishers, pp. 499–514

Scott, R. & Aughey, E. (1978) Methylcholanthrene and cadmium induced changes in rat prostate. *Br. J. Urol.*, **50**, 25–28

Sehgal, A., Osgood, C. & Zimmering, S. (1990) Aneuploidy in *Drosophila*. III: Aneuploidogens inhibit in vitro assembly of taxol-purified *Drosophila* microtubules. *Environ. mol. Mutag.*, **16**, 217–224

Shagarofsky-Tummers, A. (1992) The regulatory status of cadmium in the European Communities. In: Cook, M.E., Hiscock, S.A., Morrow, H. & Volpe, R.A., eds, *Edited Proceedings of the Seventh International Cadmium Conference, New Orleans, LA, 6–8 April 1992*, London/Reston, VA, Cadmium Association/Cadmium Council, pp. 106–109

Shaikh, Z.A., Ellis, K.J., Subramanian, K.S. & Greenberg, A. (1990) Biological monitoring for occupational cadmium exposure: the urinary metallothionein. *Toxicology*, **63**, 53–62

Shepard, T.H. (1992) *Catalog of Teratogenic Agents*, 7th Ed., Baltimore, MD, Johns Hopkins University Press, pp. 61–62

Shigematsu, I., Kitamaru, S., Takeuchi, J., Minowa, M., Nagai, M., Usui, T. & Fukushima, M. (1982) A retrospective mortality study on cadmium-exposed populations in Japan. In: Wilson, D. & Volpe, R.A., eds, *Edited Proceedings of the Third International Cadmium Conference, Miami, FL, 3–5 February 1981*, London/New York, Cadmium Association/Cadmium Council, pp. 115–118

Shimada, T., Watanabe, T. & Endo, A. (1976) Potential mutagenicity of cadmium in mammalian oocytes. *Mutat. Res.*, **40**, 389–395

Shiraishi, Y. (1975) Cytogenetic studies in 12 patients with itai-itai disease. *Humangenetik*, **27**, 31-44

Shiraishi, Y., Kurahashi, H. & Yosida, T.H. (1972) Chromosomal aberrations in cultured human leucocytes induced by cadmium sulfide. *Proc. Jpn. Acad.*, **48**, 133–137

Siemiatycki, J. (1991) *Risk Factors for Cancer in the Workplace*, Boca Raton, FL, CRC Press

Siemiatycki, J., Wacholder, S., Dewar, R., Wald, L., Bégin, D., Richardson, L., Rosenman, K. & Gérin, M. (1988) Smoking and degree of occupational exposure: are internal analyses in cohort studies likely to be confounded by smoking status? *Am. J. ind. Med.*, **13**, 59–69

Sina, J.F., Bean, C.L., Dysart, G.R., Taylor, V.I. & Bradley, M.O. (1983) Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat. Res.*, **113**, 357–391

Skerfving, S., Christoffersson, J.-O., Shütz, A., Welinder, H., Spång, G., Ahlgren, L. & Mattsson, S. (1987) Biological monitoring, by in vivo XRF measurements, of occupational exposure to lead, cadmium and mercury. *Biol. Trace Elem. Res.*, **13**, 241–251

Smith, T.J., Anderson, R.J. & Reading, J.C. (1980) Chronic cadmium exposures associated with kidney function effects. *Am. J. ind. Med.*, **1**, 319–337

Smith, N.J., Topping, M.D., Stewart, J.D. & Fletcher, J.G. (1986) Occupational cadmium exposure in jig solderers. *Br. J. ind. Med.*, **43**, 663–666

Snow, E.T. (1992) Metal carcinogenesis: mechanistic implications. *Pharmacol. Ther.*, **53**, 31–65

Snyder, R.D. (1988) Role of active oxygen species in metal-induced DNA strand breakage in human diploid fibroblasts. *Mutat. Res.*, **193**, 237–246

Sorahan, T. (1987) Mortality from lung cancer among a cohort of nickel cadmium battery workers: 1946–84. *Br. J. ind. Med.*, **44**, 803–809

Sorahan, T. & Waterhouse, J.A. (1983) Mortality study of nickel–cadmium battery workers by the method of regression models in life tables. *Br. J. ind. Med.*, **40**, 293–300

Sorahan, T. & Waterhouse, J.A.H. (1985) Cancer of the prostate among nickel–cadmium battery workers (Letter to the Editor). *Lancet*, **i**, 459

Sorell, T.L. & Graziano, J.H. (1990) Effect of oral cadmium exposure during pregnancy on maternal and fetal zinc metabolism in the rat. *Toxicol. appl. Pharmacol.*, **102**, 537–545

Spectrum Chemical Mfg Corp. (1991) *Laboratory, Pharmaceutical, Cosmetic and Biotechnology Chemicals—ACS—USP/NF—FCC—1991–1992*, Gardena, CA, pp. 74–77

Stayner, L., Smith, R., Thun, M., Schnorr, T. & Lemen, R. (1992) A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. *Ann. Epidemiol.*, **2**, 177–194

Stayner, L., Smith, R., Schnorr, T., Lemen, R. & Thun, M. (1993) Letter regarding cadmium and lung cancer. *Ann. Epidemiol.*, **3**, 114–116

Stoeppler, M. & Brandt, K. (1980) Contributions to automated trace analysis. Part V. Determination of cadmium in whole blood and urine by electrothermal atomic-absorption spectrophotometry. *Fresenius' Z. anal. Chem.*, **300**, 372–380

Stoner, G.D., Shimkin, M.B., Troxell, M.C., Thompson, T.L. & Terry, L.S. (1976) Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. *Cancer Res.*, **36**, 1744–1747

Strem Chemicals (1992) *Catalog No. 14—Metals, Inorganics and Organometallics for Research*, Newburyport, MA, pp. 22–23

Sunderman, F.W., Jr (1984) Recent advances in metal carcinogenesis. *Ann. clin. Lab. Sci.*, **14**, 93-122

Suter, K.E. (1975) Studies on the dominant-lethal and fertility effects of the heavy metal compounds methylmercuric hydroxide, mercuric chloride, and cadmium chloride in male and female mice. *Mutat. Res.*, **30**, 365–374

Sutou, S., Yamamoto, K., Sendota, H., Tomomatsu, K., Shimizu, Y. & Sugiyama, M. (1980a) Toxicity, fertility, teratogenicity, and dominant lethal tests in rats administered cadmium subchronically. I. Toxicity studies. *Ecotoxicol. environ. Saf.*, *4*, 39–50

Sutou, S., Yamamoto, K., Sendota, H. & Sugiyama, M. (1980b) Toxicity, fertility, teratogenicity, and dominant lethal tests in rats administered cadmium subchronically. II. Fertility, teratogenicity, and dominant lethal tests. *Ecotoxicol. environ. Saf.*, *4*, 51–56

Svensk Författningssamling (1979) *Förordning om ändring i kungörelsen (1973:334) om hälso- och miliöfarliga varor* [Directive for amendment to notification (1973:334) of products that are dangerous to health and the environment] (SFS 1979:771), Stockholm

Svensk Författningssamling (1980) *Förordning om ändring i förordningen (1979:771) om ändring i kungörelsen (1973:334) om hälso- och miljöfarliga varor* [Directive for amendment to notification (1979:771) about amendment to notification (1973:334) of products that are dangerous to health and the environment] (SFS 1980:84), Stockholm

Swierenga, S.H.H., Gilman, J.P.W. & McLean, J.R. (1987) Cancer risk from inorganics. *Cancer Metastasis Rev.*, **6**, 113–154

Takenaka, S., Oldiges, H., König, H., Hochrainer, D. & Oberdörster, G. (1983) Carcinogenicity of cadmium chloride aerosols in Wistar rats. *J. natl Cancer Inst.*, **70**, 367–373

Tang, X.-M., Chen, X.-Q., Zhang, J.-X. & Qin, W.-Q. (1990) Cytogenetic investigation in lymphocytes of people living in cadmium-polluted areas. *Mutat. Res.*, **241**, 243–249

Terracio, L. & Nachtigal, M. (1986) Transformation of prostatic epithelial cells and fibroblasts with cadmium chloride *in vitro*. *Arch. Toxicol.*, **58**, 141–151

Terracio, L. & Nachtigal, M. (1988) Oncogenicity of rat prostate cells transformed *in vitro* with cadmium chloride. *Arch. Toxicol.*, **61**, 450–456

Thomas, P.T., Ratajczak, H.V., Aranyi, C., Gibbons, R. & Fenters, J.D. (1985) Evaluation of host resistance and immune function in cadmium-exposed mice. *Toxicol. appl. Pharmacol.*, **80**, 446–456

Thun, M.J., Schnorr, T.M., Smith, A.B., Halperin, W.E. & Lemen, R.A. (1985) Mortality among a cohort of US cadmium production workers—an update. *J. natl Cancer Inst.*, **74**, 325–333

Thun, M.J., Schnorr, T.M. & Halperin, W.E. (1986) Retrospective mortality study of cadmium workers—an update. In: Wilson, D. & Volpe, R.A., eds., *Edited Proceedings of the Fifth International Cadmium Conference, San Francisco, CA, 4–6 February 1986*, London/New York, Cadmium Association/Cadmium Council, pp. 115–119

Thun, M.J., Elinder, C.-G. & Friberg, L. (1991) Scientific basis for an occupational standard for cadmium. *Am. J. ind. Med.*, **20**, 629-642

Tso, W.-W. & Fung, W.-P. (1981) Mutagenicity of metallic cations. *Toxicol. Lett.*, **8**, 195-200

Tsuchiya, K. (1967) Proteinuria of workers exposed to cadmium fume. The relationship to concentration in the working environment. *Arch. environ. Health*, **14**, 875-880

Tsuchiya, K., Seki, Y. & Sugita, M. (1976) Organ and tissue cadmium concentrations of cadavers from accidental deaths. *Keio J. Med.*, **25**, 83-90

Ulicny, L.J. (1992) What is the evidence for the carcinogenicity of cadmium sulphide pigments? In: Cook, M.E., Hiscock, S.A., Morrow, H. & Volpe, R.A., eds, *Edited Proceedings of the Seventh International Cadmium Conference, New Orleans, LA, 6–8 April 1992*, London/Reston, VA, Cadmium Association/Cadmium Council, pp. 139–144

Umeda, M. & Nishimura, M. (1979) Inducibility of chromosomal aberrations by metal compounds in cultured mammalian cells. *Mutat. Res.*, **67**, 221–229

UNEP (1984) *List of Environmentally Dangerous Chemical Substances and Processes of Global Significance* (Report of the Executive Director of UNEP to the 12th Session of Its Governing Council), Geneva, International Register of Potentially Toxic Chemicals

UNEP (1992) *Chemical Pollution: A Global Overview*, Geneva

UNEP (1993) *IRPTC PC Database*, Geneva

US Environmental Protection Agency (1986a) Method 6010. Inductively coupled plasma atomic emission spectroscopy. In: *Test Methods for Evaluating Solid Waste—Physical/Chemical Methods*, 3rd Ed., Vol. 1A (US EPA No. SW-846), Washington DC, Office of Solid Waste and Emergency Response, pp. 6010-1–6010-17

US Environmental Protection Agency (1986b) Method 7130. Cadmium (atomic absorption, direct aspiration). In: *Test Methods for Evaluating Solid Waste—Physical/Chemical Methods*, 3rd Ed., Vol. 1A (US EPA No. SW-846), Washington DC, Office of Solid Waste and Emergency Response, pp. 7130-1–7130-4

US Environmental Protection Agency (1986c) Method 7131. Cadmium (atomic absorption, furnace technique). In: *Test Methods for Evaluating Solid Waste—Physical/Chemical Methods*, 3rd Ed., Vol. 1A (US EPA No. SW-846), Washington DC, Office of Solid Waste and Emergency Response, pp. 7131-1–7131-5

US Environmental Protection Agency (1991) Maximum contaminant levels for inorganic chemicals. *US Code fed. Regul.*, **Title 40**, pp. 585–586

US Food and Drug Administration (1992) Standards of quality—bottled water. *US Code fed. Regul.*, **Title 21**, pp. 61–64

US National Cancer Institute (1986) *Cancer Among Blacks and Other Minorities: Statistical Profiles* (NIH Publication No. 86-2785), Bethesda, MD, US Department of Health and Human Services, pp. 9–10

US National Toxicology Program (1991) Cadmium and certain cadmium compounds. In: *Sixth Annual Report on Carcinogens. Summary 1991*, Research Triangle Park, NC, US Public Health Service, Department of Health and Human Services, pp. 114–121

US Occupational Safety and Health Administration (1992) Occupational exposure to cadmium: final rules. *Fed. Reg.*, **57**, 42102–42463

Vainio, H. & Sorsa, M. (1981) Chromosome aberrations and their relevance to metal carcinogenesis. *Environ. Health Perspectives*, **40**, 173–180

Verbost, P.M., Flik, G., Pang, P.K.T., Lock, R.A.C. & Bonga, S.E.W. (1989) Cadmium inhibition of the erythrocyte Ca^{2+} pump. A molecular interpretation. *J. biol. Chem.*, **264**, 5613–5615

Volkova, N.A. & Karplyuk, I.A. (1990) Cadmium mutagenic activity after oral administration (Russ.). *Vop. Pitan.*, **1**, 74–76

Waalkes, M.P. (1986) Effect of dietary zinc deficiency on the accumulation of cadmium and metallothionein in selected tissues of the rat. *J. Toxicol. environ. Health*, **18**, 301–313

Waalkes, M.P. & Goering, P.L. (1990) Metallothionein and other cadmium-binding proteins: recent developments. *Chem. Res. Toxicol.*, **3**, 281–288

Waalkes, M.P. & Oberdörster, G. (1990) Cadmium carcinogenesis. In: Foulkes, E.C., ed., *Biological Effects of Heavy Metals*, Vol. II, *Metal Carcinogenesis*, Boca Raton, FL, CRC Press, pp. 129–157

Waalkes, M.P. & Perantoni, A. (1988) In vitro assessment of target cell specificity in cadmium carcinogenesis: interactions of cadmium and zinc with isolated interstitial cells of the rat testes. *In vitro cell. dev. Biol.*, **24**, 558–565

Waalkes, M.P. & Rehm, S. (1992) Carcinogenicity of oral cadmium in the male Wistar (WF/NCr) rat: effect of chronic dietary zinc deficiency. *Fundam. appl. Toxicol.*, **19**, 512–520

Waalkes, M.P., Rehm, S., Riggs, C.W., Bare, R.M., Devor, D.E., Poirier, L.A., Wenk, M.L., Henneman, J.R. & Balaschak, M.S. (1988a) Cadmium carcinogenesis in the male Wistar [Crl:(WI)BR] rat: dose–response analysis of tumor induction in the prostate and testes and at the injection site. *Cancer Res.*, **48**, 4656–4663

Waalkes, M.P., Perantoni, A., Bhave, M.R. & Rehm, S. (1988b) Strain dependence in mice of resistance and susceptibility to the testicular effects of cadmium: assessment of the role of testicular cadmium-binding proteins. *Toxicol. appl. Pharmacol.*, **93**, 47–61

Waalkes, M.P., Rehm, S. & Perantoni, A. (1988c) Metal-binding proteins of the Syrian hamster ovaries: apparent deficiency of metallothionein. *Biol. Reprod.*, **39**, 953–961

Waalkes, M.P., Perantoni, A. & Palmer, A.E. (1988d) Isolation and partial characterization of the low-molecular-mass zinc/cadmium-binding protein from the testes of the patas monkey (*Erythrocebus patas*). Distinction from metallothionein. *Biochem. J.*, **256**, 131–137

Waalkes, M.P., Rehm, S., Riggs, C.W., Bare, R.M., Devor, D.E., Poirier, L.A., Wenk, M.L. & Henneman, J.R. (1989) Cadmium carcinogenesis in male Wistar [Crl:(WI)BR] rats: dose–response analysis of effects of zinc on tumor induction in the prostate, in the testes and at the injection site. *Cancer Res.*, **49**, 4282–4288

Waalkes, M.P., Rehm, S., Sass, B., Konishi, N. & Ward, J.M. (1991a) Chronic carcinogenic and toxic effects of a single subcutaneous dose of cadmium in the male Fischer rat. *Environ. Res.*, **55**, 40–50

Waalkes, M.P., Kovatch, R. & Rehm, S. (1991b) Effect of chronic dietary zinc deficiency on cadmium toxicity and carcinogenesis in the male Wistar [Hsd:(WI)BR] rat. *Toxicol. appl. Pharmacol.*, **108**, 448-456

Waalkes, M.P., Diwan, B.A., Weghorst, C.M., Bare, R.M., Ward, J.M. & Rice, J.M. (1991c) Anticarcinogenic effects of cadmium in B6C3F1 mouse liver and lung. *Toxicol. appl. Pharmacol.*, **110**, 327–335

Waalkes, M.P., Coogan, T.P. & Barter, R.A. (1992a) Toxicological principles of metal carcinogenesis with special emphasis on cadmium. *CRC Crit. Rev. Toxicol.*, **22**, 175–201

Waalkes, M.P., Rehm, S., Perantoni, A.O. & Coogan, T.P. (1992b) Cadmium exposure in rats and tumours of the prostate. In: Nordberg, G.F., Herber, R.F.M. & Alessio, L., eds, *Cadmium in the Human Environment: Toxicity and Carcinogenicity* (IARC Scientific Publications No. 118), Lyon, IARC, pp. 391–400

Wade, G.G., Mandel, R. & Ryser, H.J.-P. (1987) Marked synergism of dimethylnitrosamine carcinogenesis in rats exposed to cadmium. *Cancer Res.*, **47**, 6606–6613

Warner, C.W., Sadler, T.W., Tulis, S.A. & Smith, M.K. (1984) Zinc amelioration of cadmium-induced teratogenesis *in vitro*. *Teratology*, **30**, 47–53

Watanabe, T., Shimada, T. & Endo, A. (1977) Mutagenic effects of cadmium on the oocyte chromosomes of mice. *Jpn. J. Hyg.*, **32**, 472–481

Watanabe, T., Shimada, T. & Endo, A. (1979) Mutagenic effects of cadmium on mammalian oocyte chromosomes. *Mutat. Res.*, **67**, 349–356

Watanabe, M., Honda, S., Hayashi, M. & Matsuda, T. (1982) Mutagenic effects of combinations of chemical carcinogens and environmental pollutants in mice as shown by the micronucleus test. *Mutat. Res.*, **97**, 43–48

Watanabe, T., Koizumi, A., Fujita, H., Kumai, M. & Ikeda, M. (1985) Dietary cadmium intakes of farmers in nonpolluted areas in Japan, and the relation with blood cadmium levels. *Environ. Res.*, **37**, 33–43

Watanabe, T., Nakatsuka, H. & Ikeda, M. (1989) Cadmium and lead contents in rice available in various areas of Asia. *Sci. total Environ.*, **80**, 175–184

Watanabe, T., Nakatsuka, H., Satoh, H., Yamamoto, R. & Ikeda, M. (1992) Reduced dietary cadmium intake in past 12 years in a rural area in Japan. *Sci. total Environ.*, **119**, 43–50

Webb, M. & Samarawickrama, G.P. (1981) Placental transport and embryonic utilization of essential metabolites in the rat at the teratogenic dose of cadmium. *J. appl. Toxicol.*, **1**, 270–277

Webster, W.S. (1978) Cadmium-induced fetal growth retardation in the mouse. *Arch. environ. Health*, **33**, 36–42

Webster, W.S. & Messerle, K. (1980) Changes in the mouse neuroepithelium associated with cadmium-induced neural tube defects. *Teratology*, **21**, 79–88

Weischer, C.H. & Greve, J. (1979) Effects of cadmium-chloride-aerosols on three generations of Wistar rats (Ger.). *Zbl. Bakt. Hyg. I Abt. Orig. B*, **169**, 427–435

Whelton, B.D., Bhattacharyya, M.H., Carnes, B.A., Moretti, E.S. & Peterson, D.P. (1988) Female reproduction and pup survival and growth for mice fed a cadmium-containing purified diet through six consecutive rounds of gestation and lactation. *J. Toxicol. environ. Health*, **24**, 321–343

Whittaker, S.G., Zimmermann, F.K., Dicus, B., Piegorsch, W.W., Fogel, S. & Resnick, M.A. (1989) Detection of induced mitotic chromosome loss in *Saccharomyces cerevisiae*—an interlaboratory study. *Mutat. Res.*, **224**, 31–78

WHO (1980) *Recommended Health-based Limits in Occupational Exposure to Heavy Metals* (Technical Report Series 647), Geneva, pp. 21–35

WHO (1984) *Guidelines for Drinking-water Quality*, Vol. 1, *Recommendations*, Geneva, pp. 6, 54

WHO (1987) *Air Quality Guidelines for Europe* (WHO Regional Publications, Eur. Ser. No. 23), Copenhagen, pp. 206–207

WHO (1988) *Emission of Heavy Metal and PAH Compounds From Municipal Solid Waste Incinerators: Control Technology and Health Effects. Report on a WHO Meeting, Florence, 12–16 October 1987*, Copenhagen, pp. 31, 38–40

WHO (1989) *Evaluation of Certain Food Additives and Contaminants*, Geneva, pp. 28–31

WHO (1992a) *Cadmium—Environmental Aspects* (Environmental Health Criteria 135), Geneva

WHO (1992b) *Cadmium* (Environmental Health Criteria 134), Geneva

WHO (1992c) *Guidelines for Drinking-water Quality*, Geneva, p. 2

Wier, P.J., Miller, R.K., Maulik, D. & di Sant'Agnese, P.A. (1990) Toxicity of cadmium in the perfused human placenta. *Toxicol. appl. Pharmacol.*, **105**, 156–171

Williams, W.R., Kagamimori, S., Watanabe, M., Shinmura, T. & Hagino, N. (1983) An immunological study on patients with chronic cadmium disease. *Clin. exp. Immunol.*, **53**, 651–658

Wills, J.H., Groblewski, G.E. & Coulston, F. (1981) Chronic and multigeneration toxicities of small concentrations of cadmium in the diet of rats. *Ecotoxicol. environ. Saf.*, **5**, 452–464

Wolff, E.W. & Peel, D.A. (1985) The record of global pollution in polar snow and ice. *Nature*, **313**, 535–540

Wysowski, D.K., Landrigan, P.J., Ferguson, S.W., Fontaine, R.E., Tsongas, T.A. & Porter, B. (1978) Cadmium exposure in a community near a smelter. *Am. J. Epidemiol.*, **107**, 27–35

Yamagata, N., Iwashima, K. & Nagai, T. (1975) Gastrointestinal absorption of ingested ^{115m}Cd by a man. *Bull. Inst. public Health*, **24**, 1–6

Yu, H.S. & Chan, S.T.H. (1987) Effects of cadmium on preimplantation and early postimplantation mouse embryos *in vitro* with special reference to their trophoblastic invasiveness. *Pharmacol. Toxicol.*, **60**, 129–134

Yu, H.S., Tam, P.P.L. & Chan, S.T.H. (1985) Effects of cadmium on preimplantation mouse embryos *in vitro* with special reference to their implantation capacity and subsequent development. *Teratology*, **32**, 347–353

Zasukhina, G.D. & Sinelschikova, T.A. (1976) Mechanism of the action of certain mutagens on the DNA of human cells. *Dokl. biol. Sci.*, **230**, 409–411

Zenick, H., Hastings, L., Goldsmith, M. & Niewenhuis, R.J. (1982) Chronic cadmium exposure: relation to male reproductive toxicity and subsequent fetal outcome. *J. Toxicol. environ. Health*, **9**, 377–387

Zwennis, W.C.M. & Franssen, A.C. (1992) Assessment of occupational exposure to cadmium in The Netherlands, 1980–1989. *Am. J. ind. Med.*, **21**, 793–805