BERYLLIUM AND BERYLLIUM COMPOUNDS

Beryllium and beryllium compounds were considered by previous Working Groups, in 1971, 1979 and 1987 (IARC, 1972, 1980, 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 herein include (a) metallic beryllium, (b) beryllium–aluminium and –copper alloys and (c) some beryllium 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 beryllium, beryllium–aluminium and –copper alloys and certain beryllium compounds are presented in Table 1. The list is not exhaustive, nor does it comprise necessarily the most commercially important beryllium-containing substances; rather, it indicates the range of beryllium compounds available.

1.1.2 *Chemical and physical properties of the pure substances*

Selected chemical and physical properties of beryllium, beryllium–aluminium and –copper alloys and the beryllium compounds covered in this monograph are presented in Table 2.

The French chemist Vauquelin discovered beryllium in 1798 as the oxide, while analysing emerald to prove an analogous composition (Newland, 1984). The metallic element was first isolated in independent experiments by Wöhler (1828) and Bussy (1828), who called it 'glucinium' owing to the sweet taste of its salts; that name is still used in the French chemical literature. Wöhler's name 'beryllium' was officially recognized by IUPAC in 1957 (WHO, 1990). The atomic weight and common valence of beryllium were originally the subject of much controversy but were correctly predicted by Mendeleev to be 9 and +2, respectively (Everest, 1973).

Beryllium is the lightest of all solid, chemically stable substances and has an unusually high melting-point. It has a very low density and a very high strength-to-weight ratio. Beryllium is lighter than aluminium but is more than 40% more rigid than steel. It has excellent electrical and thermal conductivities. Its only markedly adverse feature is relatively pronounced brittleness, which has restricted the use of metallic beryllium to specialized applications (WHO, 1990).

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

Chemical name	CAS Reg. No.[a]	Synonyms and trade names	Formula
Beryllium metal	7440-41-7	*Beryllium*; beryllium-9; beryllium element; beryllium metallic; glucinium; glucinum	Be
Beryllium–aluminium alloy[b]	12770-50-2	*Aluminium alloy, nonbase, Al,Be*; aluminium–beryllium alloy	Al.Be
Beryllium–copper alloy[c]	11133-98-5	*Copper alloy, base, Cu,Be*; copper–beryllium alloy	Be.Cu
Beryl	1302-52-9	Beryllium aluminosilicate; beryllium aluminium silicate	$Al_2Be_3(SiO_3)_6$
Beryllium chloride	7787-47-5	Beryllium dichloride	$BeCl_2$
Beryllium fluoride	7787-49-7 (12323-05-6)	Beryllium difluoride	BeF_2
Beryllium hydroxide	13327-32-7 (1304-49-0)	Beryllium dihydroxide	$Be(OH)_2$
Beryllium sulfate	13510-49-1	*Sulfuric acid, beryllium salt (1:1)*	$BeSO_4$
Beryllium sulfate tetrahydrate	7787-56-6	*Sulfuric acid, beryllium salt (1:1), tetrahydrate*	$BeSO_4.4H_2O$
Beryllium oxide	1304-56-9	Beryllia; beryllium monoxide Thermalox™	BeO
Beryllium carbonate basic[d]	1319-43-3	*Carbonic acid, beryllium salt, mixture with beryllium hydroxide ($Be(OH)_2$)*	$BeCO_3.Be(OH)_2$
Beryllium nitrate	13597-99-4	Beryllium dinitrate; *nitric acid*, beryllium salt	$Be(NO_3)_2$
Beryllium nitrate trihydrate	7787-55-5	*Nitric acid, beryllium salt, trihydrate*	$Be(NO_3)_2.3H_2O$
Beryllium nitrate tetrahydrate	13510-48-0	Beryllium dinitrate tetrahydrate; *nitric acid, beryllium salt, tetrahydrate*	$Be(NO_3)_2.4H_2O$
Beryllium phosphate	13598-15-7	*Phosphoric acid, beryllium salt (1:1)*	$BeHPO_4$
Beryllium silicate[e]	13598-00-0	Phenazite; *phenakite*	$Be_2(SiO_4)$
Zinc beryllium silicate	39413-47-3 (63089-82-7)	*Silicic acid, beryllium zinc salt*	Unspecified

[a]Replaced CAS Registry numbers are shown in parentheses.

[b]Related compound registered by CAS is beryllium alloy, base, Be,Al historically (Lockalloy), Al (24–44%).Be (56–76%) [12604-81-8; replaced Registry No., 12665-28-0]; 60 beryllium–aluminium alloys are registered with CAS numbers, with different percentages of the two elements.

[c]Related compound registered by CAS is beryllium alloy, base, Be,Cu [39348-30-6]; 111 beryllium–copper alloys are registered with CAS numbers, with different percentages of the two elements.

[d]CAS name and Registry number shown were selected as being closest to the formula given by Lide (1991). Related compounds registered by CAS are: bis[carbonato(2)]dihydroxytriberyllium, $(BeCO_3)_2.Be(OH)_2$ [66104-24-3]; carbonic acid, beryllium salt (1:1), tetra-hydrate, $BeCO_3.4H_2O$ [60883-64-9]; carbonic acid, beryllium salt (1:1), $BeCO_3$ [13106-47-3]; and bis[carbonato(2-)]oxodiberyllium, $(CO_3)_2Be_2O$ [66104-25-4].

[e]Related compounds registered by CAS are: bertrandite, $Be_4(OH)_2O(SiO_3)_2$ [12161-82-9]; beryllium silicate, formula unspecified [58500-38-2]; silicic acid (H_2SiO_3), beryllium salt (1:1), $Be(SiO_3)$ [14902-94-4]; silicic acid (H_4SiO_4), beryllium salt (1:2), $Be_2(SiO_4)$ [15191-85-2]

Table 2. Physical properties of pure beryllium and beryllium compounds

Chemical name	Relative atomic/ molecular mass	Melting-point (°C)	Typical physical description	Density (g/cm^3)	Solubility
Beryllium metal	9.0122	1287	Grey, close-packed, hexagonal, brittle metal	1.85 (20 °C)	Soluble in most dilute acids and alkali; decomposes in hot water; insoluble in mercury and cold water
Beryllium chloride	79.92	399.2	Colourless to slightly yellow, orthorhombic, deliquescent crystal	1.899 (25 °C)	Soluble in water, ethanol, diethyl ether and pyridine; slightly soluble in benzene, carbon disulfide and chloroform; insoluble in acetone, ammonia and toluene
Beryllium fluoride	47.01	555	Colourless or white, amorphous, hygroscopic solid	1.986	Soluble in water, sulfuric acid, mixture of ethanol and diethyl ether; slightly soluble in ethanol; insoluble in hydrofluoric acid
Beryllium hydroxide	43.03	138 (dec.[a])	White, amorphous, amphoteric powder	1.92	Soluble in hot concentrated acids and alkali; slightly soluble in dilute alkali; insoluble in water
Beryllium sulfate	105.07	550 (dec.)	Colourless crystal	2.443	Forms soluble tetrahydrate in hot water; insoluble in cold water
Beryllium sulfate tetrahydrate	177.14	NR	Colourless, tetragonal crystal	1.713	Soluble in water; slightly soluble in concentrated sulfuric acid; insoluble in ethanol
Beryllium oxide	25.01	2530	Colourless to white, hexagonal crystal or amorphous, amphoteric powder	3.01 (20 °C)	Soluble in concentrated acids and alkali; insoluble in water
Beryllium carbonate	69.02	NR	NR	NR	Soluble in acids and alkali; insoluble in cold water; decomposes in hot water
Beryllium carbonate, basic	112.05	NR	White powder		Soluble in acids and alkali; insoluble in cold water; decomposes in hot water
Beryllium nitrate, trihydrate	187.97	60	White to faintly yellowish, deliquescent mass	1.56	Very soluble in water and ethanol
Beryllium phosphate	104.99	NR	NR	NR	Slightly soluble in water

Table 2 (contd)

Chemical name	Relative atomic/ molecular mass	Melting-point (°C)	Typical physical description	Density (g/cm^3)	Solubility
Beryllium silicate	110.11	NR	Triclinic, colourless crystal	3.0	Insoluble in acids
Zinc beryllium silicate	Unspecified	NR	Crystalline solid	NR	NR

From Ballance *et al.* (1978); Walsh & Rees (1978); IARC (1980); Sax & Lewis (1987); Lewis (1988); Budavari (1989); Lide (1991); Aldrich Chemical Co. (1992). NR, not reported; dec., decomposes

[a]Decomposes to beryllium oxide (Sax & Lewis, 1987).

Natural beryllium is 100% ^{9}Be isotope; four unstable isotopes with mass numbers of 6, 7, 8 and 10 have been made artificially. Because of its low atomic number, beryllium is very permeable to X-rays. Neutron emission after bombardment with α or γ rays is the most important of its nuclear physical properties, and beryllium can be used as a neutron source. Moreover, its low neutron absorptiveness and high-scattering cross-section make it a suitable moderator and reflector in structural materials in nuclear facilities; while most other metals absorb neutrons emitted during the fission of nuclear fuel, beryllium atoms only reduce the energy of such neutrons and reflect them back into the fission zone (Ballance *et al.*, 1978; Newland, 1984; WHO, 1990).

The chemical properties of beryllium differ considerably from those of the other alkaline earths, but it has a number of chemical properties in common with aluminium. Like aluminium, beryllium is amphoteric and shows very high affinity for oxygen; on exposure to air or water vapour, a thin film of beryllium oxide forms on the surface of the bare metal, rendering the metal highly resistant to corrosion, to hot and cold water and to oxidizing acids. Dichromate in water enhances this resistance by forming a protective film of chromate, similar to that formed on aluminium. In powder form, beryllium is readily oxidized in moist air and burns with a temperature of about 4500 °C when ignited in oxygen (Newland, 1984; Petzow *et al.*, 1985; WHO, 1990).

Cationic beryllium salts are hydrolysed in water; they form insoluble hydroxides or hydrated complexes at pH values between 5 and 8 and form beryllates above a pH of 8 (Reeves, 1986).

1.1.3 *Technical products and impurities*

Beryllium metal—purities: technical or nuclear grade, 98–> 99.5%; Grade A, 99.87%; Grade AA, 99.96%; distilled grade, > 99.99%; forms: single crystals, flakes, powders, plates, sheets, foils, wires, rods (Sax & Lewis, 1987; Alfa Products, 1990; CERAC, Inc., 1991; Aldrich Chemical Co., 1992; Atomergic Chemetals Corp., undated; D.F. Goldsmith Chemical & Metal Corp., undated); impurities vary with the production method (see section 1.2.1 and Tables 5 and 6).

Beryllium–aluminium alloy—composition limits for one alloy (%): Be, 4.5–6.0; Si, 0.2; Fe, 0.2; Mg, 0.5, Mn, 0.02; Cr, 0.02; Ni, 0.02; Ti, 0.02; Zn, 0.1; Cu, 0.05 (KBAlloys, 1985)

Beryllium–copper alloy—composition limits for one alloy (Alloy 20C or C82500) (%): Be, 2.0–2.25; Co, 0.35–0.65; total unnamed elements, 0.5 max; Cu, remainder (Stonehouse & Zenczak, 1991)

Beryllium chloride—purities: 97–99.5%; impurities (mg/kg): Al, 50; Fe, 100; Si, 30; Cd, 10; Ni, 120; Cu, 10; Co, 10; Zn, 10; Cr, 10; Mn, 10; Mg, 150 (Kawecki Berylco Industries, 1968; Alfa Products, 1990; CERAC, Inc., 1991; Strem Chemicals, 1992; Fluka Chemie AG, 1993)

Beryllium fluoride—purity: 99.5%; impurities (mg/kg): Al, 75; Fe, 75; Ni, 40; Cu, 10 (Kawecki Berylco Industries, 1968; CERAC, Inc., 1991; D.F. Goldsmith Chemical & Metal Corp., undated)

Beryllium hydroxide—contains different levels of several impurities depending on whether it is made from beryl ore or bertrandite ore (IARC, 1980)

Beryllium sulfate tetrahydrate—purities: 98.3–99.99%; impurities (%): chloride, Ca, Cd, Co, Cu, Fe, Ni, Pb and Zn, all < 0.005; K, Na, < 0.01 (Alfa Products, 1990; Aldrich Chemical Co., 1992; Fluka Chemie AG, 1993)

Beryllium oxide—purities: 99–99.99% (Alfa Products, 1990; CERAC, Inc., 1991; Aldrich Chemical Co., 1992; Strem Chemicals, 1992). The purity of beryllia is critical to its thermal conductivity: as the purity drops below 99.5%, thermal conductivity drops off rapidly. Impurities (mg/kg): Al, 46; Fe, 32; Cr, 8; Mn, < 2; Ni, 9; B, 2; Ca, 31; Co, < 1; Cu, 3; Si, 1861; Mg, 922; Li, 2; Zn, < 20; Ti, 5; Na, 173; Ag, < 1; Mo, < 3; Pb, 2. Silicon and magnesium silicates are added to beryllia powder as sintering aids (Brush Wellman, undated)

Beryllium carbonate—impurities (mg/kg): Al, 30; Fe, 100; Si, 150 (IARC, 1980)

Beryllium nitrate (trihydrate)—purity: 99.5% (D.F. Goldsmith Chemical & Metal Corp., undated); impurities (mg/kg): Al, 20; Fe, 30; Si, 50; Na, 20 (Kawecki Berylco Industries, 1968)

Impurities that occur in beryllium compounds that have been the subjects of previous monographs are: cadmium (IARC, 1987b), chromium (IARC, 1990a), cobalt (IARC, 1991), lead (IARC, 1987c), nickel (IARC, 1990b) and silica (IARC, 1987d).

1.1.4 *Analysis*

Beryllium metal

Selected methods for the determination of beryllium and beryllium compounds in various media are presented in Table 3. Other methods have been reviewed (IARC, 1980; Agency for Toxic Substances and Disease Registry, 1988; WHO, 1990).

Table 3. Methods for the analysis of beryllium and beryllium compounds (as Be)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air[a]	Collect on membrane filter; dissolve in nitric acid	FLAA	0.08 μg/m^3; 0.002 μg/ml	Kleinman *et al.* (1989a)
	Collect sample on cellulose ester membrane filter; add nitric and sulfuric acids; heat; cool; evaporate to dryness; add sodium sulfate/sulfuric acid solution; heat	GFAA	0.005 μg/sample	Eller (1987) (Method 7102)
	Collect sample on cellulose ester membrane filter; ash with nitric:perchloric acid solution (4:1) v:v; heat; repeat; heat to dryness; dilute with nitric:perchloric acid solution (4:1)	ICP	1 μg/sample	Eller (1984) (Method 7300)
Water, ground- and surface	Acidify with nitric and hydrochloric acids (Method 3005)	FLAA ICP (313 nm)	0.005 mg/L 0.3 μg/L	US Environmental Protection Agency (1986a) (Method 6010)

Table 3 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
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)	FLAA ICP (313 nm)	0.005 mg/L 0.3 μg/L	US Environmental Protection Agency (1986a,b) (Methods 6010 and 7090)
Oils, greases, waxes (organic extract)	Dissolve in xylene or methyl isobutyl ketone (Method 3040)	FLAA ICP (313 nm)	0.005 mg/L 0.3 μg/L	US Environmental Protection Agency (1986a) (Method 6010)
Sediments, sludges, soils	Digest with nitric acid and hydrogen peroxide; reflux with hydrochloric acid (Method 3050)	FLAA ICP (313 nm)	0.005 mg/L 0.3 μg/L	US Environmental Protection Agency (1986a) (Method 6010)
Aqueous samples, extracts, wastes	Acidify with nitric acid; evaporate to low volume; cool; add nitric acid; heat to complete digestion (Method 3020)	GFAA	0.2 μg/L	US Environmental Protection Agency (1986a,c) (Method 7091)
Sediments, sludges, soils	Digest with nitric acid and hydrogen peroxide; reflux with nitric acid (Method 3050)	GFAA	0.2 μg/L	US Environmental Protection Agency (1986a,c) (Method 7091)
Tissue samples	Ash in hot concentrated nitric acid	FLAA	2 μg/L	Kleinman *et al.* (1989b)
Urine	Inject untreated samples directly into a pretreated graphite tube; follow standard addition method	GFAA	0.5 μg/L	Angerer & Schaller (1985)
	Modify matrix with magnesium nitrate; follow platform technique	GFAA	0.05 μg/L	Paschal & Bailey (1986)

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

[a][Digestion with a solution of nitric acid:perchloric acid:sulfuric acid and addition of several drops of hydrofluoric acid are currently recommended in sample preparation. Detection limits can be reduced to 0.001 μg/ml and sensitivity to 0.0001 μg/ml.]

Methods used up to the 1960s included spectroscopic, fluorometric, gamma activation, spectrophotometric and automatic titrimetric techniques (Ballance *et al.*, 1978). The main deficiency of spectrophotometric methods lies in the nonspecificity of the complexing agents used to form coloured complexes with beryllium. The limit of detection of these methods was about 100 ng/sample. The fluorimetric method, which is based on fluorescent dyes (preferably morin), has a very low limit of detection, 0.02 ng/sample; its sensitivity is exceeded only by that of the gas chromatographic method. The fluorimetric method may, however, be subject to error unless several time-consuming, cumbersome processing steps are undertaken prior to analysis (WHO, 1990).

Atomic absorption spectrometry is a rapid, very convenient method for analysing biological and environmental samples. The limit of detection for the flame technique is 2–10 μg/L and lower when the sample is concentrated before analysis (WHO, 1990). The graphite furnace method is much more sensitive, with a detection limit of approximately 0.1 μg/L. Blood, urine and tissue samples can be analysed by this technique with or without digestion of the biological matrix (see Table 3).

Inductively coupled plasma atomic emission spectrometry has been introduced to determine beryllium directly in a variety of biological and environmental matrices, because of its high sensitivity and low level of interference. Owing to its high sensitivity and specificity, gas chromatography is also used for determining beryllium in environmental and biological media, particularly at ultratrace levels. Beryllium can be converted into a volatile form by chelation with trifluoroacetylacetone before injection into the chromatographic column (WHO, 1990).

1.2 Production and use

1.2.1 *Production*

More than 40 beryllium-bearing minerals are known, but only two are of economic significance. The first beryllium mineral to be exploited commercially was beryl ($3BeO.Al_2O_3.6SiO_2$), an aluminosilicate (WHO, 1990). The largest deposits of beryl are found in Brazil and the former USSR (Petkof, 1982; Stonehouse & Zenczak, 1991). Beryl ore contains about 11% beryllium oxide (up to 4% beryllium) and is often obtained as a by-product of feldspar quarrying (for typical ore composition, see Table 17). In addition to the other major components, aluminium oxide and silicon dioxide, the principal impurities in the ores include alkali metals, alkaline-earth metals, iron, manganese and phosphorus. In its purest gem quality, it occurs as emerald (chromium-containing beryl), aquamarine (iron-containing beryl) and some other semiprecious stones (Petzow *et al.*, 1985; WHO, 1990).

The other mineral of economic significance, bertrandite ($4BeO.2SiO_2.H_2O$), is a beryllium silicate hydrate. Although bertrandite ore contains less than 1% beryllium, it became economically important in the late 1960s because it can be processed to beryllium hydroxide highly efficiently. Bertrandite mined in the USA accounts for about 85% of US consumption of beryllium ore. The total world reserves of beryllium that can be recovered by mining bertrandite are estimated at 200 000 tonnes (Petzow *et al.*, 1985; WHO, 1990).

Known deposits of other beryllium-containing minerals are being studied for possible commercialization. Most notable among these are phenakite ($2BeO.SiO_2$) at Yellowknife, Northwest Territory, Canada, the chrysoberyl ($BeO.Al_2O_3$) deposits of the Seward Peninsula, Alaska, and the Sierra Blanca deposits near El Paso, Texas, USA (Stonehouse & Zenczak, 1991).

Beryllium production started in some industrialized countries around 1916. Beryllium gained commercial importance in the early 1930s, following the realization that beryllium–copper alloys are extraordinarily hard, resistant to corrosion, non-magnetic, do not spark and withstand high temperatures. In addition, the nuclear and thermal properties and high specific modulus of beryllium metal made it attractive for nuclear and aerospace

applications, including weapons. The latter use is the main reason why reliable data on the production and consumption of beryllium have been scarce and incomplete. Considerable fluctuations in the supply and demand of beryllium result from variations in government programmes in armaments, nuclear energy and aerospace. For example, the demand for beryllium in the USA that was created by the programme for development of the atomic bomb was about equivalent to total world demand up to 1940 (WHO, 1990).

Production in the rest of the world paralleled those fluctuations in the beryllium market, with 222 tonnes produced in 1965, 320 tonnes in 1969 and 144 tonnes in 1974. Data on US production are now available, and world production of beryllium as beryl is shown in Table 4. If production from bertrandite is included, the USA appears to be the world's largest producer of beryllium raw materials (WHO, 1990).

(*a*) *Processing of beryl and bertrandite*

The first step in the processing of beryl ore is normally hand-sorting to select beryl crystals containing at least 10% beryllium oxide (Ballance *et al.*, 1978) on the basis of shape and colour (Powers, 1991).

Two commercial methods have been used to process beryl to beryllium hydroxide: the fluoride process and the sulfate process. In the *fluoride process*, which was discontinued in the 1970s, beryl was sintered together with sodium hexafluorosilicate, or the less expensive sodium fluoroferrate, at 700–800 °C to convert beryllium oxide to a water-soluble salt, sodium beryllium tetrafluoride (Na_2BeF_4). The reaction product was then leached with water at room temperature and precipitated from the purified solution with caustic soda as beryllium hydroxide (Petzow *et al.*, 1985; WHO, 1990).

The *sulfate process*, the only process currently used, involves either alkali or heat treatment of beryl. With alkali treatment, which was discontinued in the 1960s, finely ground beryl was heated until fusion or sintered below the melting-point with suitable alkalis, such as hydroxides and carbonates of sodium, potassium and calcium. With heat treatment, which has been used since the 1970s, beryl is melted without additives and quenched with water; the water insoluble portion, a solid solution with silicon dioxide, is reheated to 900 °C to render a total of 90–95% of the beryl soluble. Heat-treated or alkali-treated beryl is then extracted with sulfuric acid and carried through several additional purification steps to produce a fine-grained, readily filtered beryllium hydroxide (Petzow *et al.*, 1985; WHO, 1990).

The beryllium-poor bertrandite ores ($\leq$ 0.5–0.8% BeO) mined in the USA since 1960 cannot be smelted economically by conventional methods, and a less complicated procedure has been developed in which a very pure beryllium hydroxide is produced by liquid–liquid extraction. This so-called 'SX-carbonate process' involves direct leaching of bertrandite ore with sulfuric acid, extraction of the sulfuric acid leachate with di(2-ethylhexyl)phosphoric acid in kerosene, stripping of beryllium from the organic phase with aqueous ammonium carbonate, and, through a series of heat, hydrolysis and precipitation steps, production of beryllium hydroxide (Petzow *et al.*, 1985; WHO, 1990). Beryllium hydroxide is the starting material for the production of beryllium, beryllia and beryllium alloys. For further processing, it is ignited to form the oxide (BeO) or converted to the fluoride (BeF_2) (WHO, 1990).

Table 4. World production of beryl (tonnes)

Country	1980	1981	1982	1983	1984	1986	1987	1988	1989	1990	1991[a]
Argentina	31	7	6	24[b]	15[a]	50	46	39	89[c]	85[a]	80
Brazil[d]	550	854[c]	1062	1252[a,c]	1252	907[c]	1000	913	800	850[a]	850
Madagascar	10	10	10	10	10	50 kg	35 kg	3 kg	154 kg	150 kg[c]	3
Mozambique	20	18	15	15[a]	15	1	ND	ND	ND	ND	ND
Portugal	19	18	19	18	18	ND	4	4	4	4	4
Rwanda	108	59	69	33	36	ND	ND	ND	ND	ND	ND
Republic of South Africa	ND	122	58	22	ND	3	135 kg	72 kg	ND	1[c]	1
Russia[a]	1800	1800	1800	1900	1900	1900	2000	2000	2000	1600	1300
USA[e]	6756[c]	6653[c]	4945	6046	5470[c]	5927	5499	5313	4592	4548	4339[c]
Zimbabwe	9	42	52	50[a]	50	103	83	33	46	28[c]	30
World[f]	9319	9597	8051	9375	8772	8891	8632	8302	7532	7119	6607

From Kramer (1985a, 1991a, 1992a) [some figures are estimates]; beryl has also been produced in China, perhaps in Bolivia and Namibia and in small amounts in Nepal, but the available information is inadequate to formulate reliable estimates of production. ND, no data

[a]Estimated

[b]Preliminary

[c]Revised

[d]Export data for 1980–84

[e]Includes bertrandite ore calculated as equivalent to beryl containing 11% BeO

[f]Totals are not the sum of the columns, because world values are revised figures.

(*b*) *Beryllium metal*

The chief difficulties involved in the production of beryllium metal are the reactivity and high melting-point of the metal and the extreme stability of the oxide. Of the many possible methods of producing beryllium, two have been used in industry: fusion electrolysis and reduction of halides by metals. The only industrial process currently in use, developed in the 1930s, is reduction of beryllium fluoride with magnesium. The reaction is started by heating a mixture of relatively coarse-grained beryllium fluoride and magnesium in a graphite crucible. At a temperature of about 1300 °C, the reaction produces a mixture of beryllium pebbles and magnesium fluoride (Petzow *et al.*, 1985).

All practical electrolytic methods of production are based on decomposition of beryllium fluoride, beryllium oxide or beryllium chloride mixed with halides of the alkali metals or alkaline-earth metals. Several methods for the electrolysis of beryllium fluoride were developed in the 1920s. Electrolysis was carried out at above the melting-point of beryllium, at 1290–1400 °C; these methods are now obsolete. Electrolysis of beryllium chloride can be carried out at temperatures so low that the metal neither melts nor oxidizes. The beryllium is obtained as solid flakes, which are separated by washing out the electrolyte. This method was used in France, Japan, the United Kingdom and the former USSR (Petzow *et al.*, 1985).

Beryllium pebbles or flakes still contain many impurities and must be refined before they can be used to fabricate structural pieces. The main impurities in electrolytically produced beryllium are sodium and chloride; the main impurities in beryllium produced by the magnesium reduction process are magnesium and magnesium fluoride. Other impurities include beryllium oxide, carbon and metals, the most important being aluminium, iron and silicon (Petzow *et al.*, 1985). Beryllium is available mainly as block and rolled sheet and, to a lesser extent, as extruded bar, wire and near net shapes (Smugeresky, 1986).

Several commercial grades of beryllium are produced for specific uses: structural, nuclear, instrument, optical and electronic (Smugeresky, 1986). Commercial grades of beryllium are refined exclusively by vacuum melting in beryllium oxide or magnesium oxide crucibles and casting in graphite ingot moulds. The melting of magnesium-reduced beryllium in a high vacuum produces a metal of a purity comparable to that of electrolytic beryllium. Melting the electrolytic flakes in a vacuum further reduces the content of halides and low-boiling metals. A very pure grade of beryllium, particularly with respect to the content of oxide, aluminium, iron, silicon, carbon and halides, can be produced by electrolytic refining (SR flakes) (Ballance *et al.*, 1978; Petzow *et al.*, 1985).

(*c*) *Beryllium–aluminium alloy*

Beryllium–aluminium alloys (originally termed 'lockalloy' by the inventors, who were working for the Lockheed Co.) exhibit high bend ductility and high strength and are weldable and easy to machine. A major factor in their successful development was the preparation of a relatively fine, two-phase microstructure by a gas atomization process with quenching into water. The resultant powders are dried, then hot degassed, hot compacted and extruded to bars, from which thin sheet and thin-section extrusion are produced. Lockalloys were produced commercially from the late 1960s until 1975 (Lewis, 1988). The one remaining US

manufacturer currently produces beryllium–aluminium alloys under the trade name AlBeMet™ (Brush Wellman, 1992).

(*d*) *Beryllium–copper alloy*

Alloys with copper are the most important beryllium alloys. Copper–beryllium master alloy is manufactured commercially by an arc-furnace method in which beryllium oxide is reduced by carbon in the presence of molten copper at 1800–2000 °C; the resulting alloy typically contains 4.0–4.25 wt % beryllium. The master alloy is then melted together with virgin copper or copper scrap to produce the desired alloy, which is usually cast into billets (Ballance *et al.*, 1978; Stonehouse & Zenczak, 1991).

(*e*) *Beryllium chloride*

Beryllium chloride can be prepared either directly from beryl by the chloride process or by chlorination of beryllium oxide under reducing conditions. Beryllium chloride is purified by distillation in a stream of hydrogen, followed by fractional condensation (Petzow *et al.*, 1985).

(*f*) *Beryllium fluoride*

In the production of beryllium fluoride, beryllium hydroxide is dissolved in an ammonium hydrogen fluoride solution to produce ammonium tetrafluoroberyllate. Impurities can be precipitated as hydroxides. Upon concentration, ammonium tetrafluoroberyllate crystallizes from solution and is separated; after heating, it dissociates into ammonium fluoride and beryllium fluoride (Petzow *et al.*, 1985).

(*g*) *Beryllium hydroxide*

Beryllium hydroxide exists in three forms. By adding alkali to a beryllium salt solution to make a slightly basic pH, a gelatinous beryllium hydroxide is produced. Aging of this amorphous product results in a metastable tetragonal crystalline form, which, after months of standing, is transformed into a stable, orthorhombic crystalline form. The orthorhombic modification is also precipitated by hydrolysis from a hot sodium beryllate solution containing more than 5 g/L beryllium. Granular beryllium hydroxide is the readily filtered product from sulfate extraction processing of beryl (Walsh & Rees, 1978).

(*h*) *Beryllium sulfate*

Beryllium sulfate can be obtained by heating beryllium sulfate dihydrate in air to 400 °C and from the reaction of beryl ore or beryllium oxide with sulfuric acid (Walsh & Rees, 1978; Petzow *et al.*, 1985).

(*i*) *Beryllium sulfate tetrahydrate*

Beryllium sulfate tetrahydrate is produced commercially in a highly purified state by fractional crystallization from a beryllium sulfate solution obtained by reacting beryllium hydroxide with sulfuric acid. The tetrahydrate crystallizes from the aqueous solution in well-developed crystals (Walsh & Rees, 1978; Petzow *et al.*, 1985).

(*j*) *Beryllium oxide*

Beryllium oxide is produced by the following processes: beryllium hydroxide is first converted to high-purity beryllium sulfate tetrahydrate, as described above. This salt is

calcined at carefully controlled temperatures, between 1150 and 1450 °C, selected to give the properties of the beryllium oxide powders required by individual beryllia ceramic fabricators. Alternatively, beryllium hydroxide may be purified first and then calcined directly to beryllium oxide powder (Walsh & Rees, 1978). In another process, beryl ore is fused with sodium silicic fluoride at 700–800 °C, with conversion to sodium fluoroberyllate and precipitation by means of caustic soda from the purified leached solution as beryllium hydroxide, from which the anhydrous chloride can be obtained by reaction with carbon and chlorine at 800 °C (US National Library of Medicine, 1992).

Today, practically all of the beryllium oxide produced commercially is calcined at temperatures of 1000 °C or higher and is referred to as 'high-fired'. Beryllium oxide that is calcined at temperatures lower than 1000 °C is referred to as 'low-fired'; it consists of poorly crystallized, small particles which are more reactive and more soluble in dilute acid than those of high-fired beryllium oxide (Finch *et al.*, 1988).

(*k*) *Beryllium carbonate*

Basic beryllium carbonate is formed in the reaction of beryllium salt solutions with alkali metal or ammonium carbonate solutions. If excess ammonium carbonate is used, a readily filtered precipitate of variable composition is formed on boiling. This salt is a suitable starting material for the preparation of beryllium salts of all types. Gentle calcining causes ammonia to escape, leaving beryllium basic carbonate. Further heating drives off the carbon dioxide to produce beryllium hydroxide (Petzow *et al.*, 1985).

(*l*) *Beryllium nitrate*

Beryllium nitrate trihydrate is prepared by crystallizing a solution of beryllium hydroxide or carbonate that has been treated with a slight excess of concentrated nitric acid; the dihydrates and monohydrates are also formed, depending on the concentration of the acid used. The anhydrous form may be obtained by treating an ethyl acetate solution of beryllium chloride with dinitrogen tetroxide but not by dehydration of one of the hydrated species; the latter operation results in thermal decomposition of the nitrate, with evolution of nitrous fumes (Drury *et al.*, 1978).

(*m*) *Beryllium phosphate*

Beryllium phosphate can be produced by the reaction of disodium hydrophosphate with a beryllium salt solution or by reaction of beryllium hydroxide solution with phosphoric acid (Mellor, 1946).

(*n*) *Beryllium silicate*

No information was available to the Working Group.

(*o*) *Zinc beryllium silicate*

No information was available to the Working Group.

1.2.2 *Use*

Typical use patterns for beryllium, beryllium alloys and beryllium compounds in the USA are presented in Table 5.

Table 5. Use patterns for beryllium in the USA (%)

Use category	1985	1987	1990	1991	1992
Metal and alloy in nuclear reactors and in military and aerospace applications	40	40	23	29	29
Alloy and oxide in electrical equipment	36	35	17	19	20
Alloy and oxide in electronic components	17	17	35	47	45
Alloy, metal and oxide in other applications	7	8	25	5	6

From Kramer (1985b, 1987, 1990, 1991b, 1992b)

(a) Beryllium metal

Some of the typical uses of beryllium metal are: structural material in space technology; moderator and reflector of neutrons in nuclear reactors; source of neutrons when bombarded with α particles; special windows for X-ray tubes; in gyroscopes, computer parts, inertial guidance systems; additives in solid propellant rocket fuels; beryllium–copper alloys; heat-sink material in low-weight, high-performance aircraft brakes; scanning mirrors and large mirror components of satellite optical systems; hardening of copper; and in developmental brass alloys (Sax & Lewis, 1987; WHO, 1990).

(b) Beryllium–aluminium alloy

The use of beryllium in alloys is based on a combination of properties that beryllium confers on other metals. Low density combined with strength, high melting-point, resistance to oxidation and a high modulus of elasticity make beryllium alloys light-weight materials that can withstand high acceleration and centrifugal forces. Most metals, however, form very brittle compounds with beryllium, and this and the low solubility of most elements in solid beryllium are the reasons why beryllium-rich alloys have not found extensive use (WHO, 1990). Historically, the only alloy with a high beryllium content was lockalloy, which contained 62% beryllium and 38% aluminium (Petzow *et al.*, 1985). Recently, Brush Wellman (1992) introduced a family of beryllium–aluminium alloys containing 20–60% beryllium and sold as AlBeMet™.

Aluminium–beryllium alloys are used mainly to save weight, reduce life-cycle cost and increase reliability in aerospace structures of advanced design. Small additions of beryllium to aluminium impart high strength, thermal stability and unusual resistance to oxidation (Lewis, 1988; WHO, 1990). These alloys are also used in computer information storage devices.

(c) Beryllium–copper alloy

The principal uses of beryllium stem from the discovery in the 1920s that the addition of only 2% beryllium to copper results in an alloy six times stronger than copper. Beryllium–copper alloys withstand high temperatures, are extraordinarily hard, are resistant to corrosion, do not spark and are non-magnetic. These alloys are used in many critical moving parts of aircraft engines and in key components of precision instruments, electrical relays and switches. An alloy containing 25% beryllium has limited application in camera

shutters. Beryllium–copper hammers, wrenches and other tools are used in petroleum refineries where sparks from steel against steel might cause explosions (Newland, 1984). A representative use for beryllium–copper alloys in the electronics industry is in integrated circuit sockets and electronic connectors (Stonehouse & Zenczak, 1991). These alloys are also used in sports equipment (e.g., golf clubs).

(*d*) *Beryllium chloride*

Beryllium chloride has been used as a raw material in the electrolytic production of beryllium and as the starting material for synthesis of organoberyllium compounds (Petzow *et al.*, 1985).

(*e*) *Beryllium fluoride*

Beryllium floride is used as an intermediate in the preparation of beryllium and beryllium alloys. It was used as an additive to welding and soldering fluxes because it dissolves metal oxides readily; it was also used in nuclear reactors and glass manufacture (Petzow *et al.*, 1985; Sax & Lewis, 1987). It is being investigated for use in fibre optic cables because of its low absorbance of ultraviolet radiation.

(*f*) *Beryllium hydroxide*

Beryllium hydroxide is used as an intermediate in the manufacture of beryllium and beryllium oxide (Budavari, 1989).

(*g*) *Beryllium sulfate tetrahydrate*

Beryllium sulfate tetrahydrate is used as an intermediate in the production of beryllium oxide powder for ceramics (Walsh & Rees, 1978).

(*h*) *Beryllium oxide*

Beryllium oxide has an extremely high melting-point, very high thermal conductivity, low thermal expansion and high electrical resistance. It can either be moulded or applied as a coating to a metal or other base; through the process of sintering (1480 °C), a hard, compact mass with a smooth glassy surface is formed. The ceramic properties of sintered beryllium oxide make it suitable for the production or protection of materials to be used at high temperatures in corrosive environments. Beryllium oxide ceramics have the highest thermal conductivity of the oxide ceramics (Newland, 1984; WHO, 1990). They are also used as dental materials (ceramic crowns).

Specific applications include: transistor mountings, semiconductor packages and microelectronic substrates. Transparency to microwaves has led to its use as windows, radomes and antennae in microwave devices; it is also used in high-power laser tubes. Its low density and other properties make it attractive for aerospace and military applications, such as gyroscopes and armour; general refractory uses include thermocouple sheaths and crucibles. It is also used as an additive to glass, ceramics and plastics; in the preparation of beryllium compounds; as a catalyst for organic reactions; and in nuclear reactor fuels and moderators (Livey, 1986; Sax & Lewis, 1987; US Environmental Protection Agency, 1987; Budavari, 1989).

(*i*) *Beryllium nitrate*

Beryllium nitrate was used until the late 1960s for stiffening incandescent gas mantles (Petzow *et al.*, 1985).

(*j*) *Beryllium phosphate*

Beryllium phosphate is not known to be produced commercially.

(*k*) *Beryllium silicate*

Beryllium silicate is not known to be produced commercially.

(*l*) *Zinc beryllium silicate*

Zinc beryllium silicate is not known to be produced or used commercially at present. It was used until about 1950 as a fluorescent lamp phosphor (WHO, 1990).

1.3 Occurrence

The environmental occurrence of beryllium has been reviewed extensively (Agency for Toxic Substances and Disease Registry, 1988; WHO, 1990).

1.3.1 *Natural occurrence*

Beryllium is the forty-fourth most abundant element in the Earth's crust (Drury *et al.*, 1978; Reeves, 1986), with an average content of about 6 mg/kg. It occurs in rocks and minerals (mica schist, granite, pegmatite and argillite) at concentrations of 0.038–11.4 mg/kg (Drury *et al.*, 1978). The most highly enriched beryllium deposits are found in granitic pegmatites, in which independent beryllium minerals crystallize (WHO, 1990).

Some 40 beryllium-containing minerals have been identified. Only ores containing beryl ($3BeO.Al_2O_3.6SiO_2$) and bertrandite ($4BeO.2SiO_2.H_2O$) have achieved commercial significance (Drury *et al.*, 1978). The most important environmental source of beryllium is the burning of coal. Coals contain 1.8–2.2 mg beryllium/kg dry weight (US Environmental Protection Agency, 1987), and beryllium occurs in the ash of many coals at concentrations of about 100 mg/kg (WHO, 1990). These waste products could represent an extensive beryllium reserve. The beryllium content of fuel oils has been estimated to be less than 0.1 ppm (Drury *et al.*, 1978).

1.3.2 *Occupational exposure*

The range of industrial processes in which occupational exposure to beryllium occurs has expanded over the past two decades: The number of uses has increased, and the occupational settings have diversified. It is used in many manufacturing industries (see above) and in a growing industry for recycling and processing. Nonsiliceous mineral slag used for sand blasting is also frequently contaminated with beryllium. Potential exposure settings are summarized in Table 6.

Table 6. Industries and trades in which there is potential exposure to beryllium

Ceramics
Electrical connectors
Nonferrous foundries
Nonferrous smelters
Sandblasting
Aerospace
Nuclear control equipment
Electronics
Refractories
Beryllium smelting or fabrication
Hazardous waste processing
Dental equipment and supplies
Engineering and scientific equipment
Mechanical measuring devices
Tool and die making
Soldering
Welding or flame cutting
Metal plating
Automotive parts
Telecommunication equipment
Golf club manufacture

From Cullen *et al.* (1986); WHO (1990)

The US Occupational Safety and Health Administration summarized data on occupational exposure to beryllium for the period 1 June 1979 to 31 January 1984 (Table 7), based on inspections of work places. Exposure levels in excess of the threshold limit value of 2 $\mu g/m^3$ were found mainly in the traditional beryllium industry but also in high technology industries.

(*a*) *Processing and manufacturing*

Substances to which potential exposure occurs during ore processing include ore dust, silicon dioxide fumes and acid mists and fumes of beryllium sulfate; those during beryllium oxide production include fumes of lead sulfide, copper sulfide and sulfur trioxide and dusts of beryllium oxide; those during production of beryllium metal include acid fluoride mists, fumes and dusts of beryllium ammonium fluoride, beryllium fluoride, hydrogen fluoride, ammonium fluoride, beryllium metal and beryllium oxide; and those during production of beryllium–copper alloy include beryllium oxide, copper and beryllium–copper alloy dusts and fumes. Machining potentially involves exposure to respirable particles of beryllium alloys in the absence of adequate controls (Laskin *et al.*, 1950; Preuss, 1988). Exposure concentrations in various industries have been reviewed (WHO, 1990).

Table 7. Occupational exposure to beryllium compounds (1 June 1979 to 31 January 1984)

Type of industry	No. of samples in which beryllium is detected	No. of samples ≥ 0.5 μg/m³[a]	No. of samples ≥ 2 μg/m³[b]
Traditional[c]	25	16	9
High-technology[d]	3	3	2
Secondary process[e]	5	1	0
Dental laboratory	1	0	0
Total	34	20	11

From Cullen *et al.* (1986)

[a]Criterion of the US National Institute for Occupational Safety and Health

[b]Standard of the US Occupational Safety and Health Administration

[c]Including particulate blasting, shipbuilding and repair, nonferrous foundries, nonclay refractories, beryllium machining and fabrication and metalworking

[d]Including the semiconductor industry, precision electronics industry and spacecraft and missile manufacture

[e]Including secondary nonferrous smelters, nonferrous foundries and hazardous waste reclamation

Although there are few quantitative data on exposure to beryllium before 1947, there seems to be little doubt that extremely high concentrations were encountered in the work place (US National Institute for Occupational Safety and Health, 1972). In the USA, concentrations greater than 1000 μg/m³ were not uncommon in beryllium extraction facilities (Eisenbud & Lisson, 1983). Exposures measured in December 1946 (by the filter-paper dust sampler method) ranged from 110 to 4710 μg/m³ in the furnace area of a beryllium extraction plant (Laskin *et al.*, 1950). Concentrations of 590–43 300 μg/m³ were found in a beryllium–copper alloy plant in Lorain, Ohio, USA, monitored by the Atomic Energy Commission in 1947 and 1948 (Zielinski, 1961). After institution of control measures in 1949 in a new beryllium-copper alloy production plant in Elmore, Ohio, the limit of 2 μg/m³ was considerably exceeded between 1953 and 1960, with time-weighted average values of 3.8–9.5 μg/m³ in 1953, 6.8–19.1 μg/m³ in 1956 and 23.1–54.6 μg/m³ in 1960 (Zielinski, 1961; US National Institute for Occupational Safety and Health, 1972). In the same beryllium–copper alloy plant, a new furnace was installed between 1960 and 1966. Concentrations ranged from < 0.1 μg/m³ in the mixing areas to 1050 μg/m³ in the oxide areas in 1960 and from 0.2 μg/m³ in the saw area to 249 μg/m³ in the arc furnace area in 1966. Five-day average beryllium concentrations in this plant were 60.3 μg/m³ in 1960 and 18.1 μg/m³ in 1966 (see Table 8) (Cholak *et al.*, 1967).

In a summary of beryllium concentrations in 2627 air samples taken during 1950–57 in two US beryllium production plants, Breslin and Harris (1959) reported that 10–15% of workers were exposed to concentrations greater than 2 μg/m³ and that the average concentration in each plant in many operations was 10 μg/m³. Exposures may have been higher in plants that were not monitored by the Atomic Energy Commission (US National Institute for Occupational Safety and Health, 1972).

Table 8. Concentrations of beryllium in air at a number of locations in a beryllium–copper alloy plant in Ohio (USA) during two cycles of air monitoring six years apart

Location	Year	Beryllium concentration ($\mu g/m^3$) of air per 2-h period		
		Average	Median	Range
Oxide area	1960	149.4	72.5	0.4–1050.0
	1966	10.7	8.1	0.8–29.3
Arc furnace area	1960	87.6	50.0	22.1–502.0
	1966	25.9	36.9	7.7–249.0
Mixing area	1960	21.6	14.4	< 0.1–452.0
	1966	20.0	14.7	5.9–88.5
Casting area	1960	39.8	14.6	0.2–535.0
	1966	25.4	20.5	8.5–210.5
Fisher furnace area	1960	40.8	28.8	0.2–340.0
	1966	7.3	5.5	1.5–37.8
Saw area in rolling mill	1960	25.6	21.1	< 2.5–92.5
	1966	5.7	4.0	0.2–18.4
Cropping area	1960	52.8	33.6	14.0–399.0
Ajax furnace area[a]	1966	14.4	11.1	4.6–87.5
All areas	1960	60.3	28.4	< 0.1–1050.0
	1966	18.1	11.4	0.2–249.0

From Cholak *et al.* (1967)

[a]Approximately same area as cropping area in 1960

The US Atomic Energy Commission presented exposure data from five major beryllium-processing plants for various periods during 1950–61. Up to 40–75% of the daily weighted average exposures exceeded 2 $\mu g/m^3$ (US National Institute for Occupational Safety and Health, 1972).

[The Working Group noted the uncertainty of the representativeness for exposure of workers of air monitoring data obtained in the 1940s, 1950s and 1960s.]

In the early 1970s in a beryllium extraction and processing plant in northeastern USA, peak concentrations up to 1310 $\mu g/m^3$ were observed (Kanarek *et al.*, 1973). Follow-up analyses in 1974 showed a significant decrease (Sprince *et al.*, 1978).

The US National Institute for Occupational Safety and Health conducted several surveys of air in different beryllium plants in the USA. In a beryllium production plant, concentrations of 0.3–160 $\mu g/m^3$ were found in 1971, the high values occurring in powdering operations (H.M. Donaldson, 1971; cited in WHO, 1990). In another beryllium production plant, the concentrations of airborne beryllium in 1972 rarely exceeded the threshold limit value of 2 $\mu g/m^3$ (H.M. Donaldson & P.J. Shuler, 1972; cited in WHO, 1990). Beryllium concentrations in 50 personal samples collected at a secondary copper smelter in 1982–83 ranged between < 0.2 and 0.5 $\mu g/m^3$ (Cherniak & Kominsky, 1984). In 1983, the

concentrations of beryllium in 121 personal air samples obtained in the refinery and manufacturing melt areas of a precious metals refinery ranged from 0.22 to 42 μg/m^3 (mean, 1.4 μg/m^3) (K.P. McManus *et al.*, 1986; cited in WHO, 1990). Concentrations in the beryllium shop of another plant in 1985 ranged from < 0.2 to 7.2 μg/m^3 and exceeded 0.5 μg/m^3 in 6/33 breathing-zone samples (Gunter & Thoburn, 1986).

Kriebel *et al.* (1988a) described the beryllium concentrations in a plant in which most of the beryllium refined in the USA since 1934 has been produced, the principal product always having been beryllium–copper alloys (containing ≤ 2–4% beryllium). Table 9 summarizes the daily weighted average concentrations in 16 departments in four periods. The concentrations were high for many years, with some estimated to have been in excess of 100 μg/m^3; as late as 1975, average exposures to beryllium in some jobs were greater than 10 μg/m^3. After about 1977, the levels were in compliance with the permissible exposure limit of 2 μg/m^3. The median cumulative exposure of 297 white male workers surveyed in 1977 was 65 μg/m^3-years; their median exposure was 0.4 μg/m^3, and the mean number of years worked was 17. [The Working Group noted that there was some overlap in the plants surveyed.]

Table 9. Daily weighted average concentrations of beryllium (μg/m^3) in 16 departments[a] in a US beryllium production plant in four periods

Department	Approximate no. of workers in 1943	No. of jobs in department	Period			
			1935–54	1955–64	1965–76	1977–83
Oxide	46	14	46	16	8.8	0.5
Arc furnace room	26	6	80	51	11	0.7
Detroit furnaces	24	4	51	51	33	NA
Foundry	27	5	19	19	13	NA
Melt and cast	105	6	18	18	7.6	1.1
Hot rolling	19	8	9.3	9.3	2.5	0.2
Cold rolling	29	8	9.2	5.7	2.5	0.2
Rod and wire	39	8	5.9	5.9	2.0	0.2
Annealing	10	5	13	13	5.7	0.1
Pickling	11	3	0.2	0.2	0.2	0.1
Machining, grinding	60	5	1.7	1.7	0.9	0.1
Maintenance	73	13	6.2	5.7	3.5	0.1
Inspection	12	7	1.6	1.6	0.9	0.1
Laundry	–	1	2.5	2.5	1.0	0.1
Laboratories, research and development	28	6	1.4	1.4	1.2	0.2
Stores, shipping	20	3	3.6	3.6	2.0	0.1
Total	529	102				

From Kriebel *et al.* (1988a); NA, not applicable; these departments were not operational during 1977–83.
[a]Smaller departments were grouped for presentation.

(*b*) *Machining and use*

Personal air samples taken at US factories in which machining of beryllium metal and alloys involved drilling, boring, cutting and sanding did not contain any detectable amount of beryllium (Gilles, 1976; Boiana, 1980; Lewis, 1980). In a US boat factory in which workers were engaged in grid blasting, beryllium concentrations of 6–134 μg/m^3 were measured (Love & Donohue, 1983). Breathing-zone air samples taken from workers during grinding, polishing, cutting and welding of beryllium-containing alloys in a German metal processing plant contained < 0.1–11.7 μg/m^3 beryllium in total dust; 0.1–10.0 μg/m^3 during hand cutting; 1.4–11.7 μg/m^3 during automatic cutting; 2.1–3.63 μg/m^3 during welding without exhaust extraction; and 1.12–1.34 μg/m^3 during welding with exhaust extraction (Minkwitz *et al.*, 1983; WHO, 1990).

Dental laboratory technicians were exposed to < 2 μg/m^3 beryllium in the breathing zone during the processing of beryllium-containing dental alloys in the USA when exhaust ventilation was used (Dvivedi & Shen, 1983). Air measurements in three dental laboratories in Italy where melting and finishing of dental prostheses were carried out revealed beryllium concentrations in the breathing area in the range of 0.04–1.7 μg/m^3. The mean concentration of beryllium in the urine of 46 dental technicians (0.34 μg/L; range, 0.05–1.7) was higher than that of non-occupationally exposed subjects (mean, 0.26 μg/L; range, < 0.03–0.8) (Apostoli *et al.*, 1989a). [The Working Group noted that the smoking habits of the technicians were not defined.]

1.3.3 *Air*

The major source of atmospheric beryllium is combustion of coal, and its most prevalent chemical form is probably beryllium oxide, mainly bound to particles smaller than 1 μm (WHO, 1990). In earlier reports, average atmospheric background concentrations of beryllium were reported to be less than 0.1 (Bowen, 1966) and 0.2 ng/m^3 (Sussmann *et al.*, 1959). The air of over 100 cities in the USA, sampled in 1964–65, did not contain detectable amounts of beryllium (detection limit, 0.1 ng/m^3) (Drury *et al.*, 1978). Annual average background concentrations during 1977–81 throughout the USA were around the detection limit of 0.03 ng/m^3. Annual averages at urban monitoring stations where concentrations exceeded 0.1 ng/m^3 ranged between 0.11 and 6.7 ng/m^3 during 1981–86 (US Environmental Protection Agency, 1987; WHO, 1990). These data are similar to those found in other countries: Ikebe *et al.* (1986) found an average of 0.042 ng/m^3 in 76 air samples collected in 17 Japanese cities between 1977 and 1980; the highest values were found in Tokyo (0.22 ng/m^3) and in an industrial area in Kitakyushu (0.21 ng/m^3). R. Freise and G.W. Israel (1987, cited in WHO, 1990) found annual mean values in Berlin (Germany) of 0.2–0.33 ng/m^3. A concentration of 0.06 ng/m^3 was measured in a residential area, an office area and the inner city area of Frankfurt, whereas 0.02 ng/m^3 was measured in a rural area near Frankfurt (Müller, 1979).

Atmospheric concentrations of beryllium in the vicinity of beryllium processing plants are often higher than those elsewhere. A mean concentration of 15.5 ng/m^3 and a maximum concentration of 82.7 ng/m^3 were reported near a Pennsylvania (USA) factory, whereas background levels in several locations in the area averaged only 0.2 ng/m^3 (Sussman *et al.*, 1959).

The average concentration of beryllium in air 400 m from a beryllium extracting and processing plant in the former USSR, which was not equipped with emission control devices, was 1 μg/m^3; at 1000 m, it was 10–100 ng/m^3. Between 500 and 1500 m from a mechanical beryllium-finishing plant with operational filter facilities, no beryllium was detected in air [detection limit not given] (Izmerov, 1985). Bencko *et al.* (1980) reported beryllium concentrations of 3.9–16.8 ng/m^3 (average, 8.4 ng/m^3) in the vicinity of a power (coal) plant in former Czechoslovakia.

1.3.4 *Tobacco smoke*

In a German study of three brands of cigarettes [origin of tobaccos and number of samples not given], 0.47–0.75 μg beryllium was found per cigarette. Less than 10% of the beryllium content (0.011–0.074 μg/cigarette) was released into mainstream smoke during smoking (Zorn & Diem, 1974).

1.3.5 *Water*

Beryllium concentrations in surface waters are usually in the range 0.01–0.1 μg/L (WHO, 1990). The concentrations in 15 major US river basins ranged from 0.01 to 1.22 μg/L, with a mean of 0.19 μg/L (Safe Drinking Water Committee, 1977). Water samples taken from various areas near the Seward Peninsula in Alaska contained beryllium concentrations of 0.034–2.4 μg/L (Gosink, 1976). Surface water in eastern USA and Siberia contained beryllium at concentrations ranging from 0.1 to 0.9 μg/L (Safe Drinking Water Committee, 1977). Groundwater samples from Germany contained < 5–9 ng/L, with a mean of 8 ng/L; beryllium concentrations in seawater were 10 times lower than those in surface water (Reichert, 1974). Concentrations of 0.2–0.9 ng/L (mean, 0.5) (Merrill *et al.*, 1960) and 2 ng/L (Meehan & Smythe, 1967) were reported in the Pacific Ocean. Measures and Edmond (1982) found still lower concentrations, 0.04–0.06 ng/L, in the mixed layer—up to about 500 m.

In a survey of 380 US drinking-water sources in 1962–67, beryllium was found in only 1.1% of samples, at concentrations ranging from 20 to 170 ng/L (mean, 100) (Safe Drinking Water Committee, 1977). Sauer and Lieser (1986) found beryllium at 27 ± 8 ng/L in drinking-water samples from Germany.

1.3.6 *Soils*

Beryllium occurs in most soils. Drury *et al.* (1978) reported an average of 6 mg/kg (range, 0.1–4.0) worldwide and 0.04–1.45 mg/kg in Kenya. Of 847 samples of agricultural soils collected at a depth of 20 cm throughout the USA, 66% contained < 1 mg/kg, 22% between 1 and 2 mg/kg and 12% between 2 and 7 mg/kg (Shacklette *et al.*, 1971). The mean beryllium concentration in 27 soil profiles (with 129 horizons) of uncontaminated soil from various locations in Japan was 1.31 mg/kg (Asami & Fukazawa, 1985).

In some small, unpolluted areas in which rocks contain large amounts of beryllium, the overlying soils show relatively high beryllium concentrations; e.g., soils in the Lost River Valley, Alaska, USA, contained up to 300 mg/kg, with an average of 60 mg/kg (WHO, 1990).

1.3.7 *Food*

Only limited, variable data are available on beryllium contents of food (WHO, 1990). The concentrations in various foods collected in New South Wales, Australia, ranged from 10 to 470 μg/kg ash weight (0.07–1175 μg/kg fresh weight); the highest concentrations were found in peanut shells (Meehan & Smythe, 1967).

Owing to the limited data, the daily human intake of beryllium from food has not been determined. In a study in the United Kingdom (Hamilton & Minsky, 1973), the average total dietary intake was estimated to be < 15 μg/day. The US Environmental Protection Agency (1987) estimated a total daily consumption of about 420 ng, most of which came from food (120 ng/day) and drinking-water (300 ng/day); air and dust reportedly contributed very little to the total intake of beryllium.

1.3.8 *Human tissues and secretions*

The measured concentrations of beryllium in body fluids and tissues have diminished substantially over the past 10 years, probably as a consequence of improved analytical techniques, including better procedures for minimizing beryllium contamination during collection and assay. The validity of the data reported in the older literature is therefore somewhat doubtful.

Sprince *et al.* (1976) analysed specimens taken at autopsy from patients without granulomatous disease and found less than 20 μg/kg dry weight of beryllium in lung tissue (mean, 5 μg/kg; range, 3–10; six cases) and mediastinal lymph nodes (mean, 11 μg/kg; range, 6–19; seven cases). These concentrations are within the range of 90% of the values of 2–30 μg/kg dry lung tissue found in 125 lung specimens obtained during thoracic surgery (Baumgardt *et al.*, 1986).

Caroli *et al.* (1988) analysed different parts of lung tissue from 12 subjects in an urban area of Rome (Italy), who were nonsmokers, 50 or more years old and had not been occupationally exposed to beryllium during their lifetime. The overall mean of 5 μg/kg fresh weight indicates a smaller concentration range than those above, which were expressed in dry weight.

In a survey of 66 patients with beryllium disease in the US Beryllium Case Registry, the concentrations of beryllium ranged from 4 to 45 700 μg/kg dried tissue; 82% of the patients had concentrations of more than 20 μg/kg dry weight. Peripheral lymph-node specimens from five patients contained 2–490 μg/kg beryllium and mediastinal specimens, 56–8500 μg/kg (Sprince *et al.*, 1976).

Beryllium concentrations in urine specimens from non-occupationally exposed subjects are summarized in Table 10. The mean beryllium concentration in blood from 20 non-occupationally exposed German subjects was 0.9 μg/L (SD, 0.5) (Stiefel *et al.*, 1980).

Smoking appears to influence the concentration beryllium in urine: the beryllium concentration in the urine of heavy smokers (0.31 ± 0.17 μg/L) was significantly greater than that of nonsmokers (0.20 ± 0.14 μg/L) (Apostoli *et al.*, 1989b).

An exposure concentration of 2 μg/m^3 beryllium in air was found to correspond to about 7 μg/L in urine and about 4 μg/L in blood (Zorn *et al.*, 1988).

Table 10. Urinary concentrations of beryllium, identified by graphite furnace atomic absorption, in specimens from non-occupationally exposed subjects

Country	No. of subjects	Concentration (μg/L; mean ± SD)	Reference
USA	120	0.9 ± 0.4	Grewal & Kearns (1977)
Italy	56	0.6 ± 0.2	C. Minoia *et al.* (1985; cited by Apostoli *et al.*, 1989b)
USA	NR	0.13	Paschal & Bailey (1986)
Italy	163	0.24 ± 0.16 (range, < 0.03–0.8)	Apostoli *et al.* (1989b)
Italy	579	0.4 (range, < 0.02–0.82)	Minoia *et al.* (1990)

Modified from Apostoli *et al.* (1989b); NR, not reported

1.4 Regulatory status and guidelines

Occupational exposure limits and guidelines for beryllium and beryllium compounds established in different parts of the world are given in Table 11.

Table 11. Occupational exposure limits and guidelines for beryllium and beryllium compounds

Country or region	Year	Concentration ($\mu g/m^3$)	Interpretation[a]
Argentina	1991	2	TWA, potential carcinogen
Australia	1990	2	TWA, probable human carcinogen
Belgium	1990	2	TWA, probable human carcinogen
Bulgaria	1984	1	TWA
China	1979	1	TWA
Denmark	1992	1	TWA[b]
Finland	1990	0	Suspected of having carcinogenic potential
France	1990	2	TWA, carcinogen
Germany	1992	0	A2[c]
Hungary	1990	1	STEL, probable human carcinogen, irritant, sensitizer
Indonesia	1978	2	TWA
Italy	1978	2	TWA
Japan	1991	2	TWA, probable human carcinogen
Korea, Republic of	1983	2	TWA
Mexico	1984	2	TWA
Netherlands	1986	2	TWA
Poland	1985	1	TWA

Table 11 (contd)

Country or region	Year	Concentration ($\mu g/m^3$)	Interpretation[a]
Romania	1975	1	STEL
Sweden	1991	2	TWA, causes cancer, sensitizer
Switzerland	1990	2	TWA, inhalable dust, absorbed through skin
Taiwan	1981	2	TWA
United Kingdom	1994	2 (proposal)	STEL
USA[e]			
OSHA	1989	2	TWA (PEL)
		5	Ceiling
		25	Max
NIOSH	1990	0.5	TWA, carcinogen (REL)
ACGIH	1992	2	TWA, A2[d] (TLV)
Venezuela	1978	2	TWA
		25	Ceiling

From Arbeidsinspectie (1986); Cook (1987); US Occupational Safety and Health Administration (OSHA) (1989); Arbetarskyddsstyrelsens (1991); Institut National de Recherche et de Sécurité (1990); US National Institute for Occupational Safety and Health (1990); International Labour Office (1991); American Conference of Governmental Industrial Hygienists (ACGIH) (1992); Anon. (1992); Arbejdstilsynet (1992); Deutsche Forschungsgemeinschaft (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; Max, acceptable maximal peak (of 30-min maximal duration) above the acceptable ceiling concentration for an 8-h shift; PEL, proposed exposure limit; REL, recommended exposure limit; TLV, threshold limit value

[b]Beryllium and beryllium compounds are on a list of dangerous compounds but not classified for carcinogenic effect.

[c]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 workplace, or from which such comparability can be deduced

[d]Suspected human carcinogen; chemical substance, or substances associated with industrial processes, which are suspected of inducing cancer, on the basis of either limited epidemiological evidence or demonstration of carcinogenesis in one or more animal species by appropriate methods

Stationary sources (extraction plants, ceramic plants, foundries, incinerators and propellant plants for the processing of beryllium ore, beryllium, beryllium oxide, beryllium alloys and beryllium-containing waste; machine shops for the processing of beryllium, beryllium oxide and any alloy containing more than 5% beryllium by weight) are subject to the US national emission standard for beryllium, which is 0.01 $\mu g/m^3$ (30-day average) in ambient air for those production facilities which qualify for regulation through ambient air monitoring. Other facilities must meet a total site emission limit of 10 g per 24 h (US Environmental Protection Agency, 1992).

In the European Economic Community, beryllium and beryllium compounds are not permitted in cosmetic products (Commission of the European Communities, 1991a, 1992). Waste (except domestic waste) containing or contaminated by beryllium and beryllium compounds is classified as hazardous waste (effective date, 12 December 1993) (Commission of the European Communities, 1991b). Member States must take the necessary steps to limit the introduction of beryllium and its compounds into groundwater (effective date, 26 January 1982) (Commission of the European Communities, 1980). Beryllium and beryllium compounds (except aluminium beryllium silicates) are classified as very toxic and irritant (effective date, 1 July 1992) (Commission of the European Communities, 1991c).

2. Studies of Cancer in Humans

Beryllium was considered previously by three working groups (IARC, 1972, 1980, 1987). The first group (IARC, 1972) found the four epidemiological studies available at that time (Hardy *et al.*, 1967; Stoeckle *et al.*, 1969; Mancuso & El-Attar, 1969; Mancuso, 1970) not to provide evidence of the existence of a possible relationship between exposure to beryllium compounds and the occurrence of cancer in man. The second working group (IARC, 1980) reviewed four subsequent cohort studies (Infante *et al.*, 1980; Mancuso, 1979, 1980; Wagoner *et al.*, 1980) and concluded that the evidence for an increased risk for lung cancer from occupational exposure to beryllium was limited. No new study was available at the time of the third review (IARC, 1987).

2.1 Cohort studies (see Table 12, p. 70)

Mancuso (1979) conducted a retrospective cohort mortality study of workers employed in two beryllium extraction, production and fabrication facilities in the USA: one in Lorain, Ohio, and the other in Reading, Pennsylvania (see Table 13, p. 71, for description). The cohort was limited to workers who had been employed for at least three months during 1942–48. Observed and expected numbers of deaths were compared using a modified life-table analysis. Expected deaths were calculated on the basis of five-year mortality rates for the general white male population of the USA, except that the author did not have access to the actual national mortality rates for 1968–75 and calculated expected deaths for that period by applying US mortality rates for 1965–67. As a consequence of this extrapolation, expected lung cancer death rates for the 1968–75 period were underestimated by a factor of 10% (Saracci, 1985). The standardized mortality ratio (SMR) for lung cancer among the 1222 workers in the Ohio plant was 2.00 (1.8 with Saracci's adjustment; 95% confidence interval [CI], 1.2–2.7); that among the 2044 workers at the Pennsylvania plant was 1.37 (1.25 with Saracci's adjustment; 95% CI, 0.9–1.7). The combined lung cancer SMR (with Saracci's adjustment) for the two plants was 1.42 (95% CI, 1.1–1.8). A consistently greater excess of lung cancer was seen in the two plants among workers who were followed for 15 or more years since first employment; the SMRs (with Saracci's adjustment) were 2.0 (95% CI, 1.3–3.1) for the Ohio plant and 1.5 (95% CI, 1.0–2.1) for the Pennsylvania plant. In the combined cohort, the excess of lung cancer was limited to workers who had been employed for less than five years and followed for 15 or more years since first employment. [The

Working Group noted that no analysis of risk by job title or exposure category was conducted. The period of initial employment of the study cohort preceded the imposition by the US Atomic Energy Commission in 1949 of a 2 $\mu g/m^3$ 8-h time-weighted average limit for occupational exposure to beryllium and a ceiling limit of 25 $\mu g/m^3$, applicable to all beryllium facilities under contract to the Commission (Preuss, 1988).] A study of the beryllium alloy plant in Lorain, Ohio, conducted in 1947–48 by the US Atomic Energy Commission (Zielinski, 1961), showed concentrations of beryllium ranging from 411 $\mu g/m^3$ in the general air surrounding the mixing operation to 43 300 $\mu g/m^3$ in the breathing zone of alloy operatives. Control measures were introduced throughout US plants after 1949, and exposure levels in beryllium facilities were reduced markedly. Extraction plants, for example, were able to maintain exposure levels of 2 $\mu g/m^3$ or less, while certain foundry operations had air concentrations consistently in excess of 2 $\mu g/m^3$, with maximal values greater than 1000 $\mu g/m^3$ during the period 1968–72 in the Pennsylvania plant (Wagoner *et al.*, 1980).

Mancuso (1980) re-analysed mortality in the same Ohio and Pennsylvania beryllium extraction and processing plants, but extended the period of employment of the study cohort to 1937–48 and used as a comparison group viscose rayon industry workers employed at one company during 1938–48. Mortality was followed up through 1976. Among the 3685 cohort members from the two beryllium plants, 80 lung cancer deaths were observed, whereas 57.1 were expected on the basis of the total mortality experience of the viscose rayon workers (SMR, 1.40; $p < 0.01$) and 50.6 deaths were expected on the basis of the mortality experience of viscose rayon workers employed in a single department of the industry (SMR, 1.58; $p < 0.01$). [The Working Group noted that use of the latter reference cohort may introduce a selection bias into the analysis, since the mortality experience of workers who never change departments while employed in the industry may differ from that of the total workforce of the industry, for non-occupational reasons.] Lung cancer SMRs were calculated by duration of employment in comparison with the entire group of viscose rayon employees; these values were 1.38 ($p < 0.05$; 52 observed deaths) for one year or less of employment, 1.06 (14 observed deaths) for more than one year to four years or less, and 2.22 ($p < 0.01$; 14 observed deaths) for more than four years' employment.

Wagoner *et al.* (1980) expanded the cohort mortality study of the same Pennsylvania plant analysed by Mancuso (1979, 1980) to include workers employed at some time during 1942–67 and followed them up to 1 January 1976. [This interval extends across the year 1949 when, as previously noted, the Atomic Energy Commission standard of 2 $\mu g/m^3$ was introduced and a substantial reduction in exposure to beryllium subsequently occurred (US National Institute for Occupational Safety and Health, 1972).] They also used 1965–67 national lung cancer mortality rates to calculate expected lung cancer deaths for the period 1968–75. [The adjustment of Saracci (1985) is thus appropriate in considering these results.] Wagoner *et al.* (1980) observed 47 lung cancer deaths among the 3055 workers in the study cohort, whereas 37.7 were expected (with Saracci's adjustment) on the basis of national mortality experience, yielding an SMR of 1.25 (95% CI, 0.9–1.7). When lung cancer SMRs were calculated by latency, the SMRs were 0.88 (9 deaths) for < 15 years' latency, 1.16 (18 deaths) for 15–24 years' latency and 1.68 (20 deaths) for $\geq$ 25 years' latency, the 95% CI for latter SMR being 1.0–2.6. Within latency categories, there was no pattern of increasing (or decreasing) SMR by duration of employment, dichotomized into less than five and five

years or more. Analysis by duration yields an unstable estimate for longer duration strata owing to small numbers: for $\geq$ 5 years, the SMR is 1.1 (seven deaths) and the 95% CI is 0.4–2.3 (Saracci, 1985). A decline in risk for death from chronic beryllium disease was seen in relation to the same categories of length of employment. The potential for confounding of the SMR by a different distribution of smoking habits in the US population and in the beryllium cohort was calculated on the basis of a 1968 medical survey, in which detailed smoking histories of workers at the Pennsylvania plant were obtained, and of the 1964–65 Health Interview Survey of a probability sample of the US population, in which current and past smoking habits were queried. The overall calculations suggest that reported differences in smoking habits were sufficient to increase the lung cancer risk among the beryllium workers by 14%, in the absence of beryllium exposure; however, as also discussed by Wagoner *et al.* (1980), the white male age-adjusted rate for lung cancer mortality in the county in which the Pennsylvania plant was located (31.8/100 000) was lower than the average annual white male age-adjusted mortality rate for the USA as a whole (38.0/100 000). Wagoner *et al.* (1980) calculated that the risk for mortality from lung cancer in the beryllium cohort, if adjusted for differences in mortality between the County and the USA and for residential stability of cohort members, was underestimated by a factor up to 19%. [The Working Group noted that these two factors—smoking distribution and lower regional lung cancer mortality—bias the SMR estimate in opposite directions.]

Infante *et al.* (1980) analysed the mortality experience of white males entered into the Beryllium Case Registry while alive, with a diagnosis of chronic beryllium disease or acute beryllium-related pneumonitis. The Beryllium Case Registry was established in 1952 to collect data on the epidemiology, diagnosis, clinical features, course and complications of beryllium-related diseases. Individuals who were entered into the Registry were categorized as having either acute beryllium-induced pneumonitis or chronic systemic beryllium diseases (Sprinze & Kazemi, 1980). Individuals who were referred to the Registry for evaluation of beryllium-related diseases were employed in a variety of occupations, but most worked in beryllium extraction and smelting, metal production and fluorescent tube production. A total of 421 white males who entered the Registry alive between July 1952 and December 1975 were followed through to 31 December 1975. Seven deaths from lung cancer were observed and 3.3 were expected, based on national mortality rates for the period 1952–67 (SMR, 2.12, not significant). Since published vital statistics were not available for the period 1968–75, national mortality rates for 1965–67 were applied to 1968–75. If the number of expected deaths is increased by 10%, the expected value becomes [3.63], and the adjusted SMR is [1.93; 95% CI, 0.8–4.0]. For men who were entered into the Registry with a diagnosis of beryllium-related acute pneumonitis, the SMR (with Saracci's adjustment) for lung cancer is 2.86 (95% CI, 1.0–6.2; six cases). For those who were entered with a diagnosis of chronic beryllium disease, one lung cancer death was observed, with 1.52 expected (SMR, 0.66; 95% CI, 0.1–3.7). [The Working Group noted the small expected number of lung cancer deaths, particularly among workers with chronic lung disease, and the relatively short follow-up time for those workers who were entered into the Registry after 1965 ($\leq$ 10 years). Chronic beryllium disease results from hypersensitivity to beryllium and may occur at much lower exposures than acute beryllium pneumonitis. A small number of the cases occurred among people living near the plants but who were not occupationally exposed.]

An extended analysis of mortality among people entered into the Beryllium Case Registry was reported by Steenland and Ward (1991). The study cohort, which now included women (34% of the cohort) and men of all races, numbered 689 people who were alive at entry into the Registry between July 1952 and the end of 1980. Mortality follow-up was extended through 1988 [actual US death rates were available for comparison for all years, eliminating the need for Saracci's adjustment in this and the report of Ward *et al.* (1992)]. Excess mortality was found for all cancers (SMR, 1.51; 95% CI, 1.17–1.91; 70 observed deaths), due primarily to an excess of lung cancer (SMR, 2.00; 95% CI, 1.33–2.89; 28 observed deaths); there were also excess deaths from nonmalignant respiratory disease (SMR, 34.23; 95% CI, 29.1–40.0; 158 observed deaths) and all causes of deaths (SMR, 2.19; 95% CI, 1.17–1.91; 428 observed deaths). The SMR for lung cancer was greater among cohort members with acute beryllium pneumonitis (SMR, 2.32; 95% CI, 1.35–3.72; 17 cases) than among those with chronic beryllium disease (SMR, 1.57; 95% CI, 0.75–2.89; 10 cases) (one death was due to disease of unknown type). The SMRs for nonmalignant respiratory disease were 10 times higher in the chronic disease group (SMR, 68.6) than in the acute disease group (SMR, 6.6). The SMRs for lung cancer varied little by time since first exposure (SMR, 1.95; 95% CI, 0.94–3.59 for $\leq$ 20 years since first exposure; 2.03; 95% CI, 1.20–3.21 for $>$ 20 years) or by duration of exposure. [The Working Group presumed that duration of exposure to beryllium was determined by duration of employment in a beryllium plant, although this is not specified in the published report.] Taking into account the distribution of smoking habits among 32% of the cohort members questioned in 1965 and from a national survey of the US population studied in 1965, Steenland and Ward (1991) concluded that the study cohort smoked less (current smokers, 26%) than the US referent population (39%) in 1965 and that, if the 32% sample were representative of the entire cohort, smoking was unlikely to be a confounder of the observed excess lung cancer. Selection bias was diminished in this study because: people who died before entry into the Registry were excluded; only five individuals who had cancer before entry into the Registry were found in a review of Registry records, and none of these had lung cancer; and if patients with lung cancer had entered the Registry preferentially, the follow-up interval on these subjects would have been short, whereas only three of the 28 observed lung cancer deaths occurred within five years of entry into the Registry. [The Working Group noted that the results of this Beryllium Case Registry cohort study yield a higher lung cancer SMR than was found in other studies of beryllium-exposed workers, particularly among those who were entered with acute beryllium pneumonitis and who could therefore be assumed to have had a higher intensity of exposure to beryllium. This finding is consistent with the assumption that the risk for lung cancer is proportional to the intensity of exposure to beryllium. Furthermore, it provides indirect evidence that beryllium, rather than smoking, explains the findings, as people with acute pneumonitis were unlikely to smoke more than workers with chronic beryllium disease.]

Ward *et al.* (1992) reported the results of a cohort mortality study of 9225 male workers (8905 white, 320 non-white) employed by two companies at seven beryllium plants in Ohio and Pennsylvania. The results are summarized in Tables 12–16 (pp. 70–73). [Two of these plants (in Lorain, OH, and Reading, PA) are the same as those studied by Mancuso (1979, 1980) and Wagoner *et al.* (1980) (see Table 13).] Workers had to have worked for at least two days between 1940 and 1969 to qualify for entry into the study cohort. Mortality follow-up

Table 12. Cohort studies of lung cancer in beryllium workers

Reference	Cohort or plant location	Period of employment	Termination of follow-up	Comparison population	SMR	95% CI	Lung cancers observed
Mancuso (1979)	Lorain, OH	1942–48	1974	US white males	1.8[a]	1.2–2.7	25
	Reading, PA	1942–48	1975		1.25[a]	0.9–1.7	40
	Combined				1.42[a]	1.1–1.8	65
Mancuso (1980)	Lorain, OH Reading, PA	1937–48	1976	Viscose rayon workers	1.40	[1.1–1.7]	80
Wagoner *et al.* (1980)	Reading, PA	1942–67	1975	US white males	1.25[a]	0.9–1.7	47
Infante *et al.* (1980)	Beryllium Case Registry	Entry into Registry 1952–75	1975	US white males	[1.93]	[0.8–4.0]	7
				Acute pneumonitis	2.86[a]	1.0–6.2	6
				Chronic beryllium disease	0.66[a]	0.1–3.7	1
Steenland & Ward (1991)	Beryllium Case Registry	Entry into Registry 1952–80	1988	US men and women (all races)	2.00	1.33–2.89	28
				Acute pneumonitis	2.32	1.35–3.72	17
				Chronic beryllium disease	1.57	0.75–2.89	10
Ward *et al.* (1992)	Seven beryllium processing plants	1940–69	1988	US males, all races	1.26	1.12–1.42	280

SMR, standardized mortality ratio; CI, confidence interval; [ ], calculated by the Working Group
[a]With Saracci's adjustment

was extended through to 1988 and was analysed using standard modified life-table methods. The influence of local differences in mortality was evaluated by comparing SMRs derived from national and from local county mortality rates. The effect of the dissimilar distribution of smoking habits between beryllium workers and the US population was also evaluated. In the total cohort of 9225 workers, there were 3240 deaths (35% of the total) and 269 235 person-years of follow-up, of which 52% were person-years at risk 15 years or more after first employment in the beryllium industry. The SMR for all causes was 1.05 (95% CI, 1.01–1.08), that for all cancers was 1.06 (95% CI, 0.99–1.44), and that for nonmalignant respiratory disease was 1.48 (95% CI, 1.21–1.80). With the exception of that for cancer of the respiratory system, none of the SMRs for cancers at specific sites was significantly different from 1.00. The overall SMR for lung cancer was 1.26 (95% CI, 1.12–1.42; 280 observed deaths, based on US rates). SMRs for cancers of the larynx and of the upper respiratory tract were below 1.00.

Table 13. Years during which major processes were used at the US beryllium plants in the study of Ward *et al.* (1992)

Plant location	Ore refining	Beryllium oxide production	Metal production	Beryllium–copper alloy production	Machining
Lorain, OH	1935–48	1935–48	1935–48	1935–47	–
Reading, PA	1935–66	1035–66	–	1935–present	1938–present
Lucky, OH	1950–58	1950–58	1950–58	–	–
Perkins (Cleveland), OH	1937–55	1937–62	1948–62	–	1941–63
St Clair (Cleveland), OH	–	–	–	–	1963–73
Elmore, OH	1958–77	1958–present	1958–present	1952–present	1958–present
Hazelton, PA	1958–78	1958–78	1958–78	1958–78	1958–78

The dates refer only to the processes and were not used to restrict the cohorts. For example, workers hired at the Lucky plant in 1949 were included in the study, as were a few individuals hired at the Lorain plant in 1949 and early 1950.

The SMRs for lung cancer at individual plants (Table 14) were greater than 1.00 at four of the six locations: two plants near Cleveland, OH—Perkins and St Clair—were combined into one cohort because records of the two plants could not be separately identified. The SMRs were significantly greater than 1.00 only at the Lorain, OH, and Reading, PA, plants [the same facilities studied by Mancuso (1979, 1980) and Wagoner *et al.* (1980)]. It is noteworthy that cohorts in which there was a high SMR for pneumoconiosis and other respiratory diseases, presumably indicating higher exposure to beryllium also consistently had elevated SMRs for lung cancer. When lung cancer SMRs were stratified by latency at each plant, three of the six locations showed higher SMRs for the 15–30-year and > 30-year latency categories compared with the < 15-year latency category (Table 15); however, for the total cohort, lung cancer SMRs increased stepwise with increasing latency (bottom row of Table 15). When SMRs were stratified by decade of hire (Table 16), values greater than 1.00 were seen for all three locations in which workers were hired before 1950 (the period when exposures to beryllium were also greater than subsequently), but SMRs were also greater than 1.00 in four of the five locations where workers were hired between 1950 and 1959.

Table 14. Mortality of workers employed in 1940–69 at the seven US beryllium processing plants in the study of Ward *et al.* (1992)

Plant location	Total no. of workers	Percentage of workers employed for		SMR			No. of lung cancer deaths
		< 1 year	1–5 years	Lung cancer (based on US rates)	Lung cancer (based on county rates)	Pneumoconiosis and other respiratory disease (based on US rates)	
Lorain, OH	1192	84.6	12.8	1.69**	1.60**	1.94**	57
Reading, PA	3569	53.8	22.3	1.24*	1.42**	1.34	120
Cleveland, OH (two plants)	1593	47.3	29.8	1.08	1.05	1.22	44
Lucky, OH	405	62.2	35.8	0.82	0.84	0.87	9
Elmore, OH	1323	29.0	24.9	0.99	1.06	0.69	15
Hazelton, PA	590	19.7	17.8	1.39	1.50	2.00	13
Multiple plants	257	0.8	12.1	1.67	–	2.60	13
Location unknown	296	49.3	41.6	1.33	–	3.47**	9
Total[a]	9225	49.7	23.4	1.26**	1.32*	1.48**	280

*$p < 0.05$; **$p < 0.01$

[a]See also Table 12

As seen in the bottom row of Table 16, decade of hire was one of the strongest correlates of lung cancer mortality risk in the total cohort. Poisson regression analysis, with control for age, race, calendar time and time since first employment, showed an independent effect of decade of hire on lung cancer SMRs in the total cohort. Duration of employment had no effect. [The Working Group noted that, given the much higher exposures to beryllium prior to 1950 and the fact that 73% of the total cohort worked for less than five years, duration of employment does not separate that segment of the cohort which received the highest exposures to beryllium.]

Table 15. Standardized mortality ratios (SMRs) for lung cancer by location of plants and latency since time of first employment in the US beryllium plants in the study of Ward *et al.* (1992)

Location	Latency < 15 years		Latency 15–30 years		Latency > 30 years	
	SMR	Observed deaths	SMR	Observed deaths	SMR	Observed deaths
Lorain, OH	0.38	1	2.09**	21	1.66*	35
Reading, PA	0.78	9	1.17	44	1.40*	67
Cleveland, OH	1.30	9	0.91	20	1.27	15
Lucky, OH	0.96	1	0.85	4	0.76	4
Elmore, OH	0.51	2	1.14	12	1.31	1
Hazelton, PA	1.91	4	1.26	9	–	0
Multiple plants	–	0	1.23	4	2.38*	9
Location unknown	0.64	1	1.28	5	2.30	3
Total	0.89	27	1.20	119	1.46**	134

*$p < 0.05$; **$p < 0.01$

Table 16. Standardized mortality ratios (SMRs) for lung cancer by location of plants and decade of hire in the US beryllium plants in the study of Ward *et al.* (1992)

Location	Hired before 1950		Hired 1950–59		Hired 1960–69	
	SMR	Observed deaths	SMR	Observed deaths	SMR	Observed deaths
Lorain, OH	1.69**	57	–	–	–	–
Reading, PA	1.26*	92	1.42	26	0.35	2
Cleveland, OH	1.06	12	1.32	26	0.63	6
Lucky, OH	–	–	0.82	9	–	–
Elmore, OH	–	–	1.42	12	0.45	3
Hazelton, PA	–	–	1.86	9	0.87	4
Multiple plants	2.53**	12	0.36	1	–	–
Location unknown	2.30	4	0.62	2	1.57	3
Total	1.42**	177	1.24	85	0.62	18

*$p < 0.05$; **$p < 0.01$

When lung cancer SMRs for each of the six locations were based on local county mortality rates (Ward *et al.*, 1992; see Table 14), the SMRs differed only slightly from those based on US rates. The largest difference occurred in the Reading, PA, cohort, in which the SMR based on US rates was 1.24 and that based on county rates was 1.42. For all six locations, the lung cancer SMR based on US rates was 1.26 (95%, 1.12–1.42), while that based on local county rates was 1.32 (95% CI, 1.19-1.46). When lung cancer SMRs were adjusted for the distribution of smoking habits at four of the plants in which a smoking survey was conducted in 1968 [covering 1466 (15.9%) of the 9225 members of the cohort], the SMR for the total cohort changed from 1.26 to 1.12, and the SMRs in two of the largest, oldest plants changed from 1.69 to 1.49 (Lorain, OH) and from 1.24 to 1.09 (Reading, PA). The authors noted that the major difficulty in interpreting the smoking-adjusted SMRs is that data on smoking were collected in the late 1960s, while most (94%) of the lung cancer cases occurred among workers hired in the 1940s and 1950s. Thus, the validity of the adjustment for smoking depends on the assumption that differences in smoking habits between the cohort and the US population were the same in the 1940s and 1950s as they were in the late 1960s and that smoking data obtained from 16% of the workers adequately represented the distribution of smoking in the entire cohort. The authors estimated the contribution of smoking to be 13%, i.e., smoking alone could account for a lung cancer SMR of 1.13 *versus* the 1.26 actually observed.

2.2 Case–control studies

Hinds *et al.* (1985) applied a computerized job–exposure matrix to data from a case–control study of lung cancer among males in Hawaii, USA. Between 1 September 1979 and 31 July 1982, 261 cases of newly diagnosed primary lung cancer among male residents of Oahu, Hawaii, were identified through a population-based tumour registry and a review of pathology records at all major hospitals and interviewed. Controls were identified by random-digit dialling and matched on sex and age. Information on occupation was obtained during the interview and applied to a job–exposure matrix to estimate exposure levels to various agents for each study subject. The job–exposure matrix was constructed from lists of occupational codes by Hoar *et al.* (1980), and these were used to code both the primary and secondary occupations of all subjects according to industry; each code was then linked to various levels of exposure to each agent. Each agent was grouped into three exposure levels (no exposure, low exposure, high exposure). The association of each agent with lung cancer risk was estimated by the odds ratio, which was determined by multiple logistic regression analysis and adjusted for age, ethnicity and smoking status. Excess risk for lung cancer was found to be associated with exposure to beryllium at both low (odds ratio, 1.62; 95% CI, 1.04–2.51) and high levels (1.57; 0.81–3.01). Other exposures considered in the analysis were coal-tar and pitch, petroleum, arsenic, chromium, asbestos and nickel. [The Working Group noted that it is not clear whether the odds ratio for beryllium was simultaneously controlled for the other exposures.]

Carpenter *et al.* (1988) conducted a nested case–control study of cancers of the central nervous system among workers employed at some time between 1973 and 1977 at two nuclear facilities in Oak Ridge, TN (USA); deaths of 72 white males and 17 white females from cancer of the central nervous system were identified from information on death

certificates, and four controls were matched to each case for race, sex, facility at which initially employed, year of birth and year of hire. Each job title and department combination was subjectively evaluated for potential exposure to each of 26 chemicals, including beryllium. The evaluation took into account period of employment, literature on the processes used at each facility, quantities and toxicities of chemicals used in the processes, interviews with workers involved in processes at different time periods, and the results of urine analyses and air monitoring. Each job title/department combination was given a rank for potential exposure to each of the 26 chemicals; rank 0 had probably no exposure, rank 1 had low potential, rank 2 had moderate potential and rank 3 had high potential for exposure to the specified chemical. Matched conditional logistic regression analyses were conducted and included potential confounding factors such as socioeconomic status. On the basis of 26 cases ever exposed to beryllium, the odds ratio for cancers of the central nervous system was 1.5 (95% CI, 0.6–3.9). The matched analysis by highest rank ever held *versus* rank 0 yielded odds ratios of 1.26, 12.8 and 3.29 for ranks 1, 2 and 3, respectively (all odds ratios had a p value of 0.09 or greater). When risk estimates were calculated for a 10-year latency, the odds ratios were 1.13, 0.85 and 1.77 for ranks 1, 2 and 3, respectively. A further analysis based on time spent in ranks 2 and 3, assuming a 10-year latency, yielded odds ratios of 0.77, 0.90, 1.30 and 1.88 ($p > 0.5$) for workers with < 3 years, 3–10 years, 11–20 years and 21 years or more in ranks 2 and 3 compared with ranks 0 and 1. The authors concluded that their study does not support the hypothesis that occupational exposures to any of the 26 chemicals studied appreciably increase the risk for cancers of the central nervous system; they noted specifically that, although a weak association between exposure to beryllium and cancers of the central nervous system was observed, confidence intervals [not given for analyses by rank or latency] were wide and included the null value.

2.3 Childhood cancer

A case–control study on parental occupation and childhood cancer carried out in Denver, CO, USA (Feingold *et al.*, 1992), included 252 cases of childhood cancer diagnosed during 1976–83 and 222 population controls selected by random-digit dialling. A job–exposure matrix was used to assign parental exposures for six months or longer during the year prior to the child's birth on the basis of job titles. Odds ratios were estimated for all cancers, acute lymphocytic leukaemia and brain cancer, after adjusting for age at diagnosis, year of diagnosis, sex, mother's age at time of birth, maternal smoking during pregnancy, birth weight, birth order and indicators of social class. When all cancers were considered, no association was found between childhood cancer and exposure to beryllium or its compounds for either the mother or the father (odds ratio, 1.0; 95% CI, 0.1–7.1; based on two exposed cases; and 1.6; 0.6–4.4; based on 17 exposed cases, respectively). When the exposures of the fathers were analysed for specific types of cancer, an elevated odds ratio was found for brain cancer (2.1; 0.6–7.6; 5 cases) but not for acute lymphocytic leukaemia (1.3; 0.3–5.9; 5 cases). Most of the subjects considered to have been exposed to beryllium were electrical equipment assemblers and installers (67%), metal processes and welders (20%). [The Working Group noted that other occupational exposures were not considered in the analysis.]

3. Studies of Cancer in Experimental Animals

3.1 Beryllium ores

Inhalation exposure

(*a*) *Rat*

Groups of 60 and 33 male Charles River, caesarian-derived rats and 30 Greenacres Controlled Flora rats (more than four weeks old) were exposed by inhalation to **beryl ore** (geometric mean particle diameter, 0.64 μm) or **bertrandite ore** (geometric mean particle diameter, 0.27 μm) as 15 mg/m^3 dust (the threshold limit value for inert dust in 1968) for 6 h per day on five days a week for up to 17 months. A third group, serving as controls, was housed in an inhalation chamber without exposure. The bertrandite ore atmosphere in the inhalation chamber contained 210 μg/m^3 beryllium, and the beryl ore atmosphere contained 620 μg/m^3 beryllium (for chemical composition, see Table 17). The death rates of the animals exposed to the two ores exceeded that of controls by 13%. Of the animals killed after 12 months of exposure, 5/11 treated with beryl ore had foci of squamous metaplasia or small epidermoid tumours. Of those killed at 17 months, 18/19 had lung tumours (18 bronchiolar alveolar-cell tumours, 7 adenomas, 9 adenocarcinomas and 4 epidermoid tumours). No metastasis was observed. In the group treated with bertrandite ore, granulomatous lesions and some atypical proliferations in the lung were observed, but no bronchiolar alveolar-cell tumour or other lung tumour was found. Controls had no neoplastic or granulomatous pulmonary lesion (Wagner *et al.*, 1969). [The Working Group noted the high crystalline silica content of the bertrandite ore and the incomplete reporting of the study.]

(*b*) *Hamster*

Groups of 48 and 17 male Syrian golden hamsters (more than four weeks old) were exposed by inhalation to **beryl ore** (geometric mean particle diameter, 0.64 μm) or **bertrandite ore** (geometric mean particle diameter, 0.27 μm) as 15 mg/m^3 dust for 6 h per day, five days a week for up to 17 months. A third group, serving as controls, was housed in an inhalation chamber without exposure. The bertrandite ore atmosphere in the inhalation chamber contained 210 μg/m^3 beryllium, and the beryl ore atmosphere contained 620 μg/m^3 (for chemical composition, see Table 17). The mortality of the animals exposed to the two ores exceeded that of controls by 25%. Atypical proliferations, first seen at 12 months in both groups of exposed animals, and lesions considered by the authors to be bronchiolar alveolar-cell tumours, except for their size, occurred. The lesions in the beryl-exposed animals were reported to become larger and more adenomatous after 17 months. The control hamsters had no pulmonary lesion (Wagner *et al.*, 1969). [The Working Group noted the incomplete reporting of the study.]

(*c*) *Monkey*

Groups of 12 and 4 male squirrel monkeys (*Saimiri sciurea*) (more than four weeks old) were exposed by inhalation to **beryl ore** (geometric mean particle diameter, 0.64 μm) or **bertrandite ore** (geometric mean particle diameter, 0.27 μm) as 15 mg/m^3 dust for 6 h per

day, five days a week for up to 23 months. A third group, serving as controls, was housed in an inhalation chamber without exposure. The bertrandite ore atmosphere in the inhalation chamber contained 210 μg/m^3 beryllium, and the beryl ore atmosphere contained 620 μg/m^3 (for chemical composition, see Table 17). The death rates of the animals exposed to the two ores exceeded that of controls by 11%. No tumour was found. Aggregates of dust-laden macrophages, lymphocytes and plasma cells were observed near respiratory bronchioles and small blood vessels in the lungs of exposed animals. Control monkeys had no similar change (Wagner *et al.*, 1969). [The Working Group noted the incomplete reporting and the limited duration of the study.]

Table 17. Chemical composition (of constituents representing > 0.1%) of representative bertrandite and beryl ore samples

Chemical constituent	Analysis by weight (%)	
	Bertrandite	Beryl ore
Be[a]	1.4	4.14
Al_2O_3	9.8	18.1
SiO_2	63.9[b]	
SiO_2 (as silicates)		63.6
SiO_2 (as quartz)		1.9
Fe_2O_3	1.8	1.1
MnO_2	1.8	1.0
CaF_2	8.3	
CaO	0.2	
MgO	2.3	1.1
K_2O	1.2	
Na_2O	1.5	0.5
ZnO	0.7	
CO_2	0.2	
NiO		0.5

Modified from Wagner *et al.* (1969)

[a][Probably as the oxide]

[b]23.5% of the mineral constituents were crystalline quartz and 23.5%, cristobalite (crystalline silica); the remainder was other silicates.

3.2 Beryllium metal and alloys

3.2.1 *Intratracheal instillation*

Rat: Twelve groups of 35 female Wistar rats, three months old, were treated with a single intratracheal instillation of 0.5 or 2.5 mg **beryllium metal** (100% Be), **passivated beryllium metal** (99% Be, 0.26% Cr [as chromate]), **beryllium–aluminium alloy** (62% Be, 38% Al), **beryllium–copper alloy** (4% Be, 96% Cu), **beryllium–copper–cobalt alloy** (2.4% Be, 0.4%

Co, 96% Cu) or **beryllium–nickel alloy** (2.2% Be, 97.8% Ni), with geometric mean particle sizes of 1–2 μm, suspended in 0.4 ml isotonic saline, followed by 0.2 ml saline. Forty control animals were instilled with 0.6 ml saline. The rats were killed when moribund or 18 months after instillation. The first lung neoplasm appeared 8–10 months after instillation. Lung neoplasms, mostly adenocarcinomas and adenomas, were found in 2/21 rats treated with the low dose and in 9/16 rats given the high dose of beryllium metal, in 7/20 animals treated with the low dose and in 9/26 treated with the high dose of passivated beryllium metal, and in 1/21 treated with the low dose and in 4/24 given the high dose of beryllium–aluminium alloy. No lung tumour occurred in 39 controls or in the groups treated with other alloys. The incidence of lung neoplasms was significantly ($p < 0.008$) increased over that in controls (using Fisher's exact test, one-tailed) in the groups that received 2.5 mg beryllium metal or 0.5 mg and 2.5 mg passivated beryllium metal (Groth *et al.*, 1980). [The Working Group noted the low beryllium content of the beryllium–copper alloy, the beryllium–copper–cobalt alloy and the beryllium–nickel alloy.]

3.2.2 *Intravenous injection*

Rabbit: In a study reported as a letter to the Editor, 24 young rabbits [sex and strain unspecified] received a series of intravenous injections of a washed suspension of finely divided **beryllium metal** in water (total dose, 40 mg/animal). Nine animals had died with liver necrosis within seven days, and 10 more died with this condition during the next month. Two of the surviving five rabbits died from pulmonary infections, two developed characteristic bone sarcomata, and a single rabbit survived (Barnes, 1950).

3.3 Beryllium compounds

3.3.1 *Oral administration*

Rat: **Beryllium sulfate** was administered to 52 male and 52 female Long–Evans rats (BLU:LE) in the drinking-water at a concentration of 5 ppm [5 mg/L] from weaning until natural death. The water also contained 5 ppm chromium[III] acetate, 50 ppm zinc acetate and 5 ppm copper acetate; 10 ppm manganese chloride and 1 ppm cobalt chloride; and 1 ppm sodium molybdate. An equal number of animals treated with water served as controls. The life span of the treated rats did not differ significantly from that of controls, but 20–30% of rats in each group died from pneumonia. No significant difference in tumour incidence was observed between treated and control groups (Schroeder & Mitchener, 1975). [The Working Group noted that the dose was too low for an evaluation of carcinogenicity.]

3.3.2 *Inhalation*

(*a*) *Rat*

Twenty-seven male and female albino Wistar rats, weighing 140–210 g, and 109 male and female Sherman rats, weighing 80–110 g, were exposed by inhalation to **beryllium sulfate tetrahydrate** aerosol to give a concentration of 1 μg/ft^3 Be [35.8 μg/m^3], for 8 h per day on 5.5 days a week for 180 days. Control groups of 69 male and female Wistar and 70 male and female Sherman rats were maintained in normal air. In the 52 rats that survived the

treatment, were transferred to 'normal air' and observed for periods of up to 18 months, 76 lung tumours were found, eight with metastases. The tumours included 18 adenomas, 5 squamous carcinomas, 24 acinous adenocarcinomas, 11 papillary adenocarcinomas and 7 alveolar-cell adenocarcinomas. None of the 139 control rats had lung tumours (Schepers *et al.*, 1957). [The Working Group noted the incomplete reporting of the study.]

A group of 75 male and 75 female Sprague–Dawley CD rats, six weeks of age, were exposed by inhalation to **beryllium sulfate tetrahydrate** aerosol for 7 h per day on five days a week for 72 weeks at a mean atmospheric concentration of 34.25 ± 23.66 μg/m^3 Be (average particle diameter, 0.118 μm). An equal number of control animals was exposed to an aerosol of distilled water. Subgroups of animals were killed each month up to the 56th week of exposure; 87% of all animals survived to their scheduled sacrifices. The first lung tumour was observed after nine months of exposure. All of the 43 rats that survived 13 months or more after the beginning of treatment had tumours, and all of the 56 tumours studied histologically were reported to be alveolar adenocarcinomas. No lung tumour was found in the control group (Reeves *et al.*, 1967). [The Working Group noted the incomplete reporting of the study.]

Groups of 30–50 female albino rats, weighing 155–160 g, received **beryllium oxide** or **beryllium chloride** by inhalation at concentrations of 0.8, 4, 30 or 400 μg/m^3 for 1 h per day on five days a week for four months. A group of 160 females served as controls. Only malignant epithelial lung tumours were considered: these occurred in 3/44, 4/39, 6/26 and 8/21 rats treated with beryllium oxide and in 1/44, 2/42, 8/24 and 11/19 treated with beryllium chloride, but in none of the controls (Litvinov *et al.* 1984) [The Working Group noted the incomplete reporting of the study.]

(*b*) *Rabbit*

Three groups of rabbits [sex, strain and age unspecified] were exposed by inhalation to aerosols of **beryllium oxide** (average particle diameter, 0.285 μm; range, 0.11–1.25) at doses of 1 (five rabbits), 6 (six rabbits) or 30 (eight rabbits) μg/L Be for 5 h per day on five days a week for 9–13 months. No control group was available. An osteogenic sarcoma in the left pubis with widespread visceral metastases was observed in one rabbit that had been exposed to 6 μg/L Be for 235 days over 11 months (Dutra *et al.*, 1951). [The Working Group noted the small number of animals and the short duration of exposure.]

(*c*) *Monkey*

In a study reported as an abstract, 16 rhesus monkeys (*Macaca mulatta*) were exposed daily by inhalation 'for a long period of time' to **beryllium sulfate** aerosol at a concentration of 35 μg/m^3 Be. Primary anaplastic pulmonary tumours with adenomatous and epidermoid patterns were observed in three monkeys between six months and eight years after the beginning of exposure (Vorwald, 1967).

3.3.3 *Intratracheal instillation*

(*a*) *Rat*

A group of 35 female Wistar-derived rats, three months old, received single intratracheal instillations of 50 μg Be as **beryllium hydroxide** suspended in distilled water,

followed 10 months later by a second instillation of 25 μg. A group of 35 controls received a single intratracheal instillation of 2.5 mg chrysotile asbestos. Both materials were suspended in 0.4 ml distilled water, and the instillation was followed by 0.2 ml distilled water. Of the beryllium hydroxide-treated rats sacrificed at 19 months of age, 13/25 had pulmonary tumours (six adenomas and seven adenocarcinomas); one rat had both an epidermoid carcinoma and an adenocarcinoma. The lungs of all of the animals instilled with chrysotile had small and occasionally larger scars; adenomas occurred in two rats and an adenocarcinoma in a third. Metaplastic foci were found in the lungs of 5% of the chrysotile-treated group, whereas in 90% of the animals instilled with beryllium most of the normal lung tissue was replaced by metaplastic foci and tumours (Groth *et al.*, 1980). [The Working Group noted the lack of an appropriate control group.]

Two groups of 30 male Wistar rats, 10 weeks of age, were instilled intratracheally with **beryllium oxide** (low-temperature fired, 900 °C; 1 mg as Be) or arsenic trioxide (1 mg as As) once a week for 15 weeks. A group of 16 rats served as untreated controls. All rats in the beryllium-treated group, 19 in the arsenic-treated group and all of the controls survived the treatment period and were observed for life. Two malignant (one squamous-cell carcinoma and one adenocarcinoma) and four benign lung adenomas (three suspected of malignancy) were found in rats treated with beryllium, and one malignant lung tumour (a squamous-cell carcinoma) was found in those treated with arsenic; no lung tumour was observed in the control group (Ishinishi *et al.*, 1980).

Eight groups of inbred albino rats [initial number and sex unspecified], weighing 140–150 g, received single intratracheal instillations of **high-temperature fired beryllium oxide** (2000 °C) or **low-temperature fired beryllium oxide** (600 °C) at doses of 0.036, 0.36, 3.6 and 18 mg/kg bw. A group of 300 untreated rats served as controls. All animals were observed for life. Malignant epithelial lung tumours occurred in 0/76, 0/84, 2/77 and 2/103 rats treated with the high-temperature fired beryllium oxide and in 3/69, 7/81, 18/79 and 8/26 rats treated with the low-temperature fired compound. None were found in 104 controls (Litvinov *et al.*, 1983).

(*b*) *Monkey*

In a study reported as an abstract, a group of 20 rhesus monkeys (*Macaca mulatta*) received an intrabronchial intubation and/or a bronchomural injection [unspecified] of **beryllium oxide** particulates suspended in sterile physiological saline. The first bronchogenic tumour was detected about 4.5 years after first treatment. In the course of the following year, two additional monkeys developed tumours, which were highly anaplastic, with adenomatous and epidermoid patterns (Vorwald, 1967).

3.3.4 *Intravenous injection*

(*a*) *Mouse*

In a study reported as an abstract, three groups of mice received 20–22 intravenous injections (two/week) of either **zinc beryllium silicate** (8.36 mg Zn, 0.264 mg Be), zinc silicate (2.8 mg Zn) or **beryllium oxide** (1.54 mg Be). A fourth group was untreated. 'Some' mice given zinc beryllium silicate were reported to have developed malignant bone tumours (Cloudman *et al.*, 1949).

(*b*) *Rabbit*

In a study reported as an abstract, rabbits received synthetic **zinc beryllium silicate** and its ingredients, **beryllium oxide**, zinc oxide, silicic acid and zinc silicate, intravenously in 20 doses totalling 1 g of particles 3 μm or smaller, over a six-week period. All of the seven rabbits given zinc beryllium silicate which survived the injections for seven months or more developed malignant osteosarcomas, four with visceral metastases. One rabbit killed one year after injection of beryllium oxide had a malignant osteosarcoma. Such tumours were not induced by administration of 65 other minerals in the same way (Gardner & Heslington, 1946).

In a study reported as an abstract, three groups of rabbits received 20–22 intravenous injections (two/week) of either **zinc beryllium silicate** (550 mg Zn, 17 mg Be), zinc silicate (390 mg Zn) or **beryllium oxide** (390 mg Be). A fourth group was untreated. Four of five rabbits given zinc beryllium silicate which survived over one year from the start of injections had bone tumours, three with metastases (Cloudman *et al.*, 1949).

Six groups comprising 67 rabbits of different breeds and sexes were injected intravenously twice a week with various samples of **zinc beryllium silicate** (67% ZnO, 28% SiO_2, 2% BeO and 3% MnO; or 67% ZnO, 31% SiO_2 and 2% BeO), **beryllium silicate** or zinc silicate, with particle sizes of 5 μm or less as a 1 ml suspension in water at the dose schedule indicated in Table 18. Bone sarcomas developed in 7/21 rabbits injected with beryllium silicates that survived for 30 weeks or more. The earliest evidence of malignant change was observed at 32 weeks, and the latest tumour occurred 83 weeks after the last injection. No tumour was found in any of the animals injected with zinc silicate only (Barnes *et al.*, 1950). [The Working Group noted the poor survival.]

Table 18. Results of experiments in rabbits with beryllium silicates

Material injected	Conc. of suspension (%)	No. of injections	Total amount injected (g)	Initial no./group	No. of survivors	No. with osteosarcomas
Zinc beryllium silicate	10	10	1.0	10	3	0
Zinc beryllium silicate	30	6	2.1	12	3	2
Zinc beryllium silicate	10	10	1.0	12	11	4
Beryllium silicate	20	6	1.2	11	3	1
Beryllium silicate	10	10	1.0	12	8	0
Zinc silicate	20	6	1.2	10	8	0

From Barnes *et al.* (1950)

Young, adult, male and female white rabbits [number unspecified] were given intravenous injections of either a highly purified **beryllium oxide** or a **calcined phosphor** containing beryllium oxide, zinc oxide and silica mixed in a molar ratio of 1:1:1, as 1% suspensions in physiological saline. The particles of the powders were smaller than 1 μm. The beryllium oxide-treated group received a total of 360–700 mg Be/rabbit in 20–26 injections, and the phosphor group received 64–90 mg Be/rabbit in 17–25 injections. The compounds were given three times a week over approximately six to nine weeks. One year or more after the first injection, six animals given beryllium oxide and three given calcined phosphor were

still alive. The first tumour was found 11.5 months after the start of the experiment. Osteosarcomas were found in all six beryllium oxide-treated rabbits (two were reported after the paper had been submitted for publication); some were metastases and some were multiple primary tumours. Osteosarcomas were found in 2/3 rabbits given the phosphor. About 50 untreated rabbits kept for similar or longer periods developed no malignant tumour (Dutra & Largent, 1950). [The Working Group noted the small group sizes, the limited reporting and the incomplete observations.]

A group of 13 female and 11 male rabbits of unselected strains, with an average initial body weight of 5.5 lbs [2.5 kg], received intravenous injections of insoluble beryllium compounds under sterile conditions at a dose of 5 ml at one-day or four-day intervals, in an attempt to administer a total of 1 g of the powder. Five animals received **beryllium phosphate**; six rabbits received a **zinc beryllium silicate** containing 60% ZnO, 30% SiO_2, 2% MnO and 2.3% BeO; four received another zinc beryllium silicate containing 14% **beryllium oxide** and 48% zinc oxide; and nine rabbits received **beryllium oxide** from different sources. Except for the beryllium phosphate, which was administered in a 0.1% suspension in saline, all substances were injected as 1% suspensions in saline. Eight animals died of various causes within three months of the start of treatment, and eight more rabbits died at 14–28 months from infectious diseases. Seven of the eight surviving rabbits developed osteogenic sarcomas: three in the group treated with zinc beryllium silicate containing 2.3% BeO, three in the group treated with zinc beryllium silicate containing 14% BeO and one treated with beryllium oxide. One animal that received 100 mg beryllium phosphate was still alive 2.5 years after injection (Hoagland *et al.*, 1950). [The Working Group noted the small group size and the lack of appropriate controls.]

Osteosarcomas were found in 2/4 rabbits within 18 months after a single intravenous injection of 1 g **beryllium phosphate**; no tumour was found in three rabbits that received 1 g **beryllium oxide**. Of animals injected with beryllium oxide mixed with zinc oxide, manganese oxide and/or silicon oxide, 9/31 developed osteosarcomas (Araki *et al.*, 1954). [The Working Group noted the small number of animals, the lack of an appropriate control group and the incomplete reporting.]

Ten adult, male rabbits received two intravenous injections per week for 10 weeks of 5 ml of a 1% suspension of **zinc beryllium silicate** containing 3.36% **beryllium oxide** (total dose, 1 g zinc beryllium silicate or 33.6 mg beryllium oxide). Five rabbits developed osteogenic sarcomas 9–11 months after the injection period (Janes *et al.*, 1954). [The Working Group noted the lack of an appropriate control group and the small group size.]

Fourteen rabbits were injected intravenously with 5 ml of a 1% suspension of **zinc beryllium silicate** (size of particles, 1–3 μm) in physiological saline twice a week for 10 weeks (total dose, 1 g zinc beryllium silicate). The animals died or were killed 28–57 weeks after the last injection. Osteogenic sarcomas appeared in 10/14 rabbits 30–52 weeks after the last injection (Kelly *et al.*, 1961). [The Working Group noted the lack of an appropriate control group and the small group size.]

Osteosarcomas were induced in 3/20 rabbits 15–18 months after single intravenous injections of **beryllium oxide** (total dose, 1 g/rabbit) as a 1% suspension in saline (Komitowski, 1968). [The Working Group noted the lack of an appropriate control group.]

Sixty rabbits, six months of age on average, were treated intravenously with a 1% **beryllium oxide** suspension in 5 ml physiological saline, once a week for 25 weeks. Of the 29 animals that survived until the end of the experiment, 21 developed sarcomas (Fodor, 1977). [The Working Group noted the lack of an appropriate control group and the incomplete reporting.]

3.3.5 *Intraperitoneal injection*

Mouse: In a screening assay based on the accelerated induction of lung adenomas in a strain highly susceptible to development of this neoplasm, three groups of 20 male A/J mice, five to six weeks old, were injected intraperitoneally three times a week for eight weeks with **beryllium sulfate tetrahydrate** (purity $\geq$ 99%) suspended in distilled water at doses of 0.02, 0.05 or 0.1 (maximum tolerated dose) mg/mouse per injection. An equal number of animals were treated with the vehicle only and served as controls. The authors stated that beryllium sulfate produced a significant (χ^2 analysis) increase in lung tumour incidence at total doses of 1.2 and 2.4 mg/mouse with no significant increase in lung tumour multiplicity (Ashby *et al.*, 1990). [The Working Group noted that the increases were not significant using Fisher's exact test.]

3.3.6 *Implantation and/or injection into bone*

Rabbit: Of 55 rabbits that received 1–43 injections of 10 mg **beryllium oxide** as a 1% suspension in isotonic saline into the marrow of the right femur twice weekly (20 mg/week), one developed a chondroma, three developed osteomas, 15 developed chondrosarcomas and seven developed osteochondrosarcomas. The average time between the last injection and the appearance of a tumour was 85 days. The period of observation was one to two years (Yamaguchi, 1963).

A group of 12 rabbits of mixed breeds and sexes, six weeks old, received 20 mg **zinc beryllium silicate powder** (particle diameter, $\leq$ 5 μm), suspended in 0.5 ml of water, as a single intramedullary injection into the upper end of the right tibia. A similar suspension of **zinc oxide** was injected into the left tibia as a control. All rabbits survived the injections for at least 12 months; four animals died of intercurrent infections. Osteogenic sarcomas were found in four rabbits at 12–15 months; three metastasized. The remaining four animals were killed at 15–20 months with no clinical or radiological evidence of tumours. No effect was seen with zinc oxide (Tapp, 1966).

Three groups of six rabbits of mixed breeds and sexes, six to eight weeks old, received implants of 10 mg **zinc beryllium silicate**, **beryllium oxide** or **beryllium silicate** under the periosteum of the upper end of the right tibia. Three animals from each group also received implants of zinc oxide or zinc silicate in a similar procedure into the left tibia and served as controls. Nine animals were killed between 2 and 18 months; the remaining animals lived for 25 months. Four of the animals developed central osteogenic sarcomas between 10 and 25 months after implantation; two occurred in animals treated with beryllium and metastasized, one occurred in an animal given zinc beryllium silicate and metastasized, and one occurred in an animal given beryllium silicate. No tumour occurred in the left tibia of the animals implanted with zinc oxide or zinc silicate (Tapp, 1969).

After intramedullary administration of **beryllium oxide** [purity, dose and dose schedule unspecified] (particle size, ~4 μm) in gelatin into the femur, 5/20 rabbits developed osteogenic sarcomas with lung metastases during an observation period of 24 months. The first tumour was observed 13 months after injection (Komitowski, 1974). [The Working Group noted the lack of an appropriate control group and the incomplete reporting.]

Rabbits were given intramedullary implantations of **beryllium carbonate** (173 rabbits), **beryllium acetate** (18 rabbits), **beryllium acetylacetonate** (10 rabbits), **beryllium laurate** (3 rabbits) or **beryllium stearate** (3 rabbits). Thirty animals given beryllium carbonate developed osteosarcomas 10–17 months after the first treatment; the tumours were detected radiologically between 10 and 21 months and confirmed histologically. One rabbit given beryllium acetylacetonate that survived 13 months developed an osteosarcoma (Matsuura, 1974). [The Working Group noted the incomplete reporting and the small numbers of animals in groups other than the group treated with beryllium carbonate.]

A group of 65 Fauve de Bourgogne rabbits [sex unspecified], 15–20 weeks old, received single intraosseous injections of 0.5 ml of a suspension prepared from 1 g **zinc beryllium silicate** in 15 ml distilled water and gelatin (33 mg Be) into the tibial or femoral metaphysis. Of the 65 rabbits that survived more than four months after the injection, 45 developed osteogenic sarcomas. Radiographic examination indicated that the first sarcomatous changes occurred after three months (Mazabraud, 1975). [The Working Group noted the lack of an appropriate control group.]

Three groups of 10 male rabbits [strain unspecified], six weeks of age, received implants of pellets of hydroxypropylcellulose mixed with **beryllium oxide** into the distal metaphysis of the right femur as follows: Group 1, into the internal callus one week after production of an artificial fracture at a dose of 300 mg; Group 2, into the bone-marrow cavity at a dose of 300 mg; and Group 3, into the bone-marrow cavity at a dose of 50 mg. A further group of 10 rabbits served as untreated controls. At 56 weeks, osteosarcomas had developed in 10/10 rabbits in Group 1, in 7/10 rabbits in Group 2 and in 1/10 rabbits in Group 3. Tumours appeared significantly earlier in Group 1 than in the other groups, and 80% of animals with osteosarcomas had lung metastases (Hiruma, 1991).

3.3.7 *Administration with known carcinogens*

Mouse: Five groups of 40 female and 40 male SENCAR mice, seven to nine weeks old, received a single intraperitoneal injection of 0, 0.01, 0.1, 1.0, 5.0 or 10.0 μg/mouse **beryllium sulfate** [purity unspecified]) in saline. One week after treatment, each animal received dermal applications of 2 μg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) twice a week for 26 weeks. A positive control group received 50.5 μg/mouse benzo[*a*]pyrene followed by the TPA treatment. About 95% of the animals survived the treatment. Beryllium sulfate did not induce a significant number of mouse skin papillomas (Nesnow *et al.* 1985).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

The kinetics and effects of beryllium in humans and animals have been reviewed (Eisenbud, 1984; Skilleter, 1984; Cullen *et al.*, 1986; Reeves, 1986; Skilleter, 1986; Kriebel *et al.*, 1988b; Reeves, 1989; WHO, 1990; Deodhar & Barna, 1991; Haley, 1991).

4.1.1 *Humans*

After accidental exposure of 25 people to beryllium dust, the mean serum concentration of beryllium one day later was 3.5 ppb (μg/L); six days later, it had decreased to 2.4 ppb (Zorn *et al.*, 1986). In unexposed humans who had a mean blood beryllium concentration of 0.9 ng/g (ml), 33.2% of the beryllium in blood was associated with cellular constituents, 7.3% with low-molecular-weight compounds, 8.0% with prealbumin and 51.5% with γ-globulin (Stiefel *et al.*, 1980).

Subjects in the Beryllium Case Registry had elevated concentrations of beryllium in lung tissue (e.g. 0.32 μg/g in a metastinal node) more than 20 years after termination of short-term occupational exposure to beryllium (Sprince *et al.*, 1976).

4.1.2 *Experimental systems*

Retention of carrier-free ^{7}Be as chloride after oral dosage of RF mice, Sprague–Dawley rats, beagle dogs and *Macaca speciosa* monkeys was followed in urine excreted during the first two days. The authors estimated from counts in urine that the gastrointestinal absorption was about 0.6%; however, the urinary excretion of the three monkeys studied was reported to be 3.71% (Furchner *et al.*, 1973).

An early study on the kinetics of continuously inhaled beryllium sulfate in rats showed that the pulmonary burden of beryllium reached a plateau after about 36 weeks. After cessation of exposure, clearance was faster in males than in females. Beryllium was accumulated in tracheobronchial lymph nodes, where the concentration reached a peak at 52 weeks (Reeves & Vorwald, 1967). When rats were exposed to ^{7}Be as chloride and ^{4}Be as sulfate in aqueous aerosols by inhalation using nose-only exposure, 60% of the amount of beryllium deposited initially (the sum of the total body burden and the excreted amount) was found in the lungs and 13.5% in the skeleton (Zorn *et al.*, 1977).

When dogs inhaled aerosols of ^{7}Be as oxide calcined at 500 °C (low-fired) or 1000 °C (high-fired) through the nose, disappearance from the lungs followed first-order kinetics. The clearance half-time was 240 days for high-fired beryllium oxide and 64 days for the low-fired compound. Most of the beryllium in the body was located in the skeleton, tracheobronchial lymph nodes, liver and blood. During the first 32 days after exposure, 59% of the low-fired and 68% of the high-fired beryllium oxide was excreted through the gastrointestinal tract; by 180 days, 47% of the low-fired and 54% of the high-fired was excreted by that route and the balance *via* the kidneys (Finch *et al.*, 1990).

In rats, the clearance of inhaled beryllium oxide calcined at 1000 °C through the lungs showed two successive half-times: the first, comprising 30% of the initial lung burden, was

2.5 days, and the second (70%), 833 days. One to 63 days after exposure, a small fraction (0.58–1.73%) of the initial lung burden was observed in thoracic lymph nodes. About 15% was excreted in the faeces and 1.4% in the urine (Rhoads & Sanders, 1985). The clearance from the alveoli of inhaled beryllium oxide calcined at 1000 °C was faster in hamsters than in rats (Sanders *et al.*, 1975).

The disappearance of beryllium from the lungs of rats 3–171 days after exposure to 800 mg/m^3 metallic beryllium aerosol (mass median aerodynamic diameter, 1.4 μm; geometric mean standard deviation, 1.9) by nose-only inhalation once for 50 min was reported to fit best a first-order kinetic model with a half-time of 240 days (Haley *et al.*, 1990). In a carcinogenicity study (Wagner *et al.*, 1969), described in detail in section 3.1, rats, hamsters and squirrel monkeys were exposed by inhalation to ore dusts containing beryllium, beryl (containing 4.14% beryllium) and bertrandite (containing 1.4% beryllium). Increased concentrations of beryllium were detected in the skeleton, liver and lung after 6–12 months of exposure to beryl or bertrandite; exposure to beryl led to higher tissue concentrations than did exposure to bertrandite.

The highest concentrations of beryllium after an intramuscular injection of carrier-free ^{7}Be as chloride to rats were observed initially in the skeleton, liver, kidney, lungs and spleen; 56.3% of the dose injected was still at the site of injection after one day. During a 64-day follow-up, the skeleton and, to a lesser degree, spleen showed a constant increase, while there was a gradual decrease in the other organs; 20.5% of the dose injected was still at the site of injection (Crowley *et al.*, 1949). Accumulation in the liver, kidney, spleen and, especially, the skeleton was also observed seven days after an intravenous administration of ^{7}Be to rats and rabbits. In rats receiving ^{7}Be as sulfate, the liver and spleen contained appreciable amounts of beryllium; in animals receiving carrier-free ^{7}Be, a higher percentage was found in the skeleton. These differences were less marked in rabbits (Scott *et al.*, 1950).

Accumulation of beryllium in compact bone, liver and kidney was observed in dairy cows given carrier-free ^{7}Be as chloride orally or intravenously (Mullen *et al.*, 1972).

After intravenous injection of carrier-free ^{7}Be as chloride into rats in a solution at pH 2, 47% of the dose was excreted predominantly in the urine and 43% was detected in bone and bone marrow after 24 h; only 4% was detected in liver and 0.1% in spleen. When 1 μmol unlabelled beryllium chloride was added as carrier to the solution to be injected, the proportion found in the liver increased to 25% and that in spleen to 1%. At pH 6, 59% was found in the liver after administration of carrier-free ^{7}Be and 44% after addition of unlabelled beryllium chloride. Administration of labelled plus 0.15 μmol unlabelled beryllium chloride in citrate at pH 6 elicited similar responses to carrier-free ^{7}Be at pH 2, while labelled plus 0.3 μmol unlabelled beryllium hydroxide was accumulated strongly in the liver and spleen (Klemperer *et al.*, 1952).

The uptake of intravenously administered (20–800 μg/kg bw) beryllium phosphate was much more extensive in the liver and spleen (approximately 55% of the dose) than that of beryllium sulfate or citrate in mouse; the same phenomenon was observed in rats given a single dose (200 μg/kg bw). The uptake of the two soluble compounds was practically nil at dose levels up to 50 μg/kg, while uptake of the phosphate was independent of dose (Vacher *et al.*, 1974).

Beryllium phosphate and beryllium sulfate accumulated in both nonparenchymal and parenchymal cells of the liver after intravenous administration (Skilleter & Price, 1978). Beryllium oxide granules accumulated intracellularly in marrow throughout the skeletal system after intravenous administration to rabbits of beryllium oxide [method of preparation not given] (Fodor, 1977).

After an intraperitoneal or intravenous dose of carrier-free ^{7}Be as chloride, the disappearance of beryllium was best characterized by three consecutive half-times of 0.2–0.5, 6.3–21.7 and 50.9–52.4 days in mice, rats, dogs and *Macaca speciosa* monkeys (Furchner *et al.*, 1973).

Transplacental transfer of beryllium was demonstrated in mice after intravenous injection of beryllium chloride (Bencko *et al.*, 1979). Transport of ^{7}Be [chemical unspecified] across the rat placenta after intravenous injection was also reported (Schulert *et al.*, 1969).

An estimated 1% of a single oral dose of carrier-free ^{7}Be as chloride to a dairy cow was excreted in the milk within 91 h (Mullen *et al.*, 1972).

After an intravenous injection of beryllium sulfate to rats, most of the beryllium in plasma coeluted in Sephadex chromatography with phosphate and was attached to plasma globulins. A small part of the dose remained in a low-molecular-weight form (Vacher & Stoner, 1968). One-fourth to one-third of blood-borne beryllium in unexposed guinea-pigs and rats was bound to cellular constituents; this proportion was unchanged in animals exposed to beryllium by inhalation. In both exposed and unexposed guinea-pigs, the proportion bound to prealbumin was approximately 70%; in rats, it was 65% (Stiefel *et al.*, 1980). When beryllium chloride (10^{-4} mol/L) was dissolved in different plasma constituents at their normal plasma concentrations, only a very small proportion (generally less than 2.5%) remained dialysable; only citrate (62%), maleate (30%) and bicarbonate (10%) were significantly dialysable. Phosphate decreased the dialysable part of beryllium to 0.2%, and 4% of the added beryllium remained dialysable. It was concluded that at beryllium concentrations in excess of about 10^{-7} mol/L, most of the beryllium in plasma is nondialysable phosphate, and the small dialysable part is mainly citrate (Feldman *et al.*, 1953). In line with this finding, only 3% of beryllium sulfate added to serum *in vitro* traversed a dialysis membrane within 24 h (Reeves & Vorwald, 1961). A low-affinity binding site for beryllium was observed on the outer cell surface of human and guinea-pig lymphocytes; a binding site with a higher affinity was detected in the cell nucleus (Skilleter & Price, 1984).

After repeated intraperitoneal administrations to rats of beryllum sulfate, beryllium was concentrated in nuclei in the cells of the proximal convoluted tubuli (Berry *et al.*, 1987, 1989). In hepatocytes, beryllium was accumulated in lysosomes and nuclei (Levi-Setti *et al.*, 1988). After intravenous administration, the highest concentrations were observed in lysosomes; only at doses approaching the LD_{50} (corresponding to 2–83 μmol/kg bw beryllium sulfate) was there also accumulation in the nuclei in the liver (Witschi & Aldridge, 1968).

Beryllium showed affinity to nuclei isolated from rat liver *in vitro* (Witschi & Aldridge, 1968); it was not bound to DNA or histones (Witschi & Aldridge, 1968; Parker & Stevens, 1979) but to a highly phosphorylated non-histone protein fraction (Parker & Stevens, 1979).

4.2. Toxic effects

4.2.1 *Humans*

Exposure to beryllium compounds may cause an acute chemical pneumonitis, tracheobronchitis, conjunctivitis, dermatitis and chronic granulomatous pulmonary disease with systemic manifestations (Hardy & Tepper, 1959; Freiman & Hardy, 1970). The acute pulmonary disease was first described in Germany in 1933 (Weber & Engelhardt, 1933) and the chronic form in the USA in 1946 (Hardy & Tabershaw, 1946).

Acute beryllium disease, most frequently related to intense but brief exposure, consists of respiratory tract irritation and dermatitis, sometimes with conjunctivitis. The respiratory tract symptoms range from mild nasopharyngitis to a severe chemical pulmonitis, which may be fatal (Hardy & Tepper, 1959; Kriebel *et al.*, 1988b). In fatal cases, histopathological findings in the lungs have included interstitial oedema, cellular infiltration, elevated numbers of plasma cells, alveolar cell proliferation or desquamation and, sometimes, interalveolar oedema, hyaline membranes and organizing pneumonia (Freiman & Hardy, 1970).

Chronic beryllium disease is a systemic disorder with primary manifestations in the lung, characterized by a decrease in transfer factor with restrictive and obstructive ventilatory function. Histopathologically, the disease is characterized by non-caseating granuloma formation with giant cells, as in sarcoidosis, primarily seen in the lungs but also in other tissues. Chest radiography usually shows diffuse infiltrates and hilar adenopathy (Hardy & Tepper, 1959; Freiman & Hardy, 1970; Jones Williams, 1977; Kriebel *et al.*, 1988b). An improvement in lung function and even in lung radiographic findings was reported after a significant decrease in the air concentration of beryllium due to improved engineering and ventilation in plants (Sprince *et al.*, 1978).

Beryllium compounds known to cause beryllium-induced diseases include metallic beryllium (Jones Williams, 1977), beryllium alloys (Lieben *et al.*, 1964) and beryllium oxide fumes (Cullen *et al.*, 1987). The first cases of beryllium disease were identified in the fluorescent light-bulb industry (Hardy & Tabershaw, 1946), in which beryllium-containing phosphors (zinc beryllium manganese silicate), prepared by firing the individual oxides with silica, were used (Eisenbud & Lisson, 1983).

Although chronic beryllium disease has become rare since the adoption of stringent industrial hygiene measures, sporadic cases are still reported (Karkinen-Jääskeläinen *et al.*, 1982; Cullen *et al.*, 1987; Rossman *et al.*, 1988; Kreiss *et al.*, 1989; Newman *et al.*, 1989), e.g., among workers in a precious metal refinery, where exposure to beryllium did not exceed 2 $\mu g/m^3$ (Cullen *et al.*, 1987). A conspicuous feature of chronic beryllium disease is its occasional occurrence outside facilities in which beryllium compounds are used: Sterner and Eisenbud (1951) reported 10 cases among people who had never worked in a beryllium plant but who lived within 1 km of one; the best estimate of beryllium concentrations in the air in the area was 0.01–0.1 $\mu g/m^3$. In 1983, when the US registry for beryllium diseases contained 622 cases of chronic beryllium disease, 65 had had no occupational exposure to beryllium, 42 could be attributed to air pollution (41 occurred in the vicinity of two large production plants and one in a woman living near a fluorescent-lamp plant) and 23 to household exposure to dust brought home on work clothes (Eisenbud & Lisson, 1983).

In the cohort study based on the Beryllium Case Registry, reported in detail in section 2 (p. 68), the SMR for non-neoplastic respiratory diseases was 16.4 ($p < 0.001$) and that for non-neoplastic respiratory diseases (other than influenza and pneumonia), 32.1 ($p < 0.001$) (Infante *et al.*, 1980). In an updating of the cohort (Steenland & Ward, 1991), described in detail in section 2, the SMR for nonmalignant lung disease was 26.3 (95% CI, 20.6–33.1) for workers with less than four years of exposure and 45.8 (95% CI, 36.6–56.5) for workers with longer exposure.

In a cohort study of 9225 male workers employed in seven beryllium processing facilities in the USA (Ward *et al.*, 1992; described in section 2, p. 69), the SMR for pneumoconiosis and other respiratory diseases was 1.48 (95% CI, 1.21–1.80), that for diseases of the heart was 1.06 (1.00–1.12) and that for chronic and unspecified nephritis, renal failure and other renal sclerosis, 1.49 (1.00–2.12).

A nonsymptomatic form of chronic beryllium disease—typical granulomatous changes in transbronchial biopsy specimens with positive lymphocyte transformation tests—has been reported (Newman *et al.*, 1989).

Beryllium dermatitis may be a typical contact dermatitis, localized dermal ulceration or a subcutaneous granuloma. Ulceration of granulomas develops after a particle of a beryllium-containing substance is introduced into an abrasion, laceration or cut (Hardy & Tepper, 1959). People with beryllium-induced contact dermatitis react to patch testing (Curtis, 1951; DeNardi *et al.*, 1952). Patch testing may cause a flare of the dermatitis in sensitized people; it may also induce beryllium sensitivity (Curtis, 1951)

A role of immunological mechanisms in beryllium-induced chronic disease was originally proposed by Sterner and Eisenbud (1951). The condition has the features of a type IV cell-mediated hypersensitivity disorder, the beryllium acting as a hapten (Dayan *et al.*, 1990). Cell-free extracts of blood lymphocytes from people with experimentally induced, localized, dermal granulomatous beryllium lesions cultured in the presence of beryllium oxide contained migration inhibition factor, which inhibits the migration of guinea-pig peritoneal exudate cells (Henderson *et al.*, 1972). The factor was also produced by cell cultures originating from the blood of patients with chronic beryllium disease (Jones Williams *et al.*, 1972; Marx & Burrell, 1973). Lymphocytes from such patients responded to a beryllium oxide or beryllium sulfate challenge by blast transformation and increased thymidine incorporation (Hanifin *et al.*, 1970; Deodhar *et al.*, 1973). Proliferation of lymphocytes from patients with chronic beryllium disease in response to a challenge with beryllium sulfate or fluoride was more marked in lymphocytes obtained by bronchoalveolar lavage than in those harvested from circulating blood (Epstein *et al.*, 1982; Cullen *et al.*, 1987; Saltini *et al.*, 1989). The only lymphocytes obtained from bronchoalveolar lavage which proliferated were CD4+ (helper/inducer) T cells (Saltini *et al.*, 1989).

4.2.2 *Experimental systems*

When beryllium (as lactate or sulfate) was given intravenously to rats or rabbits at a dose of 0.5 or 0.75 mg/kg Be, death invariably followed within four days; the primary cause of death was liver damage and ensuing hypoglycaemia. In rabbits, but not in rats, convulsions were observed before death (Aldridge *et al.*, 1950).

A granulomatous lung disease, morphologically and immunologically similar to chronic beryllium disease in humans, was induced in beagle dogs by inhalation of beryllium oxide calcined at 500 °C, but not with beryllium oxide calcined at 1000 °C (Haley *et al.*, 1989).

Intratracheal instillation of 10 mg beryllium oxide (calcined at 560 °C) into male Hartley guinea-pigs of an inbred strain caused focal interstitial lymphomononuclear infiltrates in the lungs, which progressed to granulomatous lung lesions with fibrosis. Lymphocytes from the blood of these animals responded to beryllium sulfate *in vitro* by increased incorporation of tritiated thymidine (lymphocyte transformation test). The animals exhibited a positive reaction to intradermal beryllium sulfate. Intravenous or oral administration of beryllium sulfate before intratracheal instillation of beryllium oxide decreased the intensity of the pulmonary reaction; a similar effect was observed when the animals were treated with prednisone, L-asparaginase or cyclophosphamide. Splenic cells from animals with beryllium-induced lung disease given intraperitoneally to another group of animals of the same strain caused a similar disease and skin reactivity to beryllium sulfate. No lung disease, skin reactivity or reaction in the lymphocyte transformation test was induced by similar treatment of another inbred strain of guinea-pigs (Barna *et al.*, 1981).

In another study using the same responsive guinea-pig strain, lymphokine production by isolated lymph node cells from animals treated with beryllium oxide endotracheally and challenged with beryllium sulfate was demonstrated *in vitro*. The cells also secreted a factor that inhibited the migration of macrophages (Barna *et al.*, 1984).

Strain A (H-2^a haplotype) mice given an intratracheal instillation challenge of beryllium sulfate or beryllium oxide (calcined at 550 and 1100 °C) after immunization with beryllium sulfate had increased numbers of lymphocytes in bronchoalveolar lavage fluids two, four and eight weeks (months for the oxide) after the challenge. The cells were mainly CD4+ T lymphocytes. By four weeks, microgranulomas were observed in the lungs, which had developed into granulomatous lesions by eight weeks in the case of the sulfate. Such changes were not observed in mice not immunized with beryllium sulfate or in pretreated mice that were not challenged, nor in two strains of mice with different H-2 haplotypes [C57Bl/6(H-2^b) and BALB/c(H-2^d)] (Huang *et al.*, 1992).

In a descriptive toxicity study (see p. 86), male Fischer 344/N rats were exposed by nose only to 800 mg/m^3 metallic beryllium dust (mass median aerodynamic diameter, 1.4 μm) for 50 min, to give an initial lung burden of 625 μg. The animals were then followed for 171 days with timed terminations at 3, 7, 10, 14, 31, 59 and 115 days. Necrotizing, haemorrhagic pulmonitis and intra-alveolar fibrosis, followed by chronic inflammatory changes, were observed. The prevailing cell type obtained by bronchoalveolar lavage was neutrophils; few lymphocytes and no granulomas were observed (Haley *et al.*, 1990). Similarly, after a 1-h exposure of rats to 4.05 mg/m^3 Be as beryllium sulfate (mass median aerodynamic diameter, 1.9 μm), progressive focal interstitial pneumonitis, but no granulomatous disease, was observed; the gross histological picture was similar three weeks and 3, 6 and 12 months after the exposure (Sendelbach *et al.*, 1989).

Intratracheal instillation of beryllium sulfate after immunization with a subcutaneous injection of beryllium sulfate fortified with ovalbumin and Freund's adjuvant resulted in

granulomatous pulmonary disease in Fischer 344 rats within six weeks, accompanied by accumulation of both T and B lymphocytes in the lung tissue (Votto *et al.*, 1987).

In a carcinogenicity study (Wagner *et al.*, 1969; see section 3.1, p. 76), granulomatous lung lesions were observed in hamsters and rats exposed to bertrandite but not in those exposed to beryl ore. [It is not clear if the granulomas were morphologically similar to those observed in humans with chronic beryllium disease or to those in dogs and guinea-pigs after short-term exposure to beryllium oxide.]

The effect of beryllium sulfate (1-h exposure by inhalation; 13 mg/m^3 Be; particle mass median aerodynamic diameter, 1.9 μm) on cell kinetics was studied in rats and mice by autoradiographic determination of the proportion of tritium-labelled cells 90 min after intraperitoneal administration of tritiated thymidine (Sendelbach *et al.*, 1986). In rats, a strong proliferative response was seen, involving type II alveolar epithelial cells and interstitial and capillary endothelial cells. In mice, the proliferative response was weaker and was limited to alveolar macrophages and interstitial and endothelial cells.

Dietary administration of beryllium carbonate at 0.125–1% caused changes typical of rachitis in the skeleton of rats (Guyatt *et al.*, 1933).

Exposure of female rats by nose-only inhalation to beryllium oxide aerosol (mass median aerodynamic diameter, 1.10 μm; calcined at approximately 1000 °C [dust concentration and length of exposure not given]), to give an initial alveolar deposition of 30 μg beryllium, decreased alveolar clearance of subsequently administered plutonium oxide by up to 40% (Sanders *et al.*, 1975).

The concentration of beryllium sulfate required to decrease the viability of canine pulmonary alveolar macrophages *in vitro* by 50% was 0.11 mmol/L; the corresponding concentration for beryllium oxide calcined at 500 °C was 1.4 mmol/L, and that for beryllium oxide calcined at 1000 °C was 3.3 mmol/L. [Because of the limited solubility of beryllium sulfate in tissue culture media, it is not clear what proportion was truly in solution.] The solubility of the high-fired beryllium oxide in 100 ml 0.1 N hydrochloric acid was considerably lower than that of the low-fired compound. There was a similar tendency for differential solubility in simulated serum ultrafiltrate, which was not, however, significant (Finch *et al.*, 1988). Similar results were obtained in a study of cultured rat tracheal epithelial cells (Steele *et al.*, 1989).

Intravenous administration of beryllium sulfate at 30 μmol/kg bw to rats decreased the stimulation of thymidine incorporation into liver DNA after partial hepatectomy (Witschi, 1968); the decrease was accompanied by decreased activities of thymidine kinase, thymidylate kinase, thymidylate synthetase, deoxycytidylate deaminase and DNA polymerase (Witschi, 1970). No effect was observed on the incorporation of ^{14}C-orotic acid into RNA, the activity of RNA polymerase, incorporation of ^{14}C-leucine into histones or acetylation of histones (Marcotte & Witschi, 1972).

Addition of beryllium sulfate at 1–5 μmol/L increased ^{3}H-thymidine incorporation into splenic lymphocyte DNA by two to three fold (Price & Skilleter, 1985). This weak mitogenic effect was limited to B lymphocytes (Newman & Campbell, 1987). Beryllium sulfate, brought into solution as a sulfosalicylic acid complex, inhibited the growth of mouse fibroblasts in culture at concentrations higher than 10^{-5} mol/L (Rössner & Bencko, 1980).

Be^{2+} at a concentration of 0.1 mmol/L inhibited the proliferation of rat hepatocytes in culture induced by epidermal growth factor by 72%, but it did not affect the binding of growth factor to its receptors on the hepatocytes (Skilleter & Legg, 1989).

Beryllium fluoride complexes were bound to microtubules polymerized in the presence of glycerol from tubulin isolated from pig brain and stabilized the polymer formed (Carlier *et al.*, 1988, 1989). Divalent beryllium ($BeSO_4$), but not beryllium fluoride, stimulated microtubule-associated protein-dependent polymerization of tubulin purified from bovine brain and stabilized the polymer formed (Hamel *et al.*, 1991, 1992).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

Kline *et al.* (1951) described the pregnancy of a 25-year-old woman who worked in a fluorescent-tube factory in 1942–44. She displayed signs of radiographic changes in lungs, cyanosis and dyspnoea in the seventh month of her second pregnancy in 1950. No beryllium was detected in a lung biopsy. The woman was treated with adrenocorticotrophic hormone and steroids and delivered a 2.75-kg child seven weeks later. Twenty-four-hour specimens of the urine of the infant collected on the second and third day after birth contained 0.4 and 0.015 μg Be. The child became severely hypoglycaemic after 48 h but was subsequently released from hospital.

Savitz *et al.* (1989) examined a subset of people covered by the 1980 US National Natality and Fetal Mortality Surveys for indications of adverse effects related to maternal or paternal occupational exposures to beryllium, as assessed from a job–exposure matrix. Paternal occupational exposure was associated with 3170 stillbirths, 552 preterm deliveries and 371 babies small for gestational age; the corresponding odds ratios (with 95% CI) were: 1.0 (0.7–1.3), 1.0 (0.5–2.0) and 0.9 (0.5–1.7), respectively. Maternal exposure to beryllium was not associated with these end-points.

4.3.2 *Experimental systems*

The effects of beryllium compounds on reproduction and prenatal development have been reviewed (Barlow & Sullivan, 1982). After oral exposure of male and female rats to a single intratracheal dose of 0.2 mg beryllium oxide (fired at 960 °C in one study and 500 °C in a second), no effect was noted in repeated breeding trials on fertility, postnatal viability or growth over 15 months. In fact, beryllium-treated rats tended to produce more litters over time than did controls (Clary *et al.*, 1975).

All offspring of Sprague–Dawley rats exposed intravenously to 0.316 mg/kg bw beryllium nitrate (one-tenth of the reported LD_{50}) on gestation day 1 died within two to three days after birth. Exposure to beryllium on day 11, but not on day 12, 13, 15 or 17 of gestation, resulted in death *in utero*; all pups in the other groups died within two to three days of delivery (Mathur *et al.*, 1987). [The Working Group noted the potential confounding effect of anaesthesia and surgery in the experimental design.]

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 19 and Appendices 1 and 2)

(*a*) *Beryllium salts*

Beryllium sulfate was mutagenic to *Bacillus subtilis* in the *rec* assay, but no effect was seen using a higher dose of beryllium chloride. [The latter was actually a null effect, as no zone of inhibition was seen.] Both beryllium chloride and beryllium nitrate were mutagenic in a *rec* assay using spores of *B. subtilis*.

A null effect was also seen with beryllium sulfate in *Escherichia coli* in the pol^+/pol^- assay for DNA modifying effects. In a spot test using four strains of *E. coli* with different repair capacities, beryllium sulfate caused zones of inhibition of growth only in repair-deficient strains. The inhibition decreased with increasing pH, with little effect above pH 5–6. The authors suggested that beryllium interferes with use of exogenous orthophosphate rather than with DNA repair.

Beryllium chloride did not induce SOS repair, measured as λ prophage induction; no inhibition of growth was seen with continuous exposure to up to 5 mM, however, suggesting lack of uptake.

Beryllium sulfate was inactive in most bacterial mutagenesis assays. It did not induce point mutations in *Salmonella typhimurium* in the absence of metabolic activation in four laboratories. Negative results were found in the presence of various metabolizing systems, except in strain TA1535, in which equivocal results were obtained in the presence of some Aroclor-induced liver enzymes; however, no toxicity was seen, even at doses up to 5 mg/plate. Beryllium chloride and beryllium nitrate at similarly high doses were not mutagenic to *S. typhimurium*. Beryllium sulfate was not mutagenic to *S. typhimurium* in a plate incorporation assay, but it gave positive results in single fluctuation tests with *E. coli* and with one strain of *S. typhimurium*. Beryllium chloride induced a modest increase in the number of mutations in the *lac*I gene when grown with *E. coli*, but no clear dose–response relationship. It did not enhance the mutagenicity of ultraviolet radiation to *E. coli*, but it enhanced the mutagenicity of 9-aminoacridine to *S. typhimurium*.

Beryllium sulfate was not mutagenic when injected intraperitoneally to adult male Swiss–Webster mice in a host-mediated assay using *S. typhimurium* strains. It did not induce mitotic recombination in *Saccharomyces cerevisiae* D3 in the presence or absence of metabolic activation, and did not induce mutation in a host-mediated assay using the same strain.

Beryllium sulfate tetrahydrate did not induce unscheduled DNA synthesis in primary hepatocytes, as measured by autoradiographic light nuclear labelling; however, a dose of 10 mg/ml was reported to be toxic.

In the only study available, beryllium chloride was reported to increase the frequency of 8-azaguanine-resistant mutants in Chinese hamster V79 cells by a factor of about 6.

Beryllium chloride and beryllium nitrate induced sister chromatid exchange in the same cells. Beryllium sulfate also increased the frequency of sister chromatid exchange in cultured human lymphocytes and in Syrian hamster embryo cells. Studies on the ability of beryllium salts to induce chromosomal aberrations *in vitro* have had mixed results. Beryllium sulfate increased the frequency of chromatid aberrations in human lymphocytes in one of two studies, and a 21-fold increase was seen in the same study with Syrian hamster embryo cells. Higher doses of beryllium sulfate were nonclastogenic to Chinese hamster lung cells; however, toxicity was seen only at 2.5 mg/ml. It had little effect on chromosomes in Chinese hamster ovary cells, but fairly high concentrations enhanced the frequency of X-ray-induced chromatid-type exchanges. Extremely high concentrations of beryllium chloride caused chromosomal 'stickiness' in cultured peripheral lymphocytes of domestic pigs; chromosomal breakage was rare, whereas chromatid breaks were frequent.

Beryllium sulfate induced morphological transformation of Syrian hamster embryo cells and enhanced the transformation of the cells by simian adenovirus SA7 [no dose–response given]. In a comparative evaluation of in-vitro transformation systems, beryllium sulfate induced morphological transformation in BALB/3T3 cells, in Syrian hamster embryo cells and in Rauscher murine leukaemia virus-infected Fischer 344 rat embryo cells. [In none of the studies were transformed cells injected into suitable hosts to verify the occurrence of malignant transformation.]

In the only report of exposure *in vivo*, beryllium sulfate given by gavage at 50 and 80% of the four-day maximal tolerated dose did not induce micronuclei in the bone marrow of mice. A marked depression of bone-marrow erythropoiesis was observed, suggesting a toxic effect to the marrow.

(*b*) *Beryllium oxide*

This sparingly soluble compound did not induce differential toxicity in *B. subtilis*, mutation in two strains of *S. typhimurium* or sister chromatid exchange in Chinese hamster V79 cells.

Both single-strand breaks and morphological cell transformation were reported to be induced by low-fired beryllium oxide, but conflicting results were obtained for both end-points with high-fired beryllium oxide. [The data were not particularly convincing.]

Considerations with regard to genotoxic mechanisms

As pointed out in a review, beryllium is uniquely amphoteric among the alkaline earth elements. It can form positive and negative ions in acidic and basic media but not at neutrality, at which it forms poorly soluble particulates. Beryllium salts are readily precipitated in the tissues and are transported in blood predominantly as colloidal phosphate–hydroxide complexes weakly associated with plasma globulins; these may be taken up by macrophages. Cultured cells essentially accumulate only colloidal or particulate beryllium, by a temperature-dependent process deduced to be endocytosis. Macrophages, the cells most active in the endocytosis of particulate materials, appear to be those most sensitive to the cytotoxicity of beryllium (reviewed by Skilleter, 1984). Beryllium was toxic to mammalian cells only at concentrations at which a precipitate was seen in the culture

Table 19. Genetic and related effects of beryllium compounds

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Beryllium chloride				
PRB, λ Prophage induction, *Escherichia coli*	–[b]	0	45	Rossman *et al.* (1984)
BSD, *Bacillus subtilis rec* assay, differential toxicity	–	0	22.5	Nishioka (1975)
BSD, *Bacillus subtilis* (spores) *rec* assay, differential toxicity	+	0	84	Kuroda *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	NR	Ogawa *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	280	Kuroda *et al.* (1991)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	0	NR	Ogawa *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	0	NR	Ogawa *et al.* (1987)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+[c]	0	450	Ogawa *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	NR	Ogawa *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	280	Kuroda *et al.* (1991)
SAS, *Salmonella typhimurium* TA2637, reverse mutation	–	0	NR	Ogawa *et al.* (1987)
SAS, *Salmonella typhimurium* TA2637, reverse mutation	+[c]	0	450	Ogawa *et al.* (1987)
ECK, *Escherichia coli* KMBL 3835 (*lac*I gene), forward mutation	+	0	0.09	Zakour & Glickman (1984)
EC2, *Escherichia coli* WP2, reverse mutation	–[d]	0	18	Rossman & Molina (1986)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus, *in vitro*	+	0	18	Miyaki *et al.* (1979)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells, *in vitro*	+	0	3.5	Kuroda *et al.* (1991)
CIA, Chromosomal aberrations, swine lymphocytes, *in vitro*	+	0	1.8	Vegni Talluri & Guiggiani (1967)
Beryllium nitrate				
BSD, *Bacillus subtilis* (spores) *rec* assay, differential toxicity	+	0	51	Kuroda *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation (spot test)	–	0	900	Tso & Fung (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	170	Kuroda *et al.* (1991)

Table 19 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Beryllium nitrate (contd)				
SA9, *Salmonella typhimurium* TA98, reverse mutation	?	0	NR	Arlauskas *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	170	Kuroda *et al.* (1991)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells, *in vitro*	+	0	2.0	Kuroda *et al.* (1991)
Beryllium sulfate				
ECD, *Escherichia coli pol* A, differential toxicity (spot test)	-	0	28	Rosenkranz & Poirier (1979)
BSD, *Bacillus subtilis rec* assay, differential toxicity	+	0	90	Kada *et al.* (1980); Kanematsu *et al.* (1980)
ERD, *Escherichia coli rec* strains, differential toxicity	+	0	2.25	Dylevoi (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	6	Simmon (1979a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	14	Dunkel *et al.* (1984)[e]
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	NR	Arlauskas *et al.* (1985)
***Salmonella typhimurium* TA100, reverse mutation (fluctuation)	+	0	4.5	Arlauskas *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	127	Ashby *et al.* (1990)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	10	Rosenkranz & Poirier (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	6	Simmon (1979a)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	?[f]	0.9	Dunkel *et al.* (1984)[e]
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	0	NR	Arlauskas *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	127	Ashby *et al.* (1990)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	6	Simmon (1979a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	14	Dunkel *et al.* (1984)[e]
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	0	NR	Arlauskas *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	127	Ashby *et al.* (1990)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	10	Rosenkranz & Poirier (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	6	Simmon (1979a)

Table 19 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Beryllium sulfate (contd)				
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	14	Dunkel *et al.* (1984)[e]
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	127	Ashby *et al.* (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	6	Simmon (1979a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	14	Dunkel *et al.* (1984)[e]
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	127	Ashby *et al.* (1990)
SAS, *Salmonella typhimurium* TA1536, reverse mutation	–	–	6	Simmon (1979a)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	–	14	Dunkel *et al.* (1984)[e]
***, *Escherichia coli* WP2 *uvr*A, reverse mutation (fluctuation test)	?	0	NR	Arlauskas *et al.* (1985)
SCH, *Saccharomyces cerevisiae* D3, mitotic recombination	–	–	430	Simmon (1979b)
URP, Unscheduled DNA synthesis, primary rat hepatocytes	–	0	86	Williams *et al.* (1982)
SIS, Sister chromatid exchange, Syrian hamster embryo cells *in vitro*	+	0	0.05	Larramendy *et al.* (1981)
CIC, Chromosomal aberrations, Chinese golden hamster ovary cells *in vitro*	–	0	9	Brooks *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+[g]	0	9	Brooks *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster lung cells *in vitro*	–	–	64	Ashby *et al.* (1990)
CIS, Chromosomal aberrations, Syrian hamster embryo cells *in vitro*	+	0	0.25	Larramendy *et al.* (1981)
TBM, Cell transformation, BALB/c 3T3 mouse cells *in vitro*	+	0	0.05	Dunkel *et al.* (1981)
TCS, Cell transformation, Syrian golden hamster embryo cells *in vitro*	+	0	0.016	Pienta *et al.* (1977)
TCS, Cell transformation, Syrian hamster embryo cells *in vitro*	+	0	0.13	DiPaolo & Casto (1979)

Table 19 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Beryllium sulfate (contd)				
TRR, Cell transformation, RLV/Fischer rat embryo cells *in vitro*	+	0	0.005	Dunkel *et al.* (1981)
T7S, Cell transformation SA7/Syrian hamster embryo cells *in vitro*	+	0	5	Casto *et al.* (1979)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	0.05	Larramendy *et al.* (1981)
CHF, Chromosomal aberrations, human MRC5 fibroblasts *in vitro*	-	0	0.005	Paton & Allison (1972)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	0.25	Larramendy *et al.* (1981)
CHL, Chromosomal aberrations, human WI38 lymphocytes *in vitro*	-	0	0.009	Paton & Allison (1972)
HMM, Host-mediated assay, *Salmonella typhimurium* TA1530 in male Swiss–Webster mice	-		1.25, im or po	Simmon *et al.* (1979)
HMM, Host-mediated assay, *Salmonella typhimurium* TA1535 in male Swiss–Webster mice	-		103, im or po	Simmon *et al.* (1979)
HMM, Host-mediated assay, *Salmonella typhimurium* TA1538 in male Swiss–Webster mice	-		1.25, im or po	Simmon *et al.* (1979)
HMM, Host-mediated assay, *Saccharomyces cerevisiae* in mice	-		103, im or po	Simmon *et al.* (1979)
MVM, Micronucleus test, mouse bone marrow *in vivo*	-		116, po × 1	Ashby *et al.* (1990)
Beryllium oxide				
BSD, *Bacillus subtilis* (spores) *rec* assay, differential toxicity	-[h]	0	0.1	Kuroda *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-[h]	-	0.08	Kuroda *et al.* (1991)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-[h]	-	0.08	Kuroda *et al.* (1991)
DIA, DNA strand breaks, rat tracheal epithelial cells	+[i]	0	0.36	Steele *et al.* (1989)
DIA, DNA strand breaks, rat tracheal epithelial cells	?[j]	0	10	Steele *et al.* (1989)

Table 19 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Beryllium oxide (contd)				
SIC, Sister chromatid exchange, Chinese hamster V79 lung cells *in vitro*	–[g]	0	0.03	Kuroda *et al.* (1991)
TCL, Cell transformation, rat tracheal epithelial cells *in vitro*	+[i]	0	0.1	Steele *et al.* (1989)
TCL, Cell transformation, rat tracheal epithelial cells *in vitro*	?[j]	0	10	Steele *et al.* (1989)

+, 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; im, intramuscularly; po, orally; NR, not reported

[b]Precipitate

[c]Comutation with 9-aminoacridine (100 μmol/plate) (not on profile)

[d]Comutation with ultraviolet radiation (not on profile)

[e]Results from four independent laboratories

[f]Negative in two laboratories, inconsistently positive in two laboratories

[g]Enhancement of effect of X irradiation (not on profile)

[h]BeO unspecified

[i]Low-fired oxide

[j]High-fired oxide

***Not displayed on profiles

medium (Rossman *et al.*, 1987). [The Working Group noted that the lack of toxicity of beryllium compounds in many studies of bacteria suggests lack of uptake.] In mammalian cells, intracellular transfer is from lysozyme to nucleus (reviewed by Skilleter, 1984).

Beryllium chloride (1–10 mM) increased misincorporation of nucleoside triphosphates during polymerization of poly-d(A–T) by *Micrococcus luteus* DNA polymerase (Luke *et al.*, 1975). In a similar system, beryllium chloride reduced the fidelity of DNA synthesis *in vitro* in the presence of avian myeloblastosis virus DNA polymerase, a synthetic prime template and complementary and noncomplementary nucleoside triphosphates. This effect was observed at concentrations at which even incorporation of complementary triphosphates was inhibited and was ascribed to the noncovalent binding of ionic divalent beryllium to DNA polymerase rather than to DNA (Sirover & Loeb, 1976). [It is not clear that such effects can occur within the cell, where the concentrations of Be^{2+} would probably be much lower; e.g. chromosomal aberrations have been reported at an extracellular concentration of < 5 μM.] The binding of beryllium by purified DNA is very weak ($K_a = 7 \times 10^3$/mol) (Truhaut *et al.*, 1968). It was reported in an abstract that beryllium can induce DNA–protein complexes (Kubinski *et al.*, 1977). [The Working Group considered that any 'genotoxic' effects of Be^{2+} are probably not caused by direct damage to DNA.]

5. Summary of Data Reported and Evaluation

5.1 Exposure data

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

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

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

5.2 Human carcinogenicity data

In an early series of cohort mortality studies of workers at two beryllium extraction, production and fabrication facilities in the USA, a consistent, marginally significant excess of deaths from lung cancer was observed. The excess increased with time since first exposure. In a more recent mortality analysis of some 9000 workers at seven beryllium plants in the USA, including the two plants studied previously, a small but significant excess in mortality from lung cancer was found in the total cohort. The risks for lung cancer were consistently higher

in those plants in which there was also excess mortality from nonmalignant respiratory disease. Also, the risk for lung cancer increased with time since first exposure and was greater in workers first hired in the period when exposures to beryllium in the work place were relatively uncontrolled. Mortality from cancers at other sites was not increased. The association between lung cancer risk and exposure to beryllium was judged not to be confounded by smoking.

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

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

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

5.3 Animal carcinogenicity data

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

In one study in rats by single intratracheal instillation, beryllium metal, passivated beryllium metal (99% beryllium, 0.26% chromium as chromate) and beryllium–aluminium

alloy (62% beryllium) produced dose-related increases in the incidence of lung tumours, which were mostly adenocarcinomas and adenomas.

Various beryllium compounds were tested by inhalation in five studies in rats, rabbits and monkeys. In two studies in rats, beryllium sulfate tetrahydrate produced lung tumours, which were mostly adenocarcinomas. In one study, both beryllium oxide and beryllium chloride produced dose-related increases in the incidence of malignant epithelial lung tumours in rats. The studies in rabbits and monkeys were considered to be inadequate for evaluation. Beryllium hydroxide and low- and high-temperature-fired beryllium oxide were tested in rats by intratracheal instillation; beryllium hydroxide produced lung adenocarcinomas and adenomas in one study, and low-temperature-fired (below 900 °C) beryllium oxide produced malignant lung tumours in two studies.

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

5.4 Other relevant data

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

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

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

In cultured mammalian cells, low-temperature-fired beryllium oxide induced single-strand breaks in DNA and morphological transformation; an unspecified beryllium oxide did not induce sister chromatid exchange in mammalian cells or differential toxicity or mutation in bacteria.

5.5 Evaluation[1]

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

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

Overall evaluation

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

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

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