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International Agency for Research on Cancer
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BERYLLIUM AND BERYLLIUM COMPOUNDS

Beryllium and beryllium compounds were considered by previous IARC Working Groups in 1971, 1979, 1987, and 1993 (IARC, 1972, 1980, 1987, 1993). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms and molecular formulae for beryllium, beryllium–aluminium and beryllium–copper alloys, and certain beryllium compounds are presented in Table 1.1. 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.

1.2 Chemical and physical properties of the agents

Beryllium (atomic number, 4; relative atomic mass, 9.01) is a metal, which belongs to Group IIA of the Periodic Table. The oxidation state of beryllium compounds is +2. Selected chemical and physical properties of beryllium, beryllium–aluminium and beryllium–copper alloys, and various beryllium compounds can be found in the previous *IARC Monograph* (IARC, 1993).

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 greater than 40% more rigid than steel. It has excellent electrical and thermal conductivities. Its only markedly adverse feature is relatively pronounced brittleness, which restricts the use of metallic beryllium to specialized applications (WHO, 1990).

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; where 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 several 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

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

Chemical name	CAS Reg. No[a]	Synonyms	Formula
Beryllium metal	7440-41-7	*Beryllium*; beryllium element; beryllium metallic	Be
Beryllium–aluminum 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	BeO
Beryllium carbonate basic[d]	1319-43-3	*Carbonic acid, beryllium salt, mixture with beryllium hydroxide ($Be(OH)_2$)*	$BeCO_3.Be(HO)_2$
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), tetrahydrate, $BeCO_3.4H_2O$ [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]

the surface of the bare metal, rendering the metal highly resistant to corrosion, to hot and cold water, and to oxidizing acids (Newland, 1984; Petzow *et al.*, 1985; WHO, 1990).

1.3 Use of the agents

Beryllium is primarily used in its metallic form, in alloys, or in beryllium oxide ceramics. Its physical and mechanical properties make it useful for many applications across a range of industries. These properties include: outstanding strength (when alloyed), high melting-point,

high specific heat, excellent thermal properties, electrical conductivity, reflectivity, low neutron absorption, and high neutron-scattering cross-sections, and transparency to X-rays (WHO, 1990; USGS, 2007).

Industries using beryllium and beryllium products include: aerospace (e.g. altimeters, braking systems, engines, and precision tools), automotive (e.g. air-bag sensors, anti-lock brake systems, steering wheel connecting springs), biomedical (e.g. dental crowns, medical laser components, X-ray tube windows), defence (e.g. heat shields, missile guidance systems, nuclear reactor components), energy and electrical (e.g. heat exchanger tubes, microwave devices, relays and switches), fire prevention (e.g. non-sparking tools, sprinkler system springs), consumer products (e.g. camera shutters, computer disk drives, pen clips), manufacturing (e.g. plastic injection moulds), sporting goods (e.g. golf clubs, fishing rods, naturally occurring and man-made gemstones), scrap recovery and recycling, and telecommunications (e.g. mobile telephone components, electronic and electrical connectors, undersea repeater housings) (Kreiss *et al.*, 2007).

1.3.1 Beryllium metal

Some typical applications of beryllium metal include: aerospace technology (structural material, inertia guidance systems, additives in solid propellant rocket fuels, aircraft brakes, mirror components of satellite optical systems, gyroscopes), nuclear technology (moderator and reflector of neutrons in nuclear reactors, neutron source when bombarded with α particles), X-ray and radiation technology (special windows for X-ray tubes), computer technology and alloys (e.g. beryllium–copper alloys; hardening of copper, and developmental brass alloys) (WHO, 1990; Petzow *et al.*, 2007).

1.3.2 Beryllium-containing alloys

Approximately 75% of manufactured beryllium is used in alloys, 95% of which is copper alloy (Jakubowski & Palczynski, 2007). Because of the properties it confers on other metals (i.e. low density combined with strength, high melting-point, resistance to oxidation, and a high modulus of elasticity), beryllium alloys are light-weight materials that can withstand high acceleration and centrifugal forces (WHO, 1990). Beryllium–copper alloys are commonly used in the electronics (e.g. switch and relay blades, electronic connector contacts, control bearings, magnetic sensing device housings, and resistance welding systems), automotive (e.g. air-bag sensors), military (e.g. electro-targeting and infrared countermeasure devices, missile systems, advanced surveillance satellites, and radar systems), and aerospace industries (e.g. landing gear bearings, weather satellites). Other applications include computers, oil exploration equipment, medical appliances, sporting equipment (e.g. golf clubs), and non-sparking tools (e.g. in petroleum refineries) (WHO, 1990; Kaczynski, 2004; Jakubowski & Palczynski, 2007).

1.3.3 Beryllium oxide

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. It is used in lasers and electronics (e.g. transistor mountings, semiconductor packages, microelectronic substrates, microwave devices, high-powered laser tubes), in aerospace and military applications (e.g. gyroscopes and armour), refractories (e.g. thermocouple sheaths and crucibles), nuclear technology (reactor fuels and moderators), and medical/dental applications (e.g. ceramic crowns). It is also used as an additive (to glass, ceramics, and plastics) in the preparation of beryllium compounds, and as a catalyst for organic reactions (WHO, 1990; Taylor *et al.*, 2003).

1.3.4 Other beryllium compounds

Other important beryllium compounds include the beryllium halides (beryllium chloride and beryllium fluoride), beryllium hydroxide, and beryllium sulfate. Beryllium chloride has been used as a raw material in the electrolytic production of beryllium, and as the starting material for the synthesis of organo-beryllium compounds (O'Neil, 2006; Petzow *et al.*, 2007). Beryllium fluoride is used as an intermediate in the preparation of beryllium and beryllium alloys. It is used in nuclear reactors and glass manufacture, and as an additive to welding and soldering fluxes (O'Neil, 2006; Petzow *et al.*, 2007). Beryllium hydroxide is used as an intermediate in the manufacture of beryllium and beryllium oxide (O'Neil, 2006). Beryllium sulfate tetrahydrate is used as an intermediate in the production of beryllium oxide powder for ceramics (Kaczynski, 2004).

1.4 Environmental occurrence

Beryllium occurs naturally in the earth's crust, and is released in the environment as a result of both natural and anthropogenic activities. The environmental occurrence of beryllium has been reviewed extensively (WHO, 1990; ATSDR, 2002; Taylor *et al.*, 2003).

1.4.1 Natural occurrence

The 44th most abundant element in the earth's crust, beryllium occurs in rocks and minerals (mica schist, granite, pegmatite, and argillite), although the most highly enriched beryllium deposits are found in granitic pegmatites, in which independent beryllium minerals crystallize. Some 50 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 economic significance. The average terrestrial abundance of beryllium is 2–5.0 mg/kg. (IARC, 1993; Jakubowski & Palczynski, 2007; USGS, 2007).

1.4.2 Air

Beryllium particulates are released in the atmosphere from both natural and anthropogenic sources. Windblown dust is the most important natural source of atmospheric beryllium (approximately 95%), with volcanic activity accounting for the remainder. The major anthropogenic source of atmospheric beryllium is the combustion of coal and fuel oil. Other sources include: municipal waste incineration, beryllium alloy and chemical use (includes ore processing, production, use and recycling), and the burning of solid rocket fuel (WHO, 2001; ATSDR, 2002). Ambient concentrations of atmospheric beryllium are generally low. Based on measurements at 100 locations, an average daily concentration of less than 0.5 ng/m^3 was reported in the United States of America (Jakubowski & Palczynski, 2007). Atmospheric concentrations of beryllium in the vicinity of beryllium-processing plants are often higher than those measured elsewhere (IARC, 1993).

1.4.3 Water

Beryllium is released in the aquatic environment from both natural and anthropogenic sources. Weathering of beryllium-containing rocks and soils is the primary source of release, although leaching of coal piles may also contribute to beryllium entering surface water. Anthropogenic sources include industrial waste water effluents (e.g. from electric utility industries). The deposition of atmospheric fall-out (of anthropogenic and natural sources) is also a source of beryllium in surface waters. However, the relative importance of this contribution to aquatic concentrations of beryllium is difficult to assess (ATSDR, 2002).

Beryllium concentrations in surface waters are usually in the range of 0.01–0.1 µg/L (WHO, 1990). The concentration of beryllium in deep ocean waters tend to be fairly uniform worldwide,

and are estimated to be approximately three orders of magnitude lower than that of surface river water (Jakubowski & Palczynski, 2007). Beryllium concentrations in drinking-water are on average 0.19 µg/L, with a range of 0.01–1.22 µg/L (Kolanz, 2001).

1.5 Human exposure

1.5.1 Exposure of the general population

The primary route of beryllium exposure for the general population is via the ingestion of contaminated food or water. The daily intake of beryllium by non-occupationally exposed persons in the USA from drinking-water is estimated to be 1 µg per day (assuming an average concentration of 0.5 µg/L, and a drinking-water consumption rate of 2 L/day). In the 1980s, the Environmental Protection Agency in the USA estimated the daily intake of beryllium in food to be approximately 0.12 µg per day (based on an arbitrary value of 0.1 ng beryllium per gram of food, and an assumption that a normal adult consumes 1200 g of food per day). Other studies have estimated the daily intake of beryllium in food to be in the range of 5–100 µg per day (ATSDR, 2002).

The inhalation of beryllium via ambient air or smoking is considered to be a minor exposure route for the general population. Assuming an average airborne concentration of less than 0.03 ng/ m^3 beryllium per day, and a breathing rate of 20 m^3 of air per day, the estimated daily intake for an adult in the USA is approximately 0.6 ng of beryllium, or less, per day. This estimated intake is likely to be higher for for persons living near point sources of beryllium emission (ATSDR, 2002).

1.5.2 Occupational exposure

The occupational environment is the predominant source of beryllium exposure for humans. Inhalation of beryllium dust and dermal contact with beryllium-containing products are the main routes of occupational exposure, although there may be the potential for in-home exposure if contaminated work garments are worn at home (ATSDR, 2002; NTP, 2004). Industries using or producing beryllium include: aerospace; automotive; biomedical; defence; energy and electrical; fire prevention; instruments, equipment and objects; manufacturing; sporting goods and jewellery; scrap recovery and recycling; and telecommunications (Kreiss *et al.*, 2007).

Based on data obtained from the primary beryllium industry and government agencies, Henneberger *et al.* (2004) estimated that 134000 workers were potentially exposed to beryllium in the USA (1500 in the primary beryllium industry, 26500 in the Department of Energy or Department of Defence, and between 26400 and 106000 in the private sector, outside of the primary industry). This figure may be an underestimate because of the limited data on potential beryllium exposures in military and nuclear weapons workplaces, and in many others where beryllium is a minor or unsuspected component (e.g. aluminium smelting, scrap recovery, and electronics recycling). The number of workers in the USA ever exposed to beryllium is likely to be far higher than 134000, as it does not include approximately 250000 construction workers that are employed at nuclear weapons reclamation sites alone (Kreiss *et al.*, 2007).

Estimates of the number of workers potentially exposed to beryllium and beryllium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 66069 workers were exposed to beryllium and beryllium compounds in the European Union, with over 80% of workers employed in the manufacture of machinery, except electrical (n = 38543); manufacture of fabricated metal products except machinery and equipment (n = 5434); manufacture of electrical machinery,

apparatus and appliances (n = 4174); manufacture of professional, scientific, measuring and controlling equipment not elsewhere classified (n = 3708); and manufacture of transport equipment (n = 3328). CAREX Canada estimates that 4000 Canadians (86% male) are exposed to beryllium in their workplaces (CAREX Canada, 2011). These industries include: building equipment contractors, medical equipment and supplies manufacturing, residential building construction, motor vehicle parts manufacture, automotive repair and maintenance, non-residential building construction, commercial/industrial machinery repair and maintenance, architectural and structural metals manufacturing.

Data on early occupational exposures to beryllium were summarized in the previous *IARC Monograph* (IARC, 1993), and data from studies on beryllium exposure published since are summarized below.

(a) Processing and manufacturing

Sanderson *et al.* (2001a) investigated historical beryllium exposures in a beryllium-manufacturing plant in the USA during 1935–92 for the purpose of reconstructing exposures for an epidemiological study. Daily weighted average (DWA) exposure estimates ranged from 1.7–767 μg/m^3 for 1935–60; 1.0–69.9 μg/m^3 for 1961–70; 0.1–3.1 μg/m^3 for 1971–80; and 0.03–1.4 μg/m^3 for 1981–92 (range of geometric means).

Seiler *et al.* (1996a, b) investigated historical beryllium exposure data (n = 643) collected in five beryllium-processing facilities in the USA during 1950–75. Descriptive data for representative job titles in November 1974 indicated that DWA beryllium exposures ranged from a minimum of 0.3 μg/m^3 for a ceramics machine operator to a maximum of 111.4 μg/m^3 for a vacuum cast furnace operator. Approximately 73% of the maximum breathing zone DWA exposures exceeded the 2 μg/m^3 standard; only 18% of the general air DWA beryllium exposures exceeded the standard.

Deubner *et al.* (2001a) analysed 34307 airborne beryllium measurements (general air, breathing zone, and personal lapel) collected during 1970–99 at a beryllium mining and extraction facility in Delta, UT, USA, and compared them to a mixed beryllium products facility and a beryllium ceramics facility located in Elmore, OH and Tucson, AZ, respectively. DWAs (n = 1519) were calculated to estimate task-specific, time-weighted average (TWA) exposures for workers at the Delta facility. The general area and breathing zone sampling data indicated that average annual beryllium concentrations at the Delta plant declined over the study period. The range of annual median general area sample concentrations at the mining and milling plant was comparable to that at the beryllium ceramics facility (0.1–0.6 μg/m^3 versus 0.1–0.4 μg/m^3, respectively). These data were lower than those observed at the mixed beryllium products facility (range of annual median general area sample concentrations, 0.1–1.0 μg/m^3). At the mining and milling facility, the highest exposures were observed in jobs involving beryllium hydrolysis and wet-grinding activities. This observation was independent of the exposure assessment method used.

Kreiss *et al.* (1997) analysed 106218 airborne beryllium measurements collected during 1984–93 at a beryllium-manufacturing plant producing pure metal, oxide, alloys, and ceramics. Of these, 90232 were area samples (30-minute samples: n = 30872; full-shift, continuous samples: n = 59360), and 15986 were personal samples (1–15 minute breathing zone samples: n = 15787; full-shift personal lapel samples: n = 179). Using these data, DWA exposures were calculated for most jobs. Median area concentrations were 0.6 μg/m^3 and 0.4 μg/m^3 for full-shift and short-term samples, respectively. Median personal concentrations were 1.4 μg/m^3 and 1.0 μg/m^3 for short-term and full-shift samples, respectively. The highest median area concentrations were observed in the alloy arc furnace

and alloy melting-casting areas, and the highest median breathing zone concentrations were observed in the beryllium powder and laundry areas.

Kent *et al.* (2001) collected full-shift particle-size-specific personal samples (n = 53) and area samples (n = 55) in five furnace areas at a beryllium-manufacturing facility. Personal samples were collected with Anderson impactors and general area samples were collected with micro-orifice uniform deposit impactors (MOUDIs). The median total mass concentration of beryllium particles (in μg/m^3) was reported by work process area and particle size. Median personal aerosol concentrations ranged from 0.8–5.6 μg/m^3 for total particle mass, and 0.05–0.4 μg/m^3 for alveolar-deposited particle mass. Median area concentrations ranged from 0.1–0.3 μg/m^3 for total particle mass, and 0.02–0.06 μg/m^3 for alveolar-deposited particle mass.

(b) Beryllium oxide ceramics

As part of a study to examine the relationship between sensitization and beryllium exposure in a beryllium ceramics plant in the USA, Kreiss *et al.* (1996) reviewed all general area (n = 5664) and personal breathing zone (n = 4208) samples collected during 1981–92. Of the area samples collected, 14% (n = 774) were full-shift samples collected from 1983 onwards; of the personal breathing zone samples, 1.7% (n = 75) were full-shift samples collected from 1991 onwards. Using average general area, full-shift area and breathing zone measurements, DWA exposures for most occupations were calculated. Of the full-shift area samples, 76% were reported to be at or below the detection limit of 0.1 μg/m^3. The median general area concentration was at or below the detection limit, with measured concentrations ranging as high as 488.7 μg/m^3. Median personal breathing zone concentrations were 0.3 μg/m^3 (maximum, 1931 μg/m^3) and 0.20 μg/m^3 (range, 0.1–1.8 μg/m^3) for the short-term and full-shift samples, respectively. Machinists were observed to have the highest exposures, with breathing zone concentrations of 63.7 μg/m^3, and a median DWA exposure of 0.9 μg/m^3.

Henneberger *et al.* (2001) conducted a follow-up to the Kreiss *et al.* (1996) study, screening workers at a US beryllium ceramics plant to determine whether the plant-wide prevalence of beryllium sensitization and disease had declined in the 6-year interval since first screening, and to explore exposure–response relationships. Historical airborne beryllium measurements (task- and time-specific) were combined with individual work histories to compute worker-specific beryllium exposures (mean, cumulative, and peak). A total of 18903 beryllium measurements were collected during 1981–98, of which 43% were short-term (1–15 minute), task-specific personal breathing zone samples, and 57% were short-term (30 minute) general area samples. Mean calculated exposures for all workers ranged from 0.05 μg/m^3 (i.e. less than the limit of detection) to 4.4 μg/m^3. When duration of employment was taken into account, short-term workers (i.e. those hired since the previous survey) had lower mean (median value: 0.28 μg/m^3 versus 0.39 μg/m^3) and peak concentrations (median value: 6.1 μg/m^3 versus 14.9 μg/m^3) than long-term workers.

Cummings *et al.* (2007) conducted a follow-up study in the same beryllium oxide ceramics manufacturing facility considered by Henneberger *et al.* (2001) to assess the effectiveness of an enhanced preventive programme to reduce beryllium sensitization. Sensitization for newly hired workers was compared with that for workers hired from 1993–98, and tested in the 1998 survey. Full-shift personal exposure data collected by the facility from 1994–2003 (n = 1203 measurements) was grouped into two time periods (1994–99 and 2000–03), and three work categories (production, production support, and administration). For the period 1994–99, median beryllium levels were 0.20 μg/m^3, 0.10 μg/m^3, and

less than the limit of detection in production, production support and administration, respectively (n = 412, full-shift personal lapel samples). For the later period, median beryllium levels were 0.18 μg/m^3, 0.04 μg/m^3, and 0.02 μg/m^3 in production, production support, and administration, respectively (n = 791, full-shift personal lapel samples).

(c) Machining and use

Martyny *et al.* (2000) conducted particle-size selective sampling on five mechanical processes (milling, deburring, lapping, lathe operations, and grinding) to examine the particle size distribution of beryllium machining exposures. Two sets of stationary samples were collected using Lovelace Multijet Cascade Impactors mounted to the machines at 'point of operation' and at 'nearest worker location', two sets of personal samples were collected in the breathing zone of workers operating the machines (one personal pump-powered lapel sampler, one personal cascade impactor), as well as ambient air samples from four fixed locations in the facility. In total, 336 measurements were collected (79 personal pump samples, 87 personal impactor samples, 71 nearest worker location samples, 87 point of operation samples, and 12 ambient air samples. Of these, 243 were samples of the five target processes (64 personal pump samples, 59 personal impactor samples, 64 nearest worker location samples, and 56 point of operation samples). For the stationary area samples, median TWA concentrations were in the range of 0.20 μg/m^3 for the 'nearest worker location' samples to 0.60 μg/m^3 for the 'point of operation' samples. For the personal breathing zone samples (collected by the personal impactors), median TWA concentrations were in the range of 0.13 μg/m^3 for lapping processes to 0.74 μg/m^3 for deburring operations. The range of 48-hour median ambient concentration was 0.02–0.07 μg/m^3.

To evaluate the effectiveness of a beryllium exposure control programme at an atomic weapons facility in Wales, United Kingdom, Johnson *et al.* (2001) analysed 585438 air monitoring records (367757 area samples collected at 101 locations, and 217681 personal lapel samples collected from 194 workers during 1981–97). Across all departments, the range of annual personal concentrations was 0.11–0.72 μg/m^3 (mean) and 0.08–0.28 μg/m^3 (median). The highest levels of exposure were observed in foundry workers, with a mean exposure level of 0.87 μg/m^3 and a median exposure level of 0.22 μg/m^3 (over all years). For the area samples, mean annual concentrations ranged from a high of 0.32 μg/m^3 in 1985 to a low of 0.02 μg/m^3 in 1997.

(d) Alloy facilities

Schuler *et al.* (2005) analysed airborne beryllium measurements collected in 1969–2000 at a beryllium–copper alloy strip and wire finishing facility. Of the 5989 available measurements, 650 were personal samples, 4524 were general area samples, and 815 were short-duration, high-volume (SD-HV) breathing zone samples. Data were grouped and analysed on the basis of work category (production, production support, administration), and by process or job within each work category. For example, 'rod and wire' production is a subcategory of 'production'; jobs within 'rod and wire' production include: wire annealing and pickling, wire drawing, straightening, point and chamfer, rod and wire packing, die grinding, and, historically, wire rolling. Median plant-wide exposure levels were 0.02 μg/m^3 (personal), 0.09 μg/m^3 (general area), and 0.44 μg/m^3 (SD-HV breathing zone). Among work categories, the highest levels of beryllium exposure were found in 'rod and wire' production (median, 0.06 μg/m^3), with the most highly exposed process or job being 'wire annealing and pickling' (median, 0.12 μg/m^3).

In a study in a beryllium alloy facility, Day *et al.* (2007) measured levels of beryllium in workplace air (n = 10), on work surfaces (n = 252), on cotton gloves worn over nitrile gloves (n = 113),

and on necks and faces of workers (n = 109). In production, geometric mean levels of beryllium were 0.95 µg/100 cm^2 (work surfaces), 42.8 µg per sample (cotton gloves), 0.07 µg per sample (necks), and 0.07 µg per sample (faces). In production support, geometric mean levels of beryllium were 0.59 µg/100 cm^2 (work surfaces), 73.8 µg per sample (cotton gloves), 0.09 µg per sample (necks), and 0.12 µg per sample (faces). The lowest levels were measured in the administration section, with geometric mean levels of beryllium of 0.05 µg/100 cm^2 (work surfaces), 0.07 µg per sample (cotton gloves), 0.003 µg per sample (necks), and 0.003 µg per sample (faces). Strong correlations were observed between beryllium in air and on work surfaces (r = 0.79), and between beryllium on cotton gloves and on work surfaces (r = 0.86), necks (r = 0.87), and faces (r = 0.86).

Yoshida *et al.* (1997) studied airborne beryllium levels at two beryllium–copper alloy manufacturing factories in Japan during 1992–95. General area samples were collected in the beryllium–copper alloy process (n = 56) and the beryllium–copper metal mould manufacturing process (n = 41) of Factory A, and in the beryllium–copper cold rolling, drawing and heat-treatment process (n = 16) and beryllium–copper slitting treatment process (n = 8) of Factory B. In all years studied, the highest geometric mean beryllium levels were observed in the beryllium–copper alloy process of Factory A (range, 0.16–0.26 µg/m^3).

Stanton *et al.* (2006) studied beryllium exposures among workers at three beryllium–copper alloy distribution centres in the USA in 2000–01. For the period 1996–2004, company records of full-shift personal lapel breathing zone samples for airborne beryllium (n = 393) were examined. A total of 54% of all samples were at or below the limit of detection. The overall median beryllium concentration was 0.03 µg/m^3 (arithmetic mean, 0.05 µg/m^3). When examined by work category (production – bulk products, production – strip metal, production support, administration) and process or job within work category, concentration ranges were 0.01–0.07 µg/m^3 (median), and 0.02–0.07 µg/m^3 (geometric mean). The highest concentrations were measured in heat-treating (bulk products) and tensioning (strip metal) processes, with levels of 1.6 µg/m^3 and 1.4 µg/m^3, respectively.

(e) Nuclear facilities

Stange *et al.* (1996a) studied beryllium exposures in the Rocky Flats Nuclear Facility in the USA. Fixed airhead (i.e. area) samples (n = 102) and personal breathing zone samples (n = 102) were collected from the main beryllium production building. The mean beryllium concentration from the area samples was 0.16 µg/m^3, and from the personal samples, 1.04 µg/m^3. No correlation (r^2 = 0.029) was observed between fixed airhead and personal breathing zone beryllium samples.

Stefaniak *et al.* (2003a) investigated historical beryllium exposure conditions at the Los Alamos Nuclear Laboratory in the USA. A total of 4528 personal breathing zone and area samples were analysed. For all technical areas, the geometric mean concentration for the period 1949–89 was 0.04 µg/m^3. Average beryllium concentrations per decade were less than 1 µg/m^3, and annual geometric mean concentrations in the area that was the largest user of beryllium were generally below 0.1 µg/m^3.

(f) Other

Meeker *et al.* (2006) compared occupational exposures among painters using three alternative blasting abrasives (specular hematite, coal slag, steel grit) on a footbridge painting project during 2002–04 in New Jersey, USA. Over the 3-year project, personal breathing zone samples were collected outside the respirators of two or three abrasive blasters. The range of beryllium concentrations measured outside personal protective equipment (n = 18 samples) was 2.5–9.5 µg/m^3, with a geometric mean exposure

level of 5.0 μg/m^3. Beryllium was also measured in bulk paint chips collected from each bridge.

Bauxite, from which aluminium is derived, may contain beryllium in varying degrees. In 965 personal samples collected during 2000–05 in four aluminium smelters, beryllium concentrations varied in the range of 0.002–13.0 μg/m^3 (arithmetic and geometric means were 0.22 and 0.05 μg/m^3, respectively) (Taiwo *et al.*, 2008).

1.5.3 Dietary exposure

There is a lack of reliable data on the concentration of beryllium in food (WHO, 1990; ATSDR, 2002). Measured concentrations of beryllium have been reported for 38 foods, fruit and fruit juices from around the world (number of samples, 2243; 2209 foods + 34 fruit and juices). Concentrations in the foods have been reported in the range of < 0.1–2200 μg/kg fresh weight, with the highest concentrations measured in kidney beans, crisp bread, garden peas, parsley and pears (2200, 112, 109, 77, and 65 μg/kg fresh weight, respectively), and with a median concentration of 22.5 μg/kg fresh weight (kidney beans were excluded from this calculation). Concentrations in the fruits and juices ranged from not detected to 74.9 μg/L, with an average concentration of 13.0 μg/L (ATSDR, 2002). Beryllium has also been measured in rice, head lettuce, and potatoes at 80 μg/kg, 330 μg/kg, and 0.3 μg/kg, respectively (Kolanz, 2001).

1.5.4 Biomarkers of exposure

Several analytical methods are available and have adequate sensitivity for measuring beryllium in biological samples. These include gas chromatography-electron capture (GC-ECD), graphite furnace atomic absorption spectrometry (GF-AAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), and inductively coupled plasma mass spectrometry (ICP-MS). Biological matrices in which these methods can measure beryllium include: blood, urine, faeces, fingernails, hair, and lung tissue. Urinary beryllium is an indicator of current exposure, but is of uncertain utility for quantitative exposure assessment. Beryllium levels in blood, serum or plasma are indicators of the intensity of current exposure (ATSDR, 2002; NTP, 2004; NRC 2007).

The average burden of beryllium in the general population is 0.20 mg/kg in the lung and is below 0.08 mg/kg in other organs (Kolanz, 2001).

The mean concentration of beryllium in urine measured in about 500 non-occupationally exposed individuals in the USA during the Third National Health and Nutrition Examination Survey (NHANES III) was 0.22 μg/g of creatinine (Paschal *et al.*, 1998). Other studies reported mean urinary beryllium concentrations in the range of < 0.03–0.4 μg/L for non-occupationally exposed individuals (Apostoli & Schaller, 2001).

2. Cancer in Humans

The previous *IARC Monograph* on beryllium and beryllium compounds was based largely on evidence of elevated lung cancer mortality among 689 individuals (predominantly workers) entered into the US Beryllium Case Registry (Steenland & Ward, 1991; Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-02-Table2.1.pdf), and in a cohort of 9225 workers employed at seven beryllium-processing plants in the USA (Ward *et al.*, 1992). The cohort study included two plants that had been previously studied (Mancuso, 1979, 1980; Wagoner *et al.*, 1980) and Infante *et al.* (1980) had reported earlier on mortality in the Beryllium Case Registry cohort.

2.1 Cohort studies and nested case–control studies

The body of evidence available for the current evaluation of the carcinogenicity of beryllium in humans includes the two previously evaluated cohort studies and a nested case–control study initially reported by Sanderson *et al.* (2001b), and reanalysed with adjustment for temporal confounders by Schubauer-Berigan *et al.* (2008).

The Beryllium Case Registry study included 689 individuals entered alive into the registry and followed for mortality through to 1988 (Steenland & Ward, 1991); 34% were from the fluorescent tube industry, and 36% were from basic manufacturing. There were 158 deaths from pneumoconiosis and other respiratory disease, the category that included beryllium disease (Standard Mortality Ratio [SMR], 34.2; 95%CI: 29.1–40.0). The overall SMR for lung cancer was 2.00 (95%CI: 1.33–2.89), based on 28 deaths. Among those with acute beryllium disease, there were 17 lung cancer deaths (SMR 2.32; 95%CI: 1.35–3.72), and among those with chronic beryllium disease, ten lung cancer deaths (SMR 1.57; 95%CI: 0.75–2.89).

The cohort study included workers at seven beryllium-processing plants in the USA involved in various phases of beryllium processing with exposure to many forms of beryllium and beryllium compounds (Ward *et al.*, 1992). The study found a significantly elevated SMR of 1.26 (95%CI: 1.12–1.42) for lung cancer in the cohort overall, with significant excesses observed for the two oldest plants located in Lorain, Ohio, and Reading, Pennsylvania.

The SMR for lung cancer at the Lorain plant was 1.69 (95%CI: 1.28–2.19), and at the Reading plant, 1.24 (95%CI: 1.03–1.48). The Lorain plant, in operation during 1935–48, is thought to have had very high beryllium exposures. The majority of workers (84.6%) were employed for less than 1 year. Ninety-eight of the 1192 individuals employed at the Lorain plant (8.2%) were identified in the Beryllium Case Registry as having beryllium disease; 91 were of the acute form which has only been associated with very high beryllium exposure, six individuals had chronic beryllium disease, and one was of unknown type. A total of 11 lung cancer deaths occurred among the 98 individuals with beryllium disease (SMR, 3.33; 95%CI: 1.66–5.95), and 46 lung cancer deaths occurred among the remaining 1094 Lorain workers (SMR, 1.51; 95%CI: 1.11–2.02). All but one of the 57 lung cancer deaths occurred in latency categories < 15 years; for 15–30 years' latency, the SMR was 2.09 [95%CI: 1.30–3.21]; and for over 30 years' latency, 1.66 [95%CI: 1.16–2.31].

The plant in Reading, Pennsylvania, in operation during 1935–2001, employed 3569 workers during 1940–69. Among those, 53.8% were employed for less than 1 year, and only 17.2% were employed for more than 10 years. When the SMRs for lung cancer at the Reading plant were analysed by latency and duration of exposure, the highest SMR was observed for the category with less than 1 year of employment and duration and more than 30 years' latency (SMR = 1.42; [95%CI: 1.01–1.93]). Further analyses by decade of hire revealed that 92/120 lung cancer deaths occurred among workers hired before 1950 (SMR, 1.26; [95%CI: 1.02–1.55]). None of the newer plants included in the study had a significantly elevated SMR for lung cancer. However, non-significantly elevated SMRs were observed for four out of five plants operating in the 1950s for workers hired during that decade. The results were adjusted for smoking based on comparing smoking histories of 1466 (15.9%) of cohort members surveyed in 1968 with a survey of the US population conducted in 1965, resulting in SMRs of 1.12, 1.49 and 1.09 for the total cohort, the Lorain plant, and the Reading plant, respectively. [The Working Group noted that it is unclear that adjustment for differences in smoking patterns between cohort members and the US population in the late 1960s would accurately reflect patterns

in the 1940s that would be most relevant to interpreting the lung cancer excess. It is possible that using data from the 1960s would overestimate the impact of smoking.] SMRs based on county referent rates were also presented and for the cohort as a whole, the SMR was slightly increased to 1.32, the SMR declined for the Lorain plant to 1.60, and increased for the Reading plant to 1.42.

Subsequent to the publication of the Ward *et al.* (1992) study, the Beryllium Industry Scientific Advisory Committee suggested that the excess of lung cancer observed at the Lorain plant might be attributable to exposure to sulfuric acid mist and fumes rather than exposure to beryllium (BISAC, 1997). A reanalysis of the cohort study used alternative referent rates (for cities in which the two oldest plants were located) to compute expected number of lung cancers, alternative smoking risk factor estimates to adjust for differences in smoking habits between the cohort and the US population, and an alternative methodology to calculate the SMR for all plants combined (Levy *et al.*, 2002). The net effect of the reanalysis was to reduce the magnitude and statistical significance of the SMRs in the Ward *et al.* (1992) study. [The Working Group noted that there are several potential methodological limitations of this reanalysis. For instance, the city referent rates used for the calculation were not published, whereas Ward *et al.* (1992) used only published rates.]

Sanderson *et al.* (2001b) conducted a nested case–control study of lung cancer within one of the beryllium processing plants studied by Ward *et al.* (1992). This plant was selected for study because it was one of the two older plants in which an elevated lung cancer SMR was observed, and because industrial hygiene measurement data were available from as early as 1947. Details of the job–exposure matrix are provided in Sanderson *et al.* (2001a). Mortality was followed-up through 1992, and 142 lung cancer cases were identified. Cases were age- and race-matched to five controls through incidence-density sampling (Sanderson *et al.*, 2001b). The main findings of the Sanderson *et al.* (2001b) study were positive associations with average and maximum exposure lagged 10 and 20 years. This association did not appear to be confounded by smoking in an analysis that excluded professional workers.

Following some letters and critiques of the Sanderson *et al.* (2001b) study (Deubner *et al.*, 2001b, 2007; Sanderson *et al.*, 2001c; Levy *et al.*, 2007), a reanalysis of the study was carried out that adjusted for year of birth and an alternative minimal exposure value (the lowest detectable exposure level divided by two) in continuous exposure–response analyses (Schubauer-Berigan *et al.*, 2008; see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-02-Table2.2.pdf). After controlling for year of birth, significantly elevated odds ratios for 10-year lagged average beryllium exposure were found in the middle two exposure quartiles. The choice of an alternative minimal exposure value decreased the trend statistic for cumulative exposure but increased it for average exposure. In the continuous analysis of average 10-year lag dose, the parameter estimates and *P*-values were highly significant with control for year of birth. [The Working Group noted that several methodological articles were published regarding the incidence-density sampling methods used in the nested case–control study (Deubner & Roth, 2009; Hein *et al.*, 2009; Langholz & Richardson, 2009; Wacholder, 2009). Three of these articles affirmed the methodology used to select controls in the study (Hein *et al.*, 2009; Langholz & Richardson, 2009; Wacholder, 2009). The Working Group noted that the issues raised in the Deubner & Roth (2009) commentary did not undermine confidence in the results of the Schubauer-Berigan *et al.* (2008) reanalysis.]

2.2 Synthesis

A large body of evidence was evaluated by the Working Group and, in conclusion, elevated lung cancer mortality was observed in a study of individuals with beryllium disease and in a cohort study of workers at seven beryllium-processing plants. The association of the elevated lung cancer risks with beryllium exposure is supported by a large number of lung cancer cases and stable rate ratios, a consistency in findings among plants, higher risks of lung cancer among workers hired before 1950 (when exposures were at their highest), a greater risk of lung cancer in the US Beryllium Case Registry cohort (especially among those highly exposed who were diagnosed with acute pneumonitis), and greatest risks for lung cancer in the plants with the highest risk for acute pneumonitis and other respiratory disease. In addition, the nested case–control studies found evidence for an exposure–response relationship that was strongest when using the 10-year lag average-exposure metric. All of the epidemiological studies involved potential exposure to metallic beryllium as well as other beryllium compounds, and were unable to discern the specific effects of beryllium metal or specific beryllium compounds.

3. Cancer in Experimental Animals

Beryllium compounds have been tested for carcinogenicity by inhalation in rats and mice, by intratracheal or intrabronchial administration in rats, by intravenous administration to rabbits, by intraperitoneally administration to mice, and by intramedullary bone administration in rabbits.

To date, by all routes of exposure and in all species tested, all beryllium compounds examined have been shown to be carcinogenic (IARC, 1993).

3.1 Inhalation exposure

3.1.1 Mouse

In p53 heterozygous mice, lung tumours occurred after a single series of three consecutive daily inhalation exposures to beryllium metal (Finch *et al.*, 1998a).

3.1.2 Rat

The first inhalation study published on beryllium was with beryllium sulfate in rats, which induced lung tumours and chronic lung disease (Schepers *et al.*, 1957). Inhalation of single doses of beryllium metal (Nickell-Brady *et al.*, 1994), and exposure to beryllium sulfate for 6 months (Schepers *et al.*, 1957) or 72 weeks (Reeves *et al.*, 1967) caused lung tumours in rats. Beryl ore dust induced lung tumours in rats (Wagner *et al.*, 1969).

3.1.3 Hamster

A study of inhalation of beryl ore for 17 months in hamsters resulted in excess atypical lung proliferative lesions, some of which described as tumours (Wagner *et al.*, 1969). It is noteworthy that similar doses caused tumours in rats (Wagner *et al.*, 1969).

See Table 3.1.

3.2 Intratracheal administration

3.2.1 Rat

A single intratracheal administration of beryllium metal, beryllium oxide, and beryllium hydroxide once per week for 15 weeks caused lung tumours in rats (Groth *et al.*, 1980). Beryllium oxide caused lung tumours in rats (Ishinishi *et al.*, 1980; Litvinov *et al.*, 1983).

See Table 3.2.

Table 3.1 Studies of cancer in experimental animals exposed to beryllium (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, p53 Heterozygous (M, F) 6–19 mo Finch *et al.* (1998a)	Beryllium metal Single exposure to 47 µg or 3×/d 63 µg 15/group/sex	Lung (tumours, both sexes combined): P53–controls 0/30, low dose 0/29, high dose 4/28 (14%) Wild-type–0/28	$P = 0.048$	
Rat, Wistar and Sherman (M, F) 18 mo (22 mo for controls) Schepers *et al.* (1957)	Beryllium sulfate tetrahydrate Inhalation 35.8 µg/m^3 5.5 d/wk during 180 d 84, 139 controls	Lung (tumours): 76 in 52 rats that survived after exposure period Controls–0/139	NR	Incomplete reporting of the study, total tumours not incidence reported, disease outbreak killed 58 rats during exposure and afterwards, data not divided up by strain or sex
Rat, SD CD rats (M, F) 72 wk Reeves *et al.* (1967)	Beryllium sulfate tetrahydrate Inhalation 34.25 µg/m^3 7 h/d, 5 d/wk, 150/group	Lung (pulmonary alveolar adenocarcinomas, multiple): 43/43 (100%) rats alive past 13 mo Controls–none	NR	Age at start, 6 wk Incomplete reporting of the study, respiratory infections, dead rats thrown out due to postmortem changes
Rat, Charles River CD (M) For each ore – up to 23 mo Wagner *et al.* (1969)	Beryl ore or bertrandite ore Inhalation 15mg/m^3, 6 h/d, 5 d/wk (210–620 µg/m^3 beryllium) 93, 33 controls	*Beryl* Lung: **12 mo** 5/11 (45%) squamous metaplasias or small epidermoid tumours **17 mo** 18/19 (95%) lung tumours (alveolar cell tumours–7 adenomas, 9 adenocarcinomas, 4 epidermoid tumours) *Bertrandite* None Controls, none	NR	High crystalline silica content of bertrandite ore Incomplete reporting of the study

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) 17 mo Wagner *et al.* (1969)	Beryl ore or bertrandite ore Inhalation 15 mg/m^3, 6 h/d, 5 d/wk 48/group	*Both ores* **12 mo** Atypical lung proliferations **17 mo** More atypical lesions in beryl-exposed hamsters No definitive tumours	NR	Incomplete reporting of the study, lung lesions called adenomas in the figure only, but were probably adenomatous hyperplasias, and not tumours
Rats, F344 (M, F) 14 mo Nickell-Brady *et al.* (1994)	Beryllium metal Inhalation (nose-only) Single exposure 40, 110, 360 and 430 µg (cohort of Lovelace High dose study) 30/group/sex	Lung (tumours): 64% Controls, NR		Age at start, 12 wk No incidence data by group or sex

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.2 Studies of cancer in experimental animals exposed to beryllium (intratracheal or intrabronchial exposure)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (F) 18 mo Groth *et al.* (1980)	Intratracheal single exposure to 0.5 or 2.5 mg beryllium metal or beryllium–aluminum alloy, beryllium–copper alloy, beryllium–copper–cobalt alloy, beryllium–nickel alloy 35/group	Lung (adenomas or carcinomas): Beryllium metal– 2/3 (67%) low dose, 6/6 (100%) high dose Passivated beryllium metal– 7/11 (64%) low dose, 4/4 (100%) high dose Alloy groups– all negative Controls, 0/21 after 19 mo Beryllium hydroxide– 13/25 (52%) adenoma or adenocarcinoma	$P < 0.008$	Age at start, 3 mo Low beryllium content of alloys Incidence of animals sacrificed at 19 mo reported
Rat, Wistar (F) 19 mo Groth *et al.* (1980)	Intratracheal 50 µg beryllium hydroxide initially followed by 25 µg 10 mo later 35/group	Lung (tumours): 13/25 (52%); Controls, 0/21	$P = 0.0021$	Incidence in rats surviving 16 mo or more
Rat, Wistar (M) Life span Ishinishi *et al.* (1980)	Intratracheal instillation 1 mg beryllium oxide once/wk for 15 wk 30; 16 controls	Lung (tumours): 6/30 (20%, 4 benign, 2 malignant) Controls, 0/16		Animals/group at start NR Untreated controls, 3/4 adenomas have histology indicative of malignancy
Rat, albino (NR) Life span Litvinov *et al.* (1983)	Intratracheal Single exposure beryllium oxide, low- and high-temp fired 0.036, 0.36, 3.6, 18 mg/kg 300 controls	Lung (tumours, malignant): High temp fired– 0/76, 0/84, 2/77 (3%), 2/103 (2%) Low temp fired– 3/69 (4%), 7/81 (9%), 18/79 (23%), 8/26 (31%) Controls, 0/104	NR	

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to beryllium (intravenous exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse Strain, sex and duration, NR Cloudman *et al.* (1949)	Zinc beryllium silicate (0.264 mg Be); beryllium oxide (1.54 mg Be) 20–22 injections (twice weekly) Number at start, NR	"Some mice" developed malignant bone tumours		Animals/group at start NR Only zinc beryllium silicate induced osteosarcomas
Rabbit Strain, sex and duration, NR Barnes & Denz (1950)	Beryllium metal Total dose, 40mg 24 animals	Bone (sarcomas): 2 surviving rabbits		Toxicity in 19 rabbits during first wk and mo (liver necrosis)
Rabbit Strain and sex, NR > 7 mo Gardner & Heslington (1946)	Zinc beryllium silicate and beryllium oxide 20 doses, total dose–1 g of particles 7 animals	Osteosarcomas: *Zinc beryllium silicate–* 7/7 (100%) that lived past 7 mo *Beryllium oxide–* 1		
Rabbit Strain and sex, NR > 1 yr Cloudman *et al.* (1949)	Zinc beryllium silicate (17 mg Be) or beryllium oxide (390 mg Be) 20–22 injections (twice weekly)	Bone (tumours): *Zinc beryllium silicate–* 4/5 (80%)		Animals/group at start NR
Rabbit Strain, NR (M, F) > 30 wk Barnes & Denz (1950)	Zinc beryllium silicate or beryllium silicate 6–10 injections 67 animals	Bone (sarcomas): *Zinc beryllium silicate–* 7/21 (33%) past 30 wk		Poor survival
Rabbit Strain, NR (M, F) > 11.5 mo Dutra & Largent (1950)	Beryllium oxide or calcined phosphor with beryllium oxide, zinc oxide and silica 20–26 injections 360–700 mg beryllium in beryllium oxide 64–90 mg beryllium in phosphor group	Osteosarcomas: *Beryllium oxide–* 6/6 (100%) *Phosphor–* 2/3 (67%) Controls, 0/50		Animals/group at start NR
Rabbit Strain, NR (M, F) 14–28 mo Hoagland *et al.* (1950)	Beryllium phosphate Zinc beryllium silicate Beryllium oxide 1–4-d intervals, unknown time period Doses not clear 24 animals	Osteosarcomas: *Zinc beryllium silicate–* 7/8 (88%) *Beryllium oxide–* 1		Small group size, lack of controls Incomplete reporting

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rabbit Strain and sex, NR 18 mo Araki *et al.* (1954)	Beryllium phosphate 1 g Beryllium oxide 1 g Beryllium oxide + zinc oxide Single dose 35 animals	Osteosarcomas: *Beryllium phosphate–* 2/4 (50%) *Beryllium oxide+zinc oxide–* 9/31 (29%)		Weight ≈2.0 kg Small numbers of animals, no appropriate controls
Rabbit (M) Strain, NR Janes *et al.* (1954)	Zinc beryllium silicate (1 g beryllium silicate, 33.6 mg beryllium oxide) Twice/wk for 10 wk 10 animals	Osteosarcomas: 5		Age at start, 9–11 mo Small group size, lack of controls
Rabbit Strain and sex, NR 57 wk Kelly *et al.* (1961)	Zinc beryllium silicate Twice/wk for 10 wk 14 animals	Osteosarcomas: 10/14 (71%)		Small group size, lack of controls
Rabbit Strain and sex, NR 15–18 mo Komitowski (1967)	Beryllium oxide Single 1 g dose 20 animals	Osteosarcomas: 3/20 (15%)		Lack of appropriate control group
Rabbit Strain and sex, NR 25 wk Fodor (1977)	Beryllium oxide (1%) Once/wk for 25 wk 60 animals	Sarcomas: 21/29 (72%)		Age at start, 6 mo Incomplete reporting, lack of appropriate control group

d, day or days; F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.4 Studies of cancer in experimental animals exposed to beryllium (other routes of exposure)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 32 wk Ashby *et al.* (1990)	Intraperitoneal Beryllium sulfate tetrahydrate 0, 0.02, 0.05, 0.1 mg/mouse/injection 3×/wk for 8 wk 20/group	Incidence (% given only): 15, 17, 33, 38% Lung tumours/mouse: 0.15, 0.17, 0.39, 0.38	r = 5.9 and 4.6 for middle and high doses (χ^2)	Age at start, 5–6 wk Purity, 99% Middle and high doses, significant
Rabbit Strain and sex, NR 1–2 yr Yamaguchi (1963)	Injection into bone marrow Beryllium oxide 10 mg twice/wk 55 animals	Bone (tumours): 26		
Rabbit, mixed breeds (M, F) 15–20 mo Tapp (1966)	Intramedullary injection Beryllium silicate powder 20 mg 12 animals	Osteogenic sarcomas: 4/12 (33%)		Age at start, 6 wk
Rabbit, mixed breeds (M, F) 25 mo Tapp (1969)	Implants (periosteal) Zinc beryllium silicate, beryllium oxide, beryllium silicate 10 mg 18 animals	Osteogenic sarcomas: 4/18 (22%)		Age at start, 6 and 8 wk
Rabbit Strain and sex, NR 24 mo Komitowski (1974)	Intramedullary injection Beryllium oxide No dose given 20 animals	Osteogenic sarcomas: 5/20 (25%)		Incomplete reporting, lack of appropriate control group
Rabbit Strain and sex, NR 21 mo Matsuura (1974)	Intramedullary implants Beryllium carbonate, beryllium acetate, beryllium acetylacetonate, beryllium laurate, beryllium stearate 173, 18, 3, 3	Osteosarcomas: *Beryllium carbonate*– 30 *Beryllium acetylacetonate*– 1		Incomplete reporting, small numbers in most groups
Rabbit, Fauve de Bourgogne, sex (NR) > 4 mo Mazabraud (1975)	Intraosseous injection Zinc beryllium silicate 1 g/cm^3 65 animals	Osteogenic sarcomas: 45/65 (69%)		Age at start, 15–20 wk Incomplete reporting Lack of appropriate control group
Rabbit (M) 56 wk Hiruma (1991)	Implants into bone Beryllium oxide 300 (after fracture), 300, 50 mg 10/group	Osteosarcomas: 10/10 (100%) 7/10 (70%) 1/10 (10%)		

F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

3.3 Intravenous administration

3.3.1 Mouse

A mouse study reported bone tumours after intravenous injection of zinc beryllium silicate (Cloudman *et al.*, 1949).

3.3.2 Rabbit

Multiple intravenous injections of beryllium metal (Barnes & Denz, 1950), beryllium oxide (Gardner & Heslington, 1946; Dutra & Largent, 1950; Araki *et al.*, 1954; Komitowski, 1967; Fodor, 1977), beryllium silicate, beryllium phosphate (Araki *et al.*, 1954), and zinc beryllium silicate (Gardner & Heslington, 1946; Cloudman *et al.*, 1949; Barnes & Denz, 1950; Hoagland *et al.*, 1950; Janes *et al.*, 1954; Kelly *et al.*, 1961) caused osteosarcomas in rabbits, which were reviewed by Groth (1980).

See Table 3.3.

[The Working Group noted that although many of these studies had defficiency in reporting methods, the rarity of the induced tumours was considered to be compelling enough to consider them as a group.]

3.4 Other routes of exposure

3.4.1 Mouse

Beryllium sulfate injected intraperitoneally caused an increased incidence and multiplicity of lung tumours in A/J mice (Ashby *et al.*, 1990).

3.4.2 Rabbit

Intramedullary bone administration of beryllium oxide (Yamaguchi, 1963; Komitowski, 1974; Hiruma, 1991), beryllium silicate (Tapp, 1966), zinc beryllium silicate (Tapp, 1969; Mazabraud, 1975), beryllium carbonate (Matsuura, 1974), and beryllium acetylacetonate (Matsuura, 1974) caused osteosarcomas or other bone tumours in rabbits.

See Table 3.4.

3.5 Synthesis

Lung tumours were induced in rats by inhalation of beryllium sulfate, beryllium metal, and beryl ore dust. In mice, lung cancer occurred after inhalation of beryllium metal. In hamsters, inhalation of beryl ore induced adenomatous hyperplasia of the lung. Intratracheal instillation of beryllium metal, beryllium hydroxide, and beryllium oxide in rats induced lung tumours. Intraperitoneal injection of beryllium sulfate induced lung tumours in mice. Intravenous injection or intramedullary injection/implantation of various beryllium compounds induced osteosarcoma in various studies in rabbits, and in one study in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

The bioavailability of beryllium particles as a function of size (geometric mean diameter), chemical composition, and specific surface area has been studied extensively. The agglomeration of beryllium particles does occur but the agglomerates dissociate again in fluid, with a corresponding decrease in particle mean diameter (Kent *et al.*, 2001; Stefaniak *et al.*, 2003b, 2004, 2007). Highly significant associations of chronic beryllium disease (CBD) and beryllium sensitization with particle-mass concentration for particles of less than 10 μm have been observed. The particle-mass concentration of alveolar-deposited particles (< 10 μm) correlates significantly with the occurrence of CBD. In a simulated phagolysosomal fluid, dissolution rate constants (k) for metallic beryllium particles and multiconstituent particles from arc-furnace processing of a beryllium–copper alloy were greater than those observed for beryllium oxide materials (Stefaniak *et al.*, 2006). Beryllium has

been detected in CBD-associated granulomas of beryllium-exposed workers by secondary ion mass-spectroscopy at an average of 9 years post exposure (Sawyer *et al.*, 2005a). These data indicate that beryllium is retained in granulomatous lesions for extended periods of time in exposed humans with CBD. Verma *et al.*, (2003) also reported elevated concentrations of beryllium in lung tissue from a person with CBD.

Acute inhalation dose–response studies in mice with a follow-up period of 350 days showed that high-dose exposures produced granulomatous beryllium lesions, which impeded the clearance of beryllium from the lungs (Finch *et al.*, 1998b).

Accidental exposure of 25 people to beryllium dust produced a mean serum concentration of 3.5 µ/L measured one day later, which decreased to a mean concentration of 2.4 µ/L after 6 days (Zorn *et al.*, 1986). These data indicate that beryllium from beryllium metal is biologically available from the lung. Exposure to beryllium metal (Williams, 1977) and beryllium alloys (Lieben *et al.*, 1964) have been reported to produce beryllium disease.

4.2 Genetic and related effects

4.2.1 Direct genotoxicity

A large number of mutagenicity studies for beryllium compounds have been published (for reviews see IARC, 1993; Gordon & Bowser, 2003). In general, results of these studies have been either negative or weakly positive, depending on the test system used.

Joseph *et al.* (2001) studied gene expression patterns in BALB/c-3T3 cells transformed with beryllium sulfate and reported a general upregulation of several cancer-related genes. Because no toxicity data were provided in these studies, the relevance of these findings to cancer cannot be interpreted. The same authors also reported the downregulation of several genes involved in DNA synthesis, repair and recombination in the tumour cells relative to controls.

Fahmy *et al.* (2008) studied the genotoxicity of beryllium chloride in mice exposed to oral doses of 93.75–750 mg/kg body weight for 3 weeks. Starting with the second lowest concentration (187.5 mg/kg bw; 1/8 of the LD_{50}), chromosomal aberrations (excluding gaps) and aneuploidy were observed both in bone-marrow cells and in spermatocytes, as a function of dose and time.

4.2.2 Indirect effects related to genotoxicity

(a) Oxidative stress

Palmer *et al.* (2008) demonstrated upregulation of the protein PD-1 (programmed death-1) in beryllium-specific CD4+ T-cells derived from broncho-alveolar lavages from beryllium-sensitized persons or CBD patients. Upregulation of PD-1 was closely correlated with the severity of T-cell alveolitis.

Subsequent studies by Sawyer *et al.* (2005b) in mouse macrophages demonstrated beryllium-induced formation of reactive oxygen species *in vitro*, with marked increases in apoptosis and activation of caspase 8. These effects were attenuated by the addition of the antioxidant manganese(III)*meso*-tetrakis(4-benzoic acid) porphyrin (MnTBAP).

The inflammatory processes associated with the development of acute or chronic beryllium disease could plausibly contribute to the development of lung cancer by elevating the rate of cell turnover, by enhancing oxidative stress, and by altering several signalling pathways involved in cell replication.

(b) Epigenetic mechanisms

Studies by Belinsky *et al.* (2002) in beryllium-induced rat lung tumours demonstrated hypermethylation of the *p16* and *estrogen-receptor-α* genes, and their attendant inactivation.

4.3 Synthesis

Several molecular mechanisms, possibly interrelated, operate in beryllium-induced carcinogenesis. Whereas mutagenicity tests with beryllium have shown only weakly positive or negative results, chromosomal aberrations and aneuploidy were observed *in vivo* in mice, at non-toxic concentrations. Like many other carcinogenic metals, beryllium is capable of producing oxidative stress, which can lead to cell injury in the form of DNA damage, activation of proto-oncogenes, and apoptotic mechanisms. In addition, the toxicity of beryllium in the lung may lead to cell killing and compensatory cell proliferation. Furthermore, the beryllium-induced chronic inflammatory response with attendant release of cytokines from beryllium-reactive CD4+ T-cells could also play a role in the development of a carcinogenic response in lung tissue.

In addition to beryllium-mediated generation of reactive oxygen species, inflammatory processes induced by beryllium may also cause an increase in reactive oxygen species, mediate cell turnover, and alter cell-signalling pathways. Furthermore, downregulation of genes involved in DNA synthesis, repair and recombination also occurs. Thus, the processes underlying beryllium-induced carcinogenesis are clearly complex, with several possible interactive mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of beryllium and beryllium compounds. Beryllium and beryllium compounds cause cancer of the lung.

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

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

References

Apostoli P & Schaller KH (2001). Urinary beryllium–a suitable tool for assessing occupational and environmental beryllium exposure? *Int Arch Occup Environ Health*, 74: 162–166. doi:10.1007/s004200000204 PMID:11355289

Araki M, Okada S, Fujita M (1954). Experimental studies on beryllium-induced malignant tumors of rabbits. *Gan*, 45: 449–451. PMID:13220941

Ashby J, Ishidate M Jr, Stoner GD *et al.* (1990). Studies on the genotoxicity of beryllium sulphate in vitro and in vivo. *Mutat Res*, 240: 217–225. doi:10.1016/0165-1218(90)90061-6 PMID:2179717

ATSDR (2002). *Toxicological Profile for Beryllium* (US NTIS PB2003–100135). Atlanta, GA: US Public Health Service, Agency for Toxic Substances and Disease Registry. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp4.pdf

Ballance J, Stonehouse AJ, Sweeney R, Walsh K (1978). *Beryllium and Beryllium Alloys*. In: *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 3. Mark HF, Othmer DF, Overberger CG *et al.*, editors. New York: John Wiley & Sons, pp. 803–823.

Barnes JM & Denz FA (1950). Beryllium bone sarcomata in rabbits. *Br J Cancer*, 4: 212–222. PMID:14772368

Belinsky SA, Snow SS, Nikula KJ *et al.* (2002). Aberrant CpG island methylation of the p16(INK4a) and estrogen receptor genes in rat lung tumors induced by particulate carcinogens. *Carcinogenesis*, 23: 335–339. doi:10.1093/carcin/23.2.335 PMID:11872642

BISAC. (1997). Is beryllium carcinogenic in humans? Beryllium Industry Scientific Advisory Committee. *J Occup Environ Med*, 39: 205–208. doi:10.1097/00043764-199703000-00009 PMID:9093971

CAREX Canada (2011). Available at: http://www.carexcanada.ca/en/beryllium/occupational_exposure_estimates/phase_2/

Cloudman AM, Vining D, Barkulis S *et al.* (1949). Bone changes observed following intravenous injections of beryllium [Abstract] *Am J Pathol*, 25: 810–811.

Cummings KJ, Deubner DC, Day GA *et al.* (2007). Enhanced preventive programme at a beryllium oxide ceramics facility reduces beryllium sensitisation among new workers. *Occup Environ Med*, 64: 134–140. doi:10.1136/oem.2006.027987 PMID:17043076

Day GA, Dufresne A, Stefaniak AB *et al.* (2007). Exposure pathway assessment at a copper-beryllium alloy facility. *Ann Occup Hyg*, 51: 67–80. doi:10.1093/annhyg/mel041 PMID:16844720

Deubner D, Kelsh M, Shum M *et al.* (2001a). Beryllium sensitization, chronic beryllium disease, and exposures at a beryllium mining and extraction facility. *Appl Occup Environ Hyg*, 16: 579–592. doi:10.1080/104732201750169697 PMID:11370937

Deubner DC, Lockey JL, Kotin P *et al.* (2001b). Re: Lung cancer case–control study of beryllium workers. Sanderson WT, Ward EM, Steenland K, Petersen MR. Am. J. Ind. Med. 2001. 39:133–144. *Am J Ind Med*, 40: 284–288. doi:10.1002/ajim.1101 PMID:11598976

Deubner DC & Roth HD (2009). Rejoinder: Progress in understanding the relationship between beryllium exposure and lung cancer. *Epidemiology*, 20: 341–343. doi:10.1097/EDE.0b013e31819f32de PMID:19295436

Deubner DC, Roth HD, Levy PS (2007). Empirical evaluation of complex epidemiologic study designs: workplace exposure and cancer. *J Occup Environ Med*, 49: 953–959. doi:10.1097/JOM.0b013e318145b28d PMID:17848851

Dutra FR & Largent EJ (1950). Osteosarcoma induced by beryllium oxide. *Am J Pathol*, 26: 197–209. PMID:15406251

Fahmy MA, Hassan NH, Farghaly AA, Hassan EE (2008). Studies on the genotoxic effect of beryllium chloride and the possible protective role of selenium/vitamins A, C and E. *Mutat Res*, 652: 103–111. PMID:18373946

Finch GL, March TH, Hahn FF *et al.* (1998a). Carcinogenic responses of transgenic heterozygous p53 knockout mice to inhaled 239PuO2 or metallic beryllium. *Toxicol Pathol*, 26: 484–491. doi:10.1177/019262339802600404 PMID:9715507

Finch GL, Nikula KJ, Hoover MD (1998b). Dose-response relationships between inhaled beryllium metal and lung toxicity in C3H mice. *Toxicol Sci*, 42: 36–48. PMID:9538046

Fodor I (1977). Histogenesis of beryllium-induced bone tumours. *Acta Morphol Acad Sci Hung*, 25: 99–105. PMID:277062

Gardner LU & Heslington HF (1946). Osteosarcoma from intravenous beryllium compounds in rabbits [Abstract] *Fed Proc*, 5: 221

Gordon T & Bowser D (2003). Beryllium: genotoxicity and carcinogenicity. *Mutat Res*, 533: 99–105. PMID:14643414

Groth DH (1980). Carcinogenicity of beryllium: review of the literature. *Environ Res*, 21: 56–62. doi:10.1016/0013-9351(80)90008-0 PMID:6771136

Groth DH, Kommineni C, Mackay GR (1980). Carcinogenicity of beryllium hydroxide and alloys. *Environ Res*, 21: 63–84. doi:10.1016/0013-9351(80)90009-2 PMID:7389706

Hein MJ, Deddens JA, Schubauer-Berigan MK (2009). Bias from matching on age at death or censor in nested case–control studies. *Epidemiology*, 20: 330–338. doi:10.1097/EDE.0b013e31819ed4d2 PMID:19289956

Henneberger PK, Cumro D, Deubner DD *et al.* (2001). Beryllium sensitization and disease among long-term and short-term workers in a beryllium ceramics plant. *Int Arch Occup Environ Health*, 74: 167–176. doi:10.1007/s004200100237 PMID:11355290

Henneberger PK, Goe SK, Miller WE *et al.* (2004). Industries in the United States with airborne beryllium exposure and estimates of the number of current workers potentially exposed. *J Occup Environ Hyg*, 1: 648–659. doi:10.1080/15459620490502233 PMID:15631056

Hiruma T (1991). Rabbit osteosarcoma induced by hydroxypropylcellulose mixed beryllium oxide pellet–comparison between implantations into bone marrow cavity and into fracture callus of the femur *Nippon Seikeigeka Gakkai Zasshi*, 65: 775–786. PMID:1960478

Hoagland MB, Grier RS, Hood MB (1950). Beryllium and growth. I. Beryllium-induced osteogenic sarcomata. *Cancer Res*, 10: 629–635. PMID:14778129

IARC (1972). Some inorganic substances, chlorinated hydrocarbons, aromatic amines, N-nitroso compounds and natural products. *IARC Monogr Eval Carcinog Risk Chem Man*, 1: 1–184.

IARC (1980). Some metals and metallic compounds. *IARC Monogr Eval Carcinog Risk Chem Hum*, 23: 1–415. PMID:6933135

IARC (1987). Silica and some silicates. *IARC Monogr Eval Carcinog Risk Chem Hum*, 42: 1–239. PMID:2824337

IARC (1993). Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. *IARC Monogr Eval Carcinog Risks Hum*, 58: 1–415. PMID:8022054

Infante PF, Wagoner JK, Sprince NL (1980). Mortality patterns from lung cancer and nonneoplastic respiratory disease among white males in the beryllium case registry. *Environ Res*, 21: 35–43. doi:10.1016/0013-9351(80)90005-5 PMID:7389704

Ishinishi N, Mizunoe M, Inamasu T, Hisanaga A (1980). Experimental study on carcinogenicity of beryllium oxide and arsenic trioxide to the lung of rats by an intratracheal instillation (author's transl) *Fukuoka Igaku Zasshi*, 71: 19–26. PMID:7372264

Jakubowski M, Palczynski C (2007). *Beryllium*. In: *Handbook on the Toxicology of Metals*, 3rd ed. Academic Press Inc., pp. 415–431.

Janes JM, Higgins GM, Herrick JF (1954). Beryllium-induced osteogenic sarcoma in rabbits. *J Bone Joint Surg Br*, 36-B: 543–552. PMID:13211729

Johnson JS, Foote K, McClean M, Cogbill G (2001). Beryllium exposure control program at the Cardiff atomic weapons establishment in the United Kingdom. *Appl Occup Environ Hyg*, 16: 619–630. doi:10.1080/104732201750169750 PMID:11370940

Joseph P, Muchnok T, Ong T (2001). Gene expression profile in BALB/c-3T3 cells transformed with beryllium sulfate. *Mol Carcinog*, 32: 28–35. doi:10.1002/mc.1061 PMID:11568973

Kaczynski DJ (2004). *Beryllium Compounds*. In: *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed., Vol. 3. New York: John Wiley & Sons, pp. 661–668 [online version]

Kelly PJ, Janes JM, Peterson LF (1961). The effect of beryllium on bone. A morphological study of the progressive changes observed in rabbit bone. *J Bone Joint Surg Am*, 43-A: 829–844. PMID:13830920

Kent MS, Robins TG, Madl AK (2001). Is total mass or mass of alveolar-deposited airborne particles of beryllium a better predictor of the prevalence of disease? A preliminary study of a beryllium processing facility. *Appl Occup Environ Hyg*, 16: 539–558. doi:10.1080/104732201750169633 PMID:11370934

Kolanz ME (2001). Introduction to beryllium: uses, regulatory history, and disease. *Appl Occup Environ Hyg*, 16: 559–567. doi:10.1080/10473220119088 PMID:11370935

Komitowski D (1967). Experimental beryllium bone neoplasms as a model of osteogenic sarcoma *Chir Narzadow Ruchu Ortop Pol*, 33: 237–242. PMID:5239633

Komitowski D (1974). Beryllium induced bone sarcomas (author's transl) *Verh Dtsch Ges Pathol*, 58: 438–440. PMID:4533381

Kreiss K, Day GA, Schuler CR (2007). Beryllium: a modern industrial hazard. *Annu Rev Public Health*, 28: 259–277. doi:10.1146/annurev.publhealth.28.021406.144011 PMID:17094767

Kreiss K, Mroz MM, Newman LS *et al.* (1996). Machining risk of beryllium disease and sensitization with median exposures below 2 micrograms/m3. *Am J Ind Med*, 30: 16–25. doi:10.1002/(SICI)1097-0274(199607)30:1<16::AID-AJIM3>3.0.CO;2-Q PMID:8837677

Kreiss K, Mroz MM, Zhen B *et al.* (1997). Risks of beryllium disease related to work processes at a metal, alloy, and oxide production plant. *Occup Environ Med*, 54: 605–612. doi:10.1136/oem.54.8.605 PMID:9326165

Langholz B & Richardson D (2009). Are nested case–control studies biased? *Epidemiology*, 20: 321–329. doi:10.1097/EDE.0b013e31819e370b PMID:19289963

Levy PS, Roth HD, Deubner DC (2007). Exposure to beryllium and occurrence of lung cancer: a reexamination of findings from a nested case–control study. *J Occup Environ Med*, 49: 96–101. doi:10.1097/JOM.0b013e31802db595 PMID:17215718

Levy PS, Roth HD, Hwang PM, Powers TE (2002). Beryllium and lung cancer: a reanalysis of a NIOSH cohort mortality study. *Inhal Toxicol*, 14: 1003–1015. doi:10.1080/08958370290084755 PMID:12396408

Lide DR, editor (1991). *CRC Handbook of Chemistry and Physics*, 72nd ed. Boca Raton, FL: CRC Press, pp. 4–43.

Lieben J, Dattoli JA, Israel HL (1964). Probable berylliosis from beryllium alloys. *Arch Environ Health*, 9: 473–477. PMID:14185553

Litvinov NN, Kazenashev VF, Bugryshev PF (1983). Blastomogenic activities of various beryllium compounds (Russ.). *Eksp Onkol*, 5: 23–26.

Mancuso T, editor (1979). *Occupational lung cancer among beryllium workers: Dusts and Disease*. Park Forest, IL: Pathotox Publishers.

Mancuso TF (1980). Mortality study of beryllium industry workers' occupational lung cancer. *Environ Res*, 21: 48–55. doi:10.1016/0013-9351(80)90007-9 PMID:6771135

Martyny JW, Hoover MD, Mroz MM *et al.* (2000). Aerosols generated during beryllium machining. *J Occup Environ Med*, 42: 8–18. doi:10.1097/00043764-200001000-00006 PMID:10652683

Matsuura K (1974). Experimental studies on the production of osteosarcoma by beryllium compounds, and the effects of irradiation (Jpn.). *Jpn J Orthop Assoc*, 48: 403–418.

Mazabraud A (1975). Experimental production of bone sarcomas in the rabbit by a single local injection of beryllium *Bull Cancer*, 62: 49–58. PMID:1063048

Meeker JD, Susi P, Pellegrino A (2006). Comparison of occupational exposures among painters using three alternative blasting abrasives. *J Occup Environ Hyg*, 3: D80–D84. doi:10.1080/15459620600854292 PMID:16857642

Newland LW (1984). *Arsenic, beryllium, selenium and vanadium*. In: *The Handbook of Environmental Chemistry*, Vol. 3, Part B, *Anthropogenic Compounds*. Hutzinger O, editor. New York: Springer-Verlag, pp. 27–67.

Nickell-Brady C, Hahn FF, Finch GL, Belinsky SA (1994). Analysis of K-ras, p53 and c-raf-1 mutations in beryllium-induced rat lung tumors. *Carcinogenesis*, 15: 257–262. doi:10.1093/carcin/15.2.257 PMID:7545909

NRC (2007). *Health Effects of Beryllium Exposure: A Literature Review*. Washington, DC: National Research Council of the National Academies.

NTP (2004). Beryllium and beryllium compounds. *Rep Carcinog*, 11: III32–III34. PMID:21089812

O'Neil MJ, editor (2006). *The Merck Index*, 14th ed. Whitehouse Station, NJ: Merck & Co., pp. 191–193.

Palmer BE, Mack DG, Martin AK *et al.* (2008). Up-regulation of programmed death-1 expression on beryllium-specific CD4+ T cells in chronic beryllium disease. *J Immunol*, 180: 2704–2712. PMID:18250483

Paschal DC, Ting BG, Morrow JC *et al.* (1998). Trace metals in urine of United States residents: reference range concentrations. *Environ Res*, 76: 53–59. doi:10.1006/enrs.1997.3793 PMID:9466897

Petzow G, Fritz Aldinger WC, Jönsson S *et al.* (2007). *Beryllium and Beryllium Compounds*. In: *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed., pp. 1–28 [online edition]

Petzow G, Fritz Aldinger WC, Jönsson S, Preuss OP (1985). *Beryllium and Beryllium Compounds*. In: *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed., Vol. A4. Gerhartz W, Yamamoto YS, Campbell FT *et al.*, editors. Weinheim, VCH: Verlagsgesellschaft, pp. 11–33.

Reeves AL, Deitch D, Vorwald AJ (1967). Beryllium carcinogenesis. I. Inhalation exposure of rats to beryllium sulfate aerosol. *Cancer Res*, 27: 439–445. PMID:6021502

Sanderson WT, Petersen MR, Ward EM (2001a). Estimating historical exposures of workers in a beryllium manufacturing plant. *Am J Ind Med*, 39: 145–157.

doi:10.1002/1097-0274(200102)39:2<145::AID-AJIM1002>3.0.CO;2-Y PMID:11170157

Sanderson WT, Ward EM, Steenland K (2001c). Re: Response to criticisisms of "Lung cancer case–control study of beryllium workers" AM. J. Ind. Med. 2001. 39: 133–144. *Am J Ind Med*, 40: 286–288. doi:10.1002/ajim.1102

Sanderson WT, Ward EM, Steenland K, Petersen MR (2001b). Lung cancer case–control study of beryllium workers. *Am J Ind Med*, 39: 133–144. doi:10.1002/1097-0274(200102)39:2<133::AID-AJIM1001>3.0.CO;2-7 PMID:11170156

Sawyer RT, Abraham JL, Daniloff E, Newman LS (2005a). Secondary ion mass spectroscopy demonstrates retention of beryllium in chronic beryllium disease granulomas. *J Occup Environ Med*, 47: 1218–1226. doi:10.1097/01.jom.0000184884.85325.36 PMID:16340702

Sawyer RT, Dobis DR, Goldstein M *et al.* (2005b). Beryllium-stimulated reactive oxygen species and macrophage apoptosis. *Free Radic Biol Med*, 38: 928–937. doi:10.1016/j.freeradbiomed.2004.12.014 PMID:15749389

Schepers GW,, Durkan TM, Delahant AB, Creedon FT (1957). The biological action of inhaled beryllium sulfate; a preliminary chronic toxicity study on rats. *AMA Arch Ind Health*, 15: 32–58. PMID:13393810

Schubauer-Berigan MK, Deddens JA, Steenland K *et al.* (2008). Adjustment for temporal confounders in a reanalysis of a case–control study of beryllium and lung cancer. *Occup Environ Med*, 65: 379–383. doi:10.1136/oem.2007.033654 PMID:17890301

Schuler CR, Kent MS, Deubner DC *et al.* (2005). Process-related risk of beryllium sensitization and disease in a copper-beryllium alloy facility. *Am J Ind Med*, 47: 195–205. doi:10.1002/ajim.20140 PMID:15712254

Seiler DH, Rice C, Herrick RF, Hertzberg VS (1996a). A study of beryllium exposure measurements. Part 1: Estimation and categorization of average exposures from daily weighted average data in the beryllium industry. *Appl Occup Environ Hyg*, 11: 89–97.

Seiler DH, Rice C, Herrick RF, Hertzberg VS (1996b). A study of beryllium exposure measurements. Part 2: Evaluation of the components of exposure in the beryllium processing industry. *Appl Occup Environ Hyg*, 11: 98–102.

Stange AW, Furman FJ, Hilmas DE (1996a). Rocky Flats beryllium health surveillance. *Environ Health Perspect*, 104: Suppl 5981–986. PMID:8933045

Stanton ML, Henneberger PK, Kent MS *et al.* (2006). Sensitization and chronic beryllium disease among workers in copper-beryllium distribution centers. *J Occup Environ Med*, 48: 204–211. doi:10.1097/01.jom.0000184864.10147.bc PMID:16474270

Steenland K & Ward E (1991). Lung cancer incidence among patients with beryllium disease: a cohort mortality study. *J Natl Cancer Inst*, 83: 1380–1385. doi:10.1093/jnci/83.19.1380 PMID:1920480

Stefaniak AB, Day GA, Hoover MD *et al.* (2006). Differences in dissolution behavior in a phagolysosomal simulant fluid for single-constituent and multi-constituent materials associated with beryllium sensitization and chronic beryllium disease. *Toxicol In Vitro*, 20: 82–95. doi:10.1016/j.tiv.2005.06.031 PMID:16061346

Stefaniak AB, Hoover MD, Day GA *et al.* (2004). Characterization of physicochemical properties of beryllium aerosols associated with prevalence of chronic beryllium disease. *J Environ Monit*, 6: 523–532. doi:10.1039/b316256g PMID:15173904

Stefaniak AB, Hoover MD, Dickerson RM *et al.* (2003b). Surface area of respirable beryllium metal, oxide, and copper alloy aerosols and implications for assessment of exposure risk of chronic beryllium disease. *AIHA J (Fairfax, Va)*, 64: 297–305. doi:10.1080/15428110308984820 PMID:12809534

Stefaniak AB, Hoover MD, Dickerson RM *et al.* (2007). Differences in estimates of size distribution of beryllium powder materials using phase contrast microscopy, scanning electron microscopy, and liquid suspension counter techniques. *Part Fibre Toxicol*, 4: 3 doi:10.1186/1743-8977-4-3 PMID:17328812

Stefaniak AB, Weaver VM, Cadorette M *et al.* (2003a). Summary of historical beryllium uses and airborne concentration levels at Los Alamos National Laboratory. *Appl Occup Environ Hyg*, 18: 708–715. doi:10.1080/10473220301381 PMID:12909539

Taiwo OA, Slade MD, Cantley LF *et al.* (2008). Beryllium sensitization in aluminum smelter workers. *J Occup Environ Med*, 50: 157–162. doi:10.1097/JOM.0b013e318161783f PMID:18301172

Tapp E (1966). Beryllium induced sarcomas of the rabbit tibia. *Br J Cancer*, 20: 778–783. PMID:5964608

Tapp E (1969). Osteogenic sarcoma in rabbits. Following subperiosteal implantation of beryllium. *Arch Pathol*, 88: 89–95. PMID:5255782

Taylor TP, Ding M, Ehler DS *et al.* (2003). Beryllium in the environment: A review. J Environ Sci Health A Tox Hazard Subst Environ Eng, 38:439–469.

USGS (2007). *2006 Minerals Yearbook – Beryllium*. Reston, VA: US Geological Survey.

Verma DK, Ritchie AC, Shaw ML (2003). Measurement of beryllium in lung tissue of a chronic beryllium disease case and cases with sarcoidosis. *Occup Med (Lond)*, 53: 223–227. doi:10.1093/occmed/kqg042 PMID:12724557

Wacholder S (2009). Bias in full cohort and nested case–control studies? *Epidemiology*, 20: 339–340. doi:10.1097/EDE.0b013e31819ec966 PMID:19289961

Wagner WD, Groth DH, Holtz JL *et al.* (1969). Comparative chronic inhalation toxicity of beryllium ores, bertrandite and beryl, with production of pulmonary tumors by beryl. *Toxicol Appl Pharmacol*, 15: 10–29. doi:10.1016/0041-008X(69)90127-6 PMID:4307951

Wagoner JK, Infante PF, Bayliss DL (1980). Beryllium: an etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers. *Environ Res*, 21: 15–34. doi:10.1016/0013-9351(80)90004-3 PMID:6771133

Ward E, Okun A, Ruder A *et al.* (1992). A mortality study of workers at seven beryllium processing plants. *Am J Ind Med*, 22: 885–904. doi:10.1002/ajim.4700220610 PMID:1463033

WHO (1990). Beryllium. *Environ Health Criteria*, 106

WHO (2001). *Beryllium and Beryllium Compounds. Concise International Chemical Assessment, 32*. Geneva: International Programme on Chemical Safety.

Williams WJ (1977). Beryllium disease–pathology and diagnosis. *J Soc Occup Med*, 27: 93–96. PMID:895082

Yamaguchi S (1963). Studies on the production of sarcoma by the use of beryllium oxide. *Nagasaki Igakkai Zasshi*, 38: 127–138. PMID:14002285

Yoshida T, Shima S, Nagaoka K *et al.* (1997). A study on the beryllium lymphocyte transformation test and the beryllium levels in working environment. *Ind Health*, 35: 374–379. doi:10.2486/indhealth.35.374 PMID:9248221

Zorn H, Stiefel T, Porcher H (1986). Clinical and analytical follow-up of 25 persons exposed accidentally to beryllium. *Toxicol Environ Chem*, 12: 163–171. doi:10.1080/02772248609357156