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A review of the toxicity of beryllium in air

Science Report – SC020104/SR1

SCHO0508BOBO-E-P

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Steve Killeen

Head of Science

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Search strategy

A search for existing reviews was carried out from the following organisations:

Organisation/Review	Year
DEFRA/Environment Agency Contaminants in Soil: CLR TOX report	-
EU Risk Assessment Reports	-
WHO (Air Quality Guidelines for Europe)	-
ATSDR Toxicological Profiles	2002
US EPA (IRIS)	1998
HSE Toxicity Reviews	1992
CoC/CoT (not located)	-
CSTEE	-
IARC Monographs	1993
WHO/IPCS (Environmental Health Criteria 224)	1990
IPCS CICAD	2001
JECFA	-
Health Effects Institute (HEI)	-
National Toxicology Program (NTP- NIEHS)	2003

A search of the primary literature (from 2002 to 2005) for the following search terms was undertaken in the PubMed, ToxLine, Medline and NIEHS – Environmental Health Perspectives websites:

“beryllium and health”
“beryllium and air”
“beryllium and toxic*”
“beryllium and epid*”
“beryllium and toxic* and human*”
“beryllium and epid* and air*”

1 Background

Beryllium has been known to be toxic to humans for some time. According to Saltini and Amicosante (2001) its toxicity to humans was first reported in the 1930s, with these authors crediting Marradi-Fabroni with the first suggestion that beryllium was responsible for pulmonary toxicity. However, it was not until the 1940s that beryllium disease was first properly described by Van Ordstrand *et al*. (1943). These authors described chemical pneumonia (pneumonitis) in workers extracting beryllium oxide. Later Hardy and Tabershaw (1946) described beryllium disease in workers involved in the manufacture of fluorescent lights. The use of beryllium in these lights was subsequently terminated. It is now known that the disease described by Van Ordstrand *et al*. is acute beryllium toxicity, while the disease described by Hardy and Tabershaw is Chronic Beryllium Disease (CBD), also known as berylliosis. In addition, it was reported that industrial exposure to beryllium also caused dermatitis (DeNardi *et al.*, 1949).

The description of these diseases in the 1940s highlighted the potential health effects of industrial exposure to beryllium. Much research has subsequently improved our knowledge of beryllium disease caused by industrial exposure. It is apparent that all known cases of beryllium disease have occurred as a result of industrial exposure, mainly in the workplace, but occasionally in family members of workers (where the disease is thought to have occurred due to inhalation of beryllium from the workers' clothing) and in some populations living in the vicinity of beryllium manufacturing and processing plants. However, while no cases of beryllium disease in humans have been shown to occur from natural exposure to beryllium, some aspects of the element's environmental chemistry are included below for completeness, together with a consideration of sources of beryllium for industry and its main uses.

An additional health effect of beryllium is its role as a human carcinogen. The International Agency for Research on Cancer (IARC) has classified beryllium as a Group 1 human carcinogen, defining it as a proven carcinogen (IARC, 1993). The US Department of Health and Human Services (US DHHS, 2003) also lists beryllium and its compounds as a known human carcinogen and this is echoed by the American Committee of Governmental Industrial Hygienists (ACGIH) (2001, 2005). However the US Environmental Protection Agency (EPA) lists beryllium in group B1, making it a 'probable' human carcinogen (US EPA, 1998).

1.1 Beryllium in the environment

Beryllium, atomic number 4, is an extremely light metal, with an atomic weight of 9.01218 and density of 1.848 g cm^3, and is an extreme trace element in rocks, its mean abundance in the upper continental crust being estimated to be about 3 mg kg^{-1}. Beryllium is an essential component of over 40 minerals (Ross, 1964), the two most important of these being bertrandite [$Be_4Si_2O_7(OH)_2$] and beryl [$Al_2Be_3Si_6O_{18}$], both of which have been extracted as sources of the metal. In addition beryl, together with emerald, which has essentially the same chemical formula but contains significant chromium resulting in its green colour, is a semi precious mineral.

In rock-forming silicate minerals, beryllium can substitute for magnesium and aluminium, being relatively enriched in such minerals as muscovite, plagioclase, pyroxenes and clay minerals. Of the igneous rocks, granites tend to be richer in

beryllium than other rock types, estimated to contain about 5 mg kg^{-1} on average (Levinson,1980; Reimann *et al*., 1998), with some residual granitic pegmatites, such as the Meldon aplite, Dartmoor, Devon, being extremely enriched, containing up to several hundred mg kg^{-1}. As mentioned below, these pegmatitic rocks are one of the commercial sources of beryllium. Of the sedimentary rocks, fine grained types such as clays and shales contain the highest quantities of beryllium, estimated to contain about 2.5 - 3 mg/kg on average (Levinson,1980; Reimann *et al*., 1998).

Appreciable concentrations of beryllium occur in coals, with values generally ranging between 1 and 2 mg/kg (Reimann *et al*., 1998), however, values of over 10 mg/kg have been recorded in some samples (Hörmann, 1969). Bouška (1981) records values of up to 30 mg kg^{-1} in poor quality brown coals from central Europe. The occurrence of beryllium in coal has a major impact on its atmospheric distribution (see below). However, it has been suggested that only about 1 per cent of the beryllium in coal is volatilised during combustion (Kubizňáková, 1987), so that much of the element remains in the ash residue from coal combustion. As such, the large quantities of fly ash generated by coal-fired power stations are potential sources of environmental contamination. In a study in the Czech Republic, Kubizňáková (1987) found that fly ash contained 1.58 – 1.87 mg/kg beryllium and that water draining a fly ash dump contained 3.15µg/L. The author further suggests that beryllium in fly ash is fairly easily mobilised and represents a source of ongoing pollution of surface waters and groundwaters. Much higher concentrations of beryllium have been found in coal ash in the United States, with a mean value of 46 mg/kg being recorded by Stadnichenko *et al*. (1961).

Elevated beryllium concentrations also occur in steel industry slags, with Procter *et al*. (2002) quoting a mean value of 8.2 mg/kg in blast furnace slags. However, it is likely that beryllium in slags is relatively immobile, as it is probably incorporated into the silicate minerals within the slag.

The concentration of beryllium in uncontaminated soils generally reflects crustal rock contents, mean values being quoted as between 3 and 6 mg/kg (Levinson, 1980; Reimann *et al*., 1998). However, much higher values have been found in soils overlying beryllium-rich bedrock, such as granitic pegmatites.

In terrestrial waters the beryllium content is generally below the detection limit of available analytical methods. However, Newcomb and Rimstidt (2002) record values of up to 10 µg/L beryllium in groundwaters from the USA, while Edmunds and Trafford (1993) found concentrations of up to 1.02 µg/L in major aquifers of the UK, with over 10 µg/L in some soil waters. Edmunds and Trafford (1993) suggest that the beryllium content of terrestrial waters strongly reflects the chemistry of the bedrocks they interact with, citing one example of a stream draining the Mourne Mountains granite in Northern Ireland having 4.7 µg/L beryllium. These authors also suggest that in addition to geological control, pH has an important influence, with acidic waters generally being relatively enriched in beryllium. As stated above, surface waters draining fly ash can contain significant concentrations of beryllium.

Much of the beryllium in the atmosphere derives from man-made sources. As outlined above, coal generally contains from 1-2 mg/kg of beryllium with some samples being markedly enriched. While it has been suggested that only 1 per cent of the beryllium in coal is released to the atmosphere during combustion (Kubizňáková, 1987), coal combustion is suggested to be the major source of atmospheric beryllium. It has been estimated by Kolanz (2001) that 97.1 per cent of atmospheric beryllium in the USA is the result of coal combustion, with 2.7 per cent contributed by volcanic eruptions and the remaining 0.2 per cent deriving from the production and industrial use of the element. However, Reimann *et al.* (1998) found elevated concentrations of beryllium in mosses from Finland and suggested that the source of the element was probably

windblown dust. Willis and Florig (2002) suggest that the major contributor to atmospheric beryllium in the USA is soil dust.

1.2 Beryllium minerals and their extraction

The USA is by far the greatest producer of beryllium with most of the production deriving from Joab County, Utah, which houses 65 per cent of the world's estimated reserves (Cunningham, 2005). Beryllium is also produced in Alaska, with other significant producers being China, Russia, Kazakhstan and Mozambique (Cunningham, 2005). The only commercially important minerals are beryl from pegmatites and bertrandite, occurring in epithermal/metasomatic deposits. Small quantities of phenakite (Be_2SiO_4) also occur along with bertrandite.

Ore processing generally involves crushing and subsequent leaching with sulphuric acid, followed by precipitation of beryllium hydroxide [$Be(OH)_2$], which in turn is converted to beryllium oxide (beryllia, BeO). From this compound beryllium metal and beryllium-containing alloys are manufactured, but the oxide itself is also used in industry.

1.3 Uses of beryllium

Beryllium is a very light metal with a high melting point (about 1,280^{o}C), it is generally a strong metal, is resistant to corrosion and is a good thermal conductor. While the metal itself and its oxide find many industrial uses, its major use is in the production of high strength alloys with copper, nickel and aluminium. For example, addition of 2 per cent beryllium to copper metal results in an alloy that is six times stronger than pure copper metal (Greenwood and Earnshaw, 1984).

Cunningham (2003) states that 75 per cent of the beryllium produced in the USA is used to manufacture copper-beryllium alloys. This alloy, which can contain from 0.2 to 2.0 per cent beryllium, is a good electrical and thermal conductor, has high strength and hardness, is resistant to corrosion and is non-magnetic. Copper-beryllium alloys are used extensively in the aerospace industries, in vehicle manufacture, computers, control systems and radar, and in telecommunications including fibre optics and cellular phones. It is also used in oil and gas drilling equipment and in heavy machinery, along with many other applications. It is perhaps pertinent to point out that despite their low beryllium contents, copper-beryllium alloys have been shown to pose a serious health risk for workers machining these alloys.

Aluminium-beryllium alloys are used as high strength lightweight alloys in aerospace and automotive industries, and it has found major use recently in the manufacture of military aircraft and missile systems (Taylor *et al*., 2003). Nickel-beryllium alloys are also used in the aerospace and automotive industries, and are also used in electronic connector parts where high temperatures are involved (Cunningham, 2003).

The second biggest use of beryllium is as the metal (Cunningham, 2003). This again finds use in the aerospace industry, where it is used in aircraft, spacecraft and satellites. It is also used in computers. In addition, beryllium is transparent to most X-rays and is used in X-ray windows. In the nuclear industry, it is used as a neutron moderator in reactors.

Beryllium oxide is converted to a ceramic, which is very strong and hard and is an extremely good heat conductor and electrical insulator. It finds use in electronic circuits, automotive ignition systems, high-speed computers and microwave ovens, amongst other applications.

One use of beryllium that is perhaps of some concern is its use in dental alloys for making bridges, crowns and plates (Taylor *et al*., 2003), and there are records of dental technicians suffering from Chronic Beryllium Disease (U.S. Agency for Toxic Substances and Disease Registry (ATSDR), 2002; Sawyer *et al.*, 2002).

1.4 Potential sources of human exposure to beryllium

As with all potentially harmful substances, human exposure can occur via inhalation, ingestion or skin contact. Inhalation represents the major pathway with regard to industrial exposure. However, dermal exposure can also lead to health problems, with such exposure having been proposed as an additional pathway into the body. Tinkle *et al.* (2003a) suggest that beryllium particles penetrating the skin represent the major source of beryllium sensitisation in workers not exposed to significant inhalant sources.

With regard to non-industrial exposure, ambient air generally contains non-detectable levels of beryllium. Higher beryllium contents are generally found in urban atmospheres, reflecting anthropogenic sources such as burning of fossil fuels. Levels up to 6.7 ng/m^3 have been recorded in urban areas of the USA (see Table 1), and elevated concentrations of atmospheric beryllium are found in atmosphere in the vicinity of coal-fired power stations (see Table 1).

It is perhaps important to point out that in view of the wide usage of beryllium it would seem that an additional potential source of atmospheric beryllium would be waste incineration and the casual burning of household waste. As beryllium is a component of such widely used items as laptop computers and mobile phones, it is possible that these items when discarded could be a future source of beryllium contamination. In a study around a waste incinerator in Barcelona, Spain, Meneses *et al*. (1999) found that soil concentrations of beryllium showed an increase over a one-year period. In 1996, soil contained 0.48 (± 0.14) mg/kg beryllium while in 1997 the soil contained 0.62 (± 0.13) mg/kg beryllium, with the differences shown to be statistically significant.

It has been shown that the air in the vicinity of factories and other facilities where beryllium is processed or beryllium-containing products are manufactured could become enriched. In early studies around a beryllium processing plant in Loraine, Ohio, USA, Eisenbud *et al*. (1949), found that within approximately 650 feet (212 metres) of the plant measured concentrations of beryllium ranged up to 460 ng/m^3, with concentrations falling to 30 ng/m^3 a mile (1.61 km) from the plant. Berylliosis was found to occur in 11 individuals in the area. Of these 10 cases, occurring within ¾ of a mile (1.21 km) of the plant, were thought to be due to atmospheric beryllium emitted from the plant. However, more recent studies (such as Thorat *et al*., 2001) suggest that beryllium particulates in air immediately adjacent to beryllium processing facilities are considerably lower than those given by Eisenbud *et al*. (1949) (see Table 1).

Table 1. Beryllium in the atmosphere of polluted and unpolluted environments.

Site	Be concentration in ng/m	Source of data
Rural areas of USA	0.03 – 0.06	1
Suburban areas of USA	0.04 – 0.07	1
Urban areas of USA	up to 6.7	2
Detroit, USA	up to 0.2	3
Urban industrial site, Dayton, Ohio, USA	0.1 – 0.2	1
Urban areas of Japan	up to 0.222	4
Urban areas of Germany	0.06 – 0.33	5/6
In vicinity of coal-fired power station, Spain	up to 1.61	7
In vicinity of coal-fired power station, former Czechoslovakia	3.9 – 16.8	8
In vicinity of Be processing plant, Pennsylvania, USA	up to 82.7	9
In vicinity of Be processing plant, former USSR, with no emission control (400 m from)	1000	8
In vicinity of Be processing plant, former USSR, with no emission control (1 km from)	10 – 100	8
In vicinity of Be processing plant, India (at boundary of)	0.01 – 2.5	10
In vicinity of Be processing plant, India (5 km from)	0.06 – 0.63	10

Notes; 1. Ross *et al*. (1977); 2. ASTDR (2002); 3. U.S. EPA (1987); 4. Ikebe *et al.* (1986); 5. Mueller (1979); 6. Freise and Israel (1987); 7. Boix *et al.* (2001); 8. Bencko *et al.* (1980); 9. Sussman *et al.* (1959); 10. Thorat *et al*. (2001).

Tobacco contains small quantities of beryllium and it has been detected in cigarettes. Zorn and Diem (1977) found concentrations of beryllium ranging from 0.47-0.74 µg in individual cigarettes from German manufacturers. It has been shown that 2-10 per cent of the beryllium in cigarettes is emitted in the smoke (Reeves, 1986). Using this data the World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) (2001) review suggests that individuals smoking 20 cigarettes a day would, in a worst-case scenario, inhale 1.5 µg/day. However, in a more recent review of literature data, Smith *et al* (1997) suggest that concentrations of beryllium in American cigarettes are somewhat lower, being quoted as ranging up to 0.0005 µg in individual cigarettes. It is therefore likely that while smokers may be subject to higher beryllium intakes than non-smokers, with increased amounts of beryllium being found in the blood and urine of smokers (Tsalev and Zaprianov, 1984), cigarette smoking is unlikely to represent a major source of beryllium inhalation in most cases. Sawyer *et al.* (2002) state that beryllium in tobacco smoke is unlikely to be a source of beryllium-sensitisation or CBD.

Kolanz (2001) estimates that in non-occupationally exposed populations, the human lung contains 0.20 mg/kg of beryllium. It is not clear whether this represents populations living in a totally unpolluted atmosphere. It is likely that populations living in urban environments would be exposed to greater atmospheric beryllium concentrations than those living in rural environments. However, it seems likely that non-occupationally exposed individuals are not exposed to high concentrations of atmospheric beryllium.

Similarly, it is unlikely that dermal exposure to beryllium will result from non-occupational exposure. While the beryllium-containing gemstone beryl (including aquamarine and emerald) is used in jewellery, it has been found that this mineral does not cause any dermal problems.

With regard to beryllium in the general population, it has been suggested (WHO/IPCS, 2001; ATSDR, 2002) that non-occupationally exposed populations have detectable beryllium in urine. However, Apostoli and Schaller (2001) failed to detect beryllium in the urine of non-occupationally exposed populations. These authors further state that previous results indicating detectable beryllium in non-occupationally exposed populations should be viewed with caution because the analytical methods used were unsuitable.

In terms of beryllium ingestion, no effect has been shown in humans. It is generally stated that at least 99 per cent of ingested beryllium is excreted and very little finds its way into the blood. However, dogs have been found to develop ulcers after being given 12 mg/kg/day of beryllium as the soluble salt beryllium sulphate for 143-172 weeks (Morgareidge *et al.*, 1975, 1976). This has led the US EPA (2003) to impose a maximum contaminant level of 4 µg/L for beryllium in drinking waters, based on its potential to cause stomach ulceration. The WHO (1996) excludes beryllium from its guideline evaluation, stating that "it is unlikely to occur in drinking waters".

The concentrations of beryllium in potable waters are generally very low, with Lee and Helsel (2005) recently finding that over 95 per cent of waters from aquifers in the USA used to supply potable waters contained 0.03 µg/L (the detection limit) or less. The authors found occasional values of up to 7µg/L. The study of British aquifers by Edmunds and Trafford (1993) revealed a highest concentration of 1.02µg/L beryllium. It therefore seems very unlikely that drinking water represents a major pathway for beryllium into the human body.

An additional health effect of beryllium ingestion that has been demonstrated in animals is beryllium rickets in rats fed 35-840 mg/kg day of beryllium in the form of beryllium carbonate (Guyatt *et al*., 1933; Jacobson, 1933; Kay and Skill, 1934). This health effect is not due directly to beryllium, but is due to the binding of phosphorus in the gut by beryllium, so preventing its absorption (ATSDR, 2002).

A compilation of beryllium concentrations in foodstuffs derived from literature values by ATSDR (2002) reveals a broad range of concentrations. Concentrations as high as 2200 µg/kg were found to occur in kidney beans, 109 µg/kg in garden peas and 112 µg/kg in crisp bread, these being the highest values listed. Fruits and fruit juices have been found to contain beryllium at levels up to 74.9 µg/L. However, no information is given concerning the soils in which the vegetables and plants were grown, so it is not possible to suggest any preferential enrichment by various plants etc. In addition, given the range of values recorded by different authors using different analytical methods, it would seem unsafe to suggest any preferential uptake by any group of plants or vegetables. As stated earlier, a very high percentage of ingested beryllium is excreted by the human body and hence even if high-beryllium containing foods are ingested, it is unlikely that there will be any serious health effect on humans.

The overwhelming majority of the existing literature strongly indicates that intake of beryllium orally or through dermal contact has no ill health effects on humans. However, it should be pointed out that Deubner *et al.* (2001b) have suggested that contributions of oral and dermal industrial exposure to beryllium need to be considered when assessing overall beryllium exposure. Similarly Tinkle *et al*. (2003a) suggest that beryllium-containing particles penetrating the skin could be a pathway into the body.

One use of beryllium that results in direct human contact is its use in dentistry for fabricating bridges, crowns and plates. Use of these has resulted in allergic skin reactions in the mouth and gingivitis.

2 Introduction

As stated earlier, beryllium toxicity is essentially limited to industrial exposure and the pathway into the body is almost exclusively via inhalation. Several compounds of beryllium are soluble and inhalation of such compounds has been shown to cause health problems. However, it is the inhalation of materials that contain insoluble beryllium that seems to cause the most serious health problems. The major beryllium-containing materials used in industry are beryllium metal, beryllium oxide and various beryllium alloys, the most important being copper-beryllium alloy. Cases of berylliosis have been shown to occur in workers handling all of these beryllium-containing materials (Maier, 2002).

However, it seems likely that not all forms of beryllium-containing materials pose the same health risk. Wegner *et al.* (2000) studied beryl gemstone cutters and found little in the way of adverse health effects even though there was high atmospheric beryllium, with one factory having over 2 µg/m. Similarly Deubner *et al*. (2001a) found that workers at a beryllium mine where bertrandite is extracted experienced no respiratory health problems. In addition, the authors suggest that in the absence of beryllium oxide particles, exposure to ore dusts of beryl and bertrandite or beryllium salts carries a lower risk of respiratory health effects. In another study, Kreiss *et al*. (1993) found higher rates of chronic beryllium disease in workers in the beryllium ceramics industry where beryllium oxide is the essential component. Paustenbach *et al.* (2001) also suggest that beryllium oxide is the most hazardous of the industrial beryllium sources.

All cases of beryllium disease have been entered in a national Beryllium Case Registry in both the USA and the U.K.

2.1 Toxicokinetics

2.1.1 Absorption

Inhalation is by far the major pathway into the body, with beryllium subsequently absorbed through the lungs. However, in the ATSDR (2002) review it is suggested that there is insufficient information to determine rates or degree of absorption. The ATSDR reports studies where elevated serum levels of beryllium (in excess of three times the concentration in non-exposed individuals) have been found in workers within a day of exposure to beryllium metal dust. Within two to eight weeks, serum levels of beryllium returned to normal. In a separate study, men exposed to the soluble salt beryllium chloride showed increased concentrations of beryllium in serum of four times those of non-exposed individuals for ten days.

Studies on animals have generally used soluble beryllium salts. Rats and guinea pigs inhaling beryllium nitrate were found to have elevated beryllium concentrations in blood less than a day after exposure (ATSDR, 2002).

While very soluble beryllium salts will exert an immediate effect on the respiratory system, sparingly soluble substances will generally not do so. When insoluble or low-solubility beryllium-containing particles are inhaled most are thought to be removed by mucocilliary transport into the gastrointestinal tract, however, according to Maier, (2002) some is transferred to the regional lymph nodes and pulmonary intersitium

where it may be retained for many years after exposure. This retained beryllium is slowly solubilised and is the source of adverse health effects. It is generally believed that there are two phases of beryllium removal from lungs, a rapid phase and slow phase. The WHO/IPCS (2001) review quotes data from studies on rats, which suggests that the half-life for rapid removal is about 1-60 days, while the half-life for the slow phase is in the range of 0.6-2.3 years. The WHO/IPCS (2001) review suggests the rapid phase of beryllium removal corresponds to soluble beryllium while the slow phase corresponds to insoluble and sparingly soluble beryllium-containing substances. The ATSDR (2002), quoting data from Rhoads and Sanders (1985) for sparingly soluble beryllium oxide deposition in rat lungs, also describes its removal as biphasic, with the rapid phase clearing 30 per cent of the compound, having a half-life of 2.5 days, and the slow phase removal of the remaining 70 per cent having a half-life of 833 days.

Several beryllium compounds, such as the salts beryllium fluoride, beryllium chloride and beryllium sulphate, are soluble. Beryllium metal is insoluble, while beryllium oxide is sparingly soluble. While inhalation of any gaseous, or particulates of, beryllium metal, beryllium-containing alloys, beryllium oxide or beryllium salts poses a risk of respiratory health effects, it has been shown that the degree of solubility of the inhaled beryllium source strongly influences the degree of the health effects and the onset of berylliosis. Insoluble beryllium forms are retained in the lung for longer periods of time than soluble beryllium forms and pose a greater risk for development of CBD (ASTDR, 2002). In a study of CBD and beryllium sensitisation in a cohort of former workers who had been exposed to beryllium, Rosenman *et al.* (2005) found that sensitised individuals with no CBD had been exposed to higher concentrations of soluble beryllium than those with CBD. The authors presume that the difference is due to soluble beryllium being removed from the body relatively rapidly and the body burden of beryllium therefore being lower.

Thus inhalation of beryllium metal and beryllium containing alloys, being insoluble, is a serious health hazard. Some workers (for example, see Kreiss *et al*., 1993; Paustenbach *et al.,* 2001) have suggested that beryllium oxide is the form of beryllium most detrimental to human health. However, it seems likely that different forms of beryllium oxide can cause differing degrees of health impact. Thus the temperature at which beryllium oxide is calcined determines its solubility, which decreases with increasing temperature. It has been found in animal experiments that beryllium oxide calcined at a temperature of 500^{o}C was removed from the lung more rapidly than beryllium oxide calcined at 1000^{o}C (ASTDR, 2002). This has led Maier (2002) to suggest that beryllium oxide calcined at the lower temperature is less immunogenic than beryllium oxide calcined at higher temperatures.

Another factor suggested as being an important consideration for the long-term health effects of beryllium exposure is the size of particles inhaled. Thus Kolanz *et al.* (2001) and Stefaniak *et al*. (2003) have strongly suggested that it is particle size and total surface area of the particles that governs the degree of health effect. Kent *et al.* (2001) found a dose response between beryllium sensitisation and alveolar deposited beryllium-containing particles of <10 µm. However, in a very recent study, Rosenman *et al.* (2005) found that workers who had been exposed to beryllium-containing fumes, which they suggested would have contained the finest particles, did not show increased incidence of CBD.

2.1.2 Distribution

Inhaled beryllium can become distributed around the human body following absorption. From the lung it is transferred to blood, and so can move around the body where it is

transferred to tracheal lymph nodes and ultimately the skeleton, which is the main site for storage (WHO/IPCS, 2001). Small amounts are transferred to the liver and other organs (ASTDR, 2002). It has been shown that beryllium can be bound to the iron-transport protein ferritin and this could influence its transport in the body (Sawyer *et al*., 2002). Sawyer *et al.* (2004) have found that beryllium forms covalent bonds with phosphate in ferritin and is consequently strongly bound. These authors suggest that ferritin-bound beryllium can be transported to the lung where it can be taken up by lung macrophages so promoting beryllium-antigen formation. Sawyer *et al.* (2004) describe ferritin-bound beryllium as a "Trojan Horse" and hypothesise that it releases beryllium to the lung, triggering antigen formation over a long period and that this action is the cause of CBD onset many years after exposure.

It has been suggested on the basis of modelling using the chemical thermodynamic speciation code MINTEQA2 that beryllium inside cells can be several times more soluble than beryllium outside cells in plasma or interstitial fluid (Sutton and Burastero, 2003). In addition, beryllium can form complexes with biomolecules, it being a potential target of adenosine phosphates. It has been shown to form strong complexes with both ATP and ADP (Boukhalfa *et al.,* 2004). Sawyer *et al*. (2002), in their review of CBD, quote literature data suggesting that beryllium interacts with nuclear acidic proteins, G proteins and protein kinases and interferes with protein phosphorylation. In addition, beryllium inhibits the activities of regulatory enzymes.

With regard to animals, a study by Zorn *et al*. (1977) on rats exposed to radioactively labelled beryllium in the form of soluble salts from inhalation, suggests that immediately after initial exposure, 60 per cent of the radioactivity was located in the lungs, 13.5 per cent in the skeleton, 9.5 per cent in muscle, 5 per cent in the blood, 1.5 per cent in the kidney, 1.4 per cent in the brain with smaller quantities found in the liver, heart and spleen. Excreta contained 10 per cent of the total body radioactivity. Measurements after 408 hours' exposure suggested that 92 per cent of the total body radioactivity was in excreta with 6.8 per cent in the skeleton.

It is suggested in the WHO/IPCS (2001) review that a significant part of inhaled beryllium is transferred to bone and is stored there, the half-life of this storage being 450 days.

2.1.3 Metabolism

The ATSDR (2002) suggests that beryllium and its compounds are not biotransformed, however it is likely that soluble salts can in part be converted to insoluble forms in the lung.

2.1.4 Elimination

It is apparent that ingested beryllium is almost totally (at least 99%) excreted via faeces. It is generally thought that beryllium in the gastrointestinal tract precipitates as a sparingly soluble phosphate and so is excreted (WHO/IPCMS, 2001). Sutton and Burastero (2003), on the basis of modelling using the chemical thermodynamic speciation code MINTEQA2, have confirmed that any beryllium in the gastrointestinal tract will occur as beryllium phosphate. With regard to inhaled beryllium, subjects exposed to elevated levels of atmospheric beryllium in the workplace have higher concentrations in urine than subjects not exposed (ATSDR, 2002; Apostoli and

Schaller, 2001). Much inhaled low-solubility beryllium-containing substances would be expected to be removed from the lung by mucocilliary action and transferred to the gastrointestinal tract, from where it will be excreted. However, some beryllium is thought to remain in the lung for several years where it will slowly dissolve (Maier, 2002; also see section 2.1.1, above), move into the bloodstream and subsequently be excreted. Beryllium inhalation can cause lung damage and consequently decrease the ability of the lung to clear the particles (ASTDR, 2002).

In animal experiments, it has been found that the major excretion route for inhaled beryllium is governed by its form. Thus for soluble beryllium, and that solubilised in the lung, the major route of excretion is via urine. For insoluble and so unabsorbed beryllium, the major excretion route is via faeces (WHO/IPCS, 2001). It has been demonstrated that the half-life of inhaled beryllium in animals varies greatly, with much of the variation thought to be due to the form of the inhaled beryllium (ATSDR, 2002).

3 Acute effects

Acute beryllium disease, or acute beryllium pulmonary syndrome, was first described by Van Ordstrand *et al*. (1943). It has been suggested that this disease is caused by short-term respiratory exposure to high concentrations of soluble beryllium compounds. In a 1940s study, Eisenbud *et al*. (1948) suggests that all affected workers were exposed to >0.1 mg/m^3 beryllium generally as beryllium sulphate or fluoride. Symptoms in exposed workers were generally similar to pneumonia, with reddening and swelling of lungs. It is apparent that lung damage healed fairly quickly when the affected workers were removed from exposure to beryllium (ATSDR, 2002). However, the American College of Chest Physicians (1965) reported that 10 fatalities occurred in 93 workers affected by acute beryllium pneumonitis in two beryllium refineries in the pre-1950s.

Experiments with animals subjected to acute beryllium inhalation in the form of soluble salts results in a relatively high death rate. However, exposure doses are generally very high. Animals exposed to beryllium oxide showed lower death rates, due probably to the lower solubility of the oxide (ATSDR, 2002). In studies reported in the ATSDR (2002), rats inhaling soluble beryllium sulphate so that concentrations of beryllium were 4.3 mg/m^3 or 2.59 mg/m^3, all died within 14 and 18 days, respectively. However, in a separate study of rats exposed to 31 mg/m^3 beryllium as beryllium oxide, 10 per cent died. Of 74 rats exposed for 50 minutes to aerosolic beryllium metal at a concentration of 0.8 mg/m^3, 20 died 12-15 days after exposure. It seems likely that rats and monkeys are more sensitive to acute beryllium exposure than hamsters and guinea pigs (ATSDR, 2002).

The occurrence of acute beryllium disease is currently very rare since the realisation of the problems of beryllium toxicity in the workplace in the 1940s. Only odd cases resulting from accidental exposure have been recorded in more recent times (Eisenbud and Lisson, 1983).

4 Sub-chronic effects and beryllium sensitisation

Newman *et al*. (1989) suggested a classification of chronic beryllium disease into three stages, beryllium sensitisation, subclinical chronic beryllium disease, with no clinical or histopathological manifestations of the disease, and finally, clinical chronic beryllium disease. Sensitisation of humans results from an immune reaction to inhaled, and to some extent dermal exposure to, beryllium-containing materials. Beryllium hypersensitivity results in sensitisation and proliferation of T-lymphocytes and is assessed using the beryllium-stimulated lymphocyte proliferation test (BeLPT) on blood (Bargon *et al*., 1986; Kreiss *et al*., 1989). Many individuals showing positive test results, therefore being beryllium sensitive, do not have clinical symptoms of CBD. Subsequently, individuals showing beryllium sensitisation often develop chronic beryllium disease, but it is a matter of debate whether all beryllium-sensitised individuals develop the disease.

It has been shown that beryllium sensitisation is not dependent on degree of exposure (Willis and Florig, 2002). Furthermore, Viet *et al*. (2000) suggested that sensitisation can be caused by only brief exposure to beryllium-containing materials. Recently, Rosenman *et al*. (2005), in a study of a cohort of former workers in a beryllium processing facility in Pennsylvania, which closed in 1978, found that sensitised individuals with no recognisable symptoms of CBD had been subject to shorter duration periods of beryllium exposure and had been exposed to higher concentrations of soluble beryllium than those with CBD.

A relatively small percentage of people are genetically predisposed to develop hypersensitivity when exposed to beryllium-containing materials. Estimates of the percentage of individuals who are so predisposed varies widely, with most workers suggesting that in any exposed population, about 1-12 per cent will be susceptible to beryllium sensitisation. However, a very recently published study on CBD and sensitisation in former beryllium plant workers found that 14.6 per cent had CBD or were sensitised. In addition, due to perceived problems with the BeLPT, McCanlies *et al.* (2003) suggested that estimates of percentages of exposed populations suffering beryllium sensitisation are likely to be underestimates. The degree of exposure and the type of exposure, which form of beryllium, particle size and so on, are also important constraints on development of beryllium sensitivity.

It has been suggested that a major factor in developing beryllium sensitivity and subsequent disease involves a genetic component. Animal studies such as those on mice (Huang *et al*., 1992) and guinea pigs (Barna *et al*., 1984) first suggested a genetic component. Sensitivity was also known to occur within family groups. Subsequently, work by Richeldi *et al*. (1993, 1997), Wang *et al*. (1999) and Maier *et al.* (2002), amongst others, showed that in humans a genetic component is very likely to be involved in beryllium sensitisation and subsequent CBD.

Tinkle *et al.* (2003b) state that beryllium sensitisation is a cell-mediated immune response where a leukocyte antigen is presented to a T cell. T cell activation causes cloning and generation of beryllium specific memory T-cells. The cellular process is said by Tinkle *et al* (2003b) to be driven by proinflammatory cytokines. The leukocyte antigen, HLA-DPB1 Glu^{69} has been found in a high percentage of sensitised individuals

and in those suffering from CBD (Richeldi *et al*., 1997, Saltini *et al*., 2001; Amicosante *et al*., 2002; McCanlies *et al*., 2003, 2004).

While agreeing that HLA-DPB1 Glu^{69} is associated with beryllium sensitivity reaction, Saltini *et al*. (2001) suggest that the gene tumour necrosis factor TNF-α is also implicated in both sensitisation and CBD. Furthermore, these authors found that HLA – DRArg74 is associated with sensitisation but not CBD. Amicosante *et al*. (2002) also point out that the gene tumour necrosis factor, TNF-α, increases CBD risk, while Dotti *et al*. (2004) conclude that TNF-α may play a central role in beryllium hypersensitivity.

It has also been suggested that beryllium can cause an allergic reaction on skin. Sawyer *et al*. (2002) are of the opinion that dermatitis caused by beryllium contact is in fact a beryllium sensitive reaction. The same authors mention that dental bridges containing beryllium can cause beryllium sensitisation in the mouth. Tinkle *et al*. (2003a) showed that beryllium oxide caused sensitisation in mice due to particles penetrating the skin. These researchers postulate that skin sensitisation of workers exposed to beryllium-containing materials could also be important and could be an added factor to respiratory exposure for body load of beryllium, with the consequent effect of sensitisation and possibly development of CBD being linked to the total exposure from both routes.

McCanlies *et al*. (2003) have suggested that the genetic information regarding beryllium sensitisation and CBD could be used to test individuals for susceptibility with regard to potential employment.

5 Chronic effects

Hardy and Tabershaw (1946) were the first to identify beryllium inhalation as a cause of a chronic lung disease occurring in workers involved in the manufacture of fluorescent lights. This disease was subsequently termed Chronic Beryllium Disease (CBD), and is also known as berylliosis. CBD is a disease which causes inflammation of the lung due to the formation of alveolar granulomas. Symptoms of the disease can include coughing, chest tightness, shortness of breath, tiredness and night sweats. Other acute systemic effects in cases of severe CBD include damage to the right ventricle of the heart, liver necrosis, kidney stones and loss of weight. These effects have been suggested to be secondary to CBD. CBD is incurable; mortality rates have been variously quoted, with Williams (1994) suggesting that 36 per cent of those registered in the UK Beryllium Case Registry had died of respiratory failure as of 1993. In the USA, some 62 per cent of those included in the Beryllium Case Registry had died of respiratory diseases (Eisenbud and Lisson, 1983). However, McCanlies *et al*. (2003) point out that the figures used are likely to be inaccurate, as prior to the advent of the beryllium-stimulated lymphocyte proliferation test, it was difficult to distinguish CBD from other granulomatous lung diseases. In addition, McCanlies *et al*. (2003) suggest that some CBD patients would have been excluded as they were not registered or because their GP did not recognise CBD.

All of the information on CBD derives from workplace exposure, exposure of families of workers using beryllium-containing substances, and populations living in the vicinity of plants manufacturing or utilising beryllium-containing materials. As the biggest producer and user of beryllium is the USA, most of the studies on beryllium exposure derive from that country.

No animal models have been found for CBD (ASTDR, 2002), with the data on the disease deriving essentially from studies of human exposure.

From early studies of CBD it soon became apparent that within cohorts of beryllium workers a relatively small percentage became affected. One reason for the low percentage of workers affected was obviously individual exposure. However, even where it might be anticipated that various cohorts would have suffered similar exposure levels, less than a fifth of the individuals developed CBD. In addition, it was found that there was frequently a long latency of up to 40 years between exposure and development of CBD symptoms.

Rossman (2001) charts the history of research into the pathogenesis of CBD and notes that it was first suggested that the disease was due to a hypersensitivity reaction of the lung to beryllium in the 1950s (Sterner and Eisenbud, 1951). Proof that CBD was due to hypersensitivity was obtained in the 1980s by Epstein *et al*. (1982) when they found increased lymphocytes, which were predominantly T-cells, the cause of granuloma, in patients with CBD. These T-lymphocytes are beryllium specific, showing that beryllium causes a cell-mediated immune response with the T-lymphocytes congregating around beryllium particles so causing granulomas. Beryllium sensitive individuals also showed an allergic skin reaction to beryllium-containing patches applied to the skin surface.

As stated in the previous section, beryllium sensitised individuals can be identified by blood tests using the beryllium lymphocyte proliferation test (BeLPT). Using this test several studies have been performed on beryllium exposed workers to ascertain the numbers affected by sensitisation. A summary of the results obtained in some of these studies is listed in Table 2. It is apparent from the literature data that about 1.5 – 15 per cent of exposed individuals develop beryllium sensitisation, with the remaining workers showing no sign of any health problems. McCanlies *et al.* (2003) suggest that previous

results for beryllium sensitisation have underestimated the number of affected individuals, possibly due to problems of reproducibility of BeLPT results. However, from the data available it seems probable that less than 20 per cent are likely to have become sensitised. It is perhaps significant that the most recent study by Rosenman *et al.* (2005), on sensitisation and CBD rates in a cohort of former workers from a beryllium producing plant which closed in 1978, showed a sensitisation rate of 14.6 per cent, the highest recorded in any such studies (see table 1). The fact that such a relatively low percentage of exposed workers develop sensitivity to beryllium has been suggested to be due to two factors, a genetic component and the degree of exposure to beryllium.

Table 2. Beryllium sensitisation and CBD occurrence in beryllium exposed workers in the USA

Source	Site	No. of subjects	Overall % with Be sensitisation	% with sensitisation and CBD
Kreiss *et al*. (1997)	Beryllium metal, alloy, and oxide production plant	627	9.4	4.6
Stange *et al*. (1996)	Rocky Flats nucl. weapons facility, Denver,CO.	4,397	1.8	0.66
Stange *et al*. (2001)	Rocky Flats nucl. weapons facility, Denver,CO.	5,173	4.54	1.57
Kreiss *et al*. (1996)	Beryllium ceramics plant	136	5.9	5.7
Henneberger *et al*. (2001)	Beryllium ceramics plant	151	9.9	5.3
Rosenman *et al.* (2005)	Beryllium production plant eastern Pennsylvania	577	14.6	7.6

Notes: The Kreiss *et al*. (1997) survey was based on current workers at the plant. The Kreiss *et al.* (1996) cohort was composed of current workers from all occupations in the plant. The Henneberger *et al.* (2001) study was a follow up to the Kreiss *et al.* (1996) study, 76 workers included in the Kreiss study were re-examined with the rest being new workers. Stange *et al*. (1996) examined current and former workers involved in all occupations at the plant. Stange *et al*. (2001) examined current and former workers and the cohort includes 2,891 individuals from the earlier survey who were re-examined. The Rosenman *et al*. (2005) study was conducted on previous workers from a beryllium facility that closed in 1978.

The second major factor involved in beryllium sensitisation and CBD is environmental, with individuals exposed to higher beryllium levels likely to be more affected. Henneberger *et al*. (2001) found that there was a higher incidence of CBD in long-term workers than short-term workers in a beryllium ceramics factory. These authors suggested that this may either reflect a longer period of exposure or could be due to the latency period of the disease. It has been noted by several authors that there is no obvious dose-response for total beryllium exposure and sensitisation and CBD. However, it has been shown by Kent *et al*. (2001) that a dose response was apparent between beryllium sensitisation and CBD, when only considering alveolar-deposited beryllium-containing particles of <10 µm. Stefaniak *et al*. (2003) also suggest that total surface area of the beryllium containing substance is a better measure of exposure.

The occupation of the individuals within the beryllium exposure site is thought to strongly influence the degree of exposure, with Martyny *et al*. (2000) finding that machinists were at greater risk, being exposed to a large percentage of particles of <10 µm. The survey of workers and former workers at the Rocky Flats plant by Stange *et al*. (2001) found that of 201 beryllium machinists, 8.46 per cent had CBD and a further 3.48 per cent were beryllium sensitised, compared to an overall rate in the total cohort (5,173) of 1.57 per cent with CBD and 2.98 per cent with beryllium sensitivity. Kreiss *et al*. (1996), in their study of a cohort working with beryllium oxide-based ceramics, also report that machinists had a higher incidence of sensitisation and CBD at 14.7 per cent, compared to 1.2 per cent of other workers. However, it has been found that individuals with minimal exposure, such as secretaries employed in plants where beryllium is manufactured or processed, also develop sensitisation (Maier, 2002). Stange *et al*. (2001) found that of 2,254 administrative workers, 1.29 per cent had CBD and a further 3.06 per cent were sensitised. Rosenman *et al*. (2005) also note in their study of a cohort of former workers in a beryllium processing facility in Pennsylvania that closed in 1978, that non-production workers had CBD and report that 13 cases of sensitisation occurred in clerical and office personnel.

As outlined in Section 2, the chemical form of beryllium involved in the exposure is also of importance. Thus beryllium ore minerals such as beryl and bertrandite have been shown to pose minimal risk. It is thought that the degree of solubility of the inhaled particles is of major importance, with less soluble substances more problematic than soluble ones. The insoluble forms of beryllium, the metal, its alloys and beryllium oxide have been found to be the major sources of sensitisation and the development of CBD. However, some researchers (such as Kreiss *et al*., 1993; Paustenbach *et al*., 2001) have suggested that of these, beryllium oxide causes the greatest problem.

However, beryllium oxide produced at higher temperatures is thought to exert a greater affect than the same substance produced at lower temperatures, possibly due to the higher temperature oxide being less soluble than that produced at lower temperature (Maier, 2002). Rosenman *et al*. (2005) report that sensitised individuals with no recognisable symptoms of CBD had been subject to shorter periods of beryllium exposure and had been exposed to higher concentrations of soluble beryllium than those with CBD.

The time lag from exposure and sensitisation to development of CBD can be anything from a few months to decades. Based on a review of the literature, McCanlies *et al*., (2003) suggest that 36-100 per cent of sensitised individuals show signs of CBD. However, the authors also point out that the initial stages of CBD could be asymptomatic. Maier (2002) suggests that of individuals who develop sensitisation, 10 per cent each year progress to CBD. However, it is by no means certain that all sensitised individuals will progress to the disease (Maier, 2002; McCanlies *et al*., 2003). In a recent publication, Newman *et al*. (2005) found that about 50 per cent of beryllium sensitised individuals have CBD when initially assessed. These researchers went on to assess a cohort of beryllium sensitised individuals every two years after initial diagnosis. The results show that the rate of progression from sensitisation to CBD is 6-8 per cent per year with 31 per cent of individuals who originally showed no symptoms of CBD progressing to the disease during the duration of the study (average 4.8 years, range 1.7-11.6 years). Of the sensitised individuals, 69 per cent remained free of CBD after the duration period of the study. Newman *et al*. (2005) point out that individuals who had worked as machinists were more likely to progress to CBD than any other workers, suggesting that rate of progression may be influenced by beryllium loading of the lungs. Newman *et al.* (2005) further indicate that the time from first

exposure to development of CBD ranged from 3.5 to 44.5 years, although there is no information as to when sensitisation occurred.

Rosenman *et al.* (2005), in their study of sensitisation and CBD in a cohort of previously employed beryllium workers, found that of the 14.6 per cent of individuals who were sensitised, over half had CBD (7.6 per cent of whole cohort). This relatively high incidence of CBD compared to other studies was suggested by the authors as reflecting the fact that other studies had mainly surveyed currently employed individuals, while this study was conducted in former workers from a plant that closed in 1978. The authors suggest that the high rate of CBD could be due to the longer latency period from last exposure. In a study of former workers in a beryllium ceramics facility, Kreiss *et al*. (1993) found that all sensitised individuals (1.6 per cent of 505 workers) had CBD. In the Rosenman *et al.* (2005) survey, only just over half of sensitised individuals were found to have CBD. A comparison of the results of the Kreiss *et al.* (1993) study with their own has led Rosenman *et al.* (2005) to suggest that latency alone cannot explain the results. It seems probable that degree of exposure, probably to very fine particles, is implicated.

It has also been suggested that progression from sensitisation to CBD might involve a genetic factor (Saltini *et al.,* 2001; Maier *et al.,* 2003).

While respiratory exposure to beryllium has been regarded as the almost exclusive pathway into the human body and, therefore, the major cause of beryllium sensitisation and subsequently CBD, it has also been proposed that exposure of skin to beryllium could be an additional pathway into the body. Tinkle *et al*. (2003a) point out that industrial practices for handling beryllium in modern industry have markedly reduced opportunities for beryllium inhalation. Despite this, it is apparent that rates of sensitisation and CBD have not declined as much as anticipated. Tinkle *et al.* (2003a) showed that beryllium oxide caused sensitisation in mice due to particles penetrating the skin, and suggest that the lack of marked decrease in sensitisation and CBD in workers exposed to beryllium could be due to beryllium-containing particles penetrating the skin and so causing sensitisation. Thus skin absorption of beryllium-containing particles could represent an alternative pathway into the human body. Deubner *et al*. (2001b) also suggest that dermal exposure and even ingestion of beryllium particles could combine to increase absorption of beryllium and contribute to sensitisation.

With regard to the dermal effects of beryllium, as outlined above there can be an allergic reaction resulting in the formation of granulomas very like those found in the lungs of CBD sufferers (ATSDR, 2002). Where skin has been penetrated by beryllium or beryllium oxide, ulcerative lesions form with similar structure to granulomas (Sawyer *et al.,* 2002). Another dermal effect reported is contact dermatitis; this has been shown to occur in workers exposed to airborne beryllium salts (ATSDR, 2002). Workers affected by contact dermatitis generally recover when removed from exposure, however Sawyer *et al*. (2002) suggest that the dermatitis caused by beryllium is a sensitivity reaction. It has been reported that some individuals fitted with dental bridges containing beryllium suffer beryllium sensitisation and gingivitis (Sawyer *et al*., 2002).

6 Genotoxicity

Laboratory experiments into the genotoxicity of beryllium have been somewhat contradictory (Gorden and Bowser, 2003). Mutation and chromosome aberration assays on bacteria have generally given negative results. Few studies have been conducted on mammalian cells, though those that have have given mixed results. Some studies on mammalian cells *in vitro* have indicated that beryllium salts have caused sister chromatid exchange and possible chromosome aberration (IARC, 1993), however Anderson (1983), did not find any sister chromatid exchange on beryllium sulphate treatment of human lymphocytes. IARC (1993) reports on one study utilising beryllium chloride where gene mutation occurred in mammalian cells. In addition, in another study with cultured mammalian cells, low temperature beryllium oxide was found to cause breaks in single strand DNA. IARC (1993) also notes that in an *in vivo* study on mice subjected to beryllium sulphate, no micronuclei were induced in bone marrow.

Gorden and Bowser (2003) suggest that at least some of the contradictory evidence is due to the use and preparation of the different forms of beryllium used in the experimental work.

However, Gorden and Bowser (2003) do suggest that soluble beryllium compounds are weakly mutagenic in mammalian cells. The authors also suggest that there is strong evidence that beryllium can cause malignancy in mammalian cells.

7 Carcinogenicity

Beryllium has been classed as a Group 1 human carcinogen by the International Agency for Research on Cancer (IARC, 1993). The US Department of Health and Human Services, (US DHHS, 2003) also lists beryllium and its compounds as known human carcinogens. However, the US Environmental Protection Agency lists beryllium in group B1, making it only a 'probable' human carcinogen (US EPA, 1998).

The first studies to suggest the carcinogenicity of beryllium-containing materials on humans were retrospective mortality studies performed on individuals who had worked in beryllium processing facilities in Ohio and Pennsylvania, USA. These studies carried out in the period from the late 1960s through to the 1980s suggested increased incidence of lung cancer deaths in beryllium workers (see references in ATSDR, 2002). These original works have been strongly criticised for their serious limitations, and it has been suggested that the findings are flawed (USEPA, 1998; ATSDR, 2002). The criticisms that have been levelled at these early works, as listed in the ATSDR (2002) review, have included: not taking sufficient account of the smoking habits of the cohort; inclusion of non-production workers; no account being taken of age differences and in some cases a lack of analysis of the effects of latency of the disease.

A later study of retrospective mortality conducted by Ward *et al*. (1992) on workers from seven beryllium processing plants in Pennsylvania and Ohio, found increased rates of lung cancer in two of the plants. Both of these plants had opened prior to 1950, when there was little limitation on beryllium concentrations in the workplace atmosphere. In four plants opened after 1950, no increased lung cancer rates were found. Higher rates of lung cancer were generally found in those employed for at least a year, with a 30-year latency period. This study has also been subject to criticisms, including: a lack of availability of beryllium exposure levels; no job histories for the cohort and the inclusion of non-production workers; limitations in the account taken of the confounding effects of cigarette smoking; and the inclusion of a large number of workers employed for relatively short periods of time (almost 75 per cent); and no account taken of whether these workers had been exposed to other carcinogens in previous employments. While this study has been criticised, it is generally held to be the first fairly convincing evidence of increased lung cancer rates in workers exposed to beryllium. The data from observed and expected lung cancer rates in workers from beryllium plants studied by Ward *et al*. (1992) are summarised in table 3.

The most convincing evidence of a causative association of inhaled beryllium and lung cancer was provided by the study of Sanderson *et al*. (2001). These workers found a general correlation with occupation within a facility, and hence estimated beryllium exposure and lung cancer cases when a lag time of 10 to 20 years was considered. However, the methodology of this work has subsequently been criticised by Deubner *et al.* (2001a).

An additional study, which adds weight to the case for beryllium inhalation being a factor in lung cancer, was the epidemiological study of Steenland and Ward (1991).

Of 689 patients who had suffered from beryllium disease, 34 per cent with the acute disease and 64 per cent with CBD, 70 deaths resulted from cancer with 28 of these being lung cancer. Lung cancer deaths were more pronounced in the acute beryllium disease sufferers. As acute beryllium disease generally reflects a very high dose of beryllium, it has been suggested that lung cancers are more likely to be caused by such high doses.

Table 3. Lung cancer rates in beryllium plants in Pennsylvania and Ohio, based on data from Ward *et al.* (1992), with adjustment for smoking. Modified from WHO/IPCMS (2001).

Plant	Lung cancer cases found	Lung cancer cases expected
Lorain, Ohio*	57	38.2
Reading, Pennsylvania*	120	109.8
All 4 other plants**	103	102.8
Total	280	250.8

Notes: Opened prior to 1950; ** Opened after 1950

Animal experiments have shown that with high doses of inhaled beryllium salts, rats and monkeys develop lung cancers. Beryllium metal in high doses caused 64 per cent of an exposed group of rats to develop lung cancer and rats exposed to beryllium oxide also developed tumours. While exposure to beryl ore caused cancers in rats, both rats and hamsters exposed to bertrandite ore were found not to develop lung cancers. In general, animal experiments have been criticised for using large doses (ATSDR, 2002), however, they seem to confirm the carcinogenicity of beryllium.

The US EPA (1998) has estimated the health risk from lung cancer due to continuous exposure to beryllium to be 2.4×10^{-3} per ug/m^3. The agency further estimates that an individual exposed to 0.0004 ug/m^3 beryllium for the whole of his or her life would theoretically have an increased cancer risk of one in 10^6. Using the US EPA figures, Willis and Florig (2002) suggest that for an individual exposed to 2 µg/m^3 of beryllium for a 2,000-hour work year and a 40-year working life, the lifetime lung cancer risk would be 0.0005, which is an order of magnitude smaller than the risk for CBD. These authors further suggest that the lifetime lung cancer mortality rate for an individual living in close proximity to a beryllium-emitting industrial site in compliance with the US EPA limits for concentrations around beryllium plants (0.01 ug/m^3) will be approximately 2×10^{-5}. This is considerably lower than the CBD risk for a genetically susceptible individual exposed to the same limit, which Willis and Florig (2002) have estimated to be 0.002. McCanlies *et al*. (2003) also suggest that the risk of CBD in sensitised individuals dwarfs that of lung cancer.

8 Reproductive and developmental toxicity

No studies are available regarding reproductive or development toxicity following beryllium inhalation in humans or animals (ATSDR, 2002). A study on male and female rats intratracheally injected with beryllium oxide prior to mating, resulted in no consistent effect on reproduction (Clary *et al*., 1975). Some limited effects were observed on the development of rat foetuses when pregnant females were intratracheally injected with beryllium chloride and beryllium oxide. There was some increase of foetal mortality and decrease of foetal body weight, and an increased percentage of internal abnormalities.

Bose (1973) noted that beryllium sulphate suppressed mitosis in embryos of snails, with early embryos suffering high mortality at 500 µg/mL. The mortality rate was reduced at 100 µg/mL. Slonim and Ray (1975) demonstrated that beryllium in the form of the sulphate salt was toxic to salamander embryos with beryllium, in concentrations of 10 mg/L and 100 mg/L in hard water resulting in zero and 100 per cent mortality, respectively. The mortality rates were significantly higher in soft water, with mortality rates of 22.5 per cent after 24 hours in 10 mg/L of beryllium (as sulphate) and 80 per cent after 96 hours, compared with 0 per cent mortality in hard water.

In a more recent study, Sharma *et al.* (2002) found that a single dose of 50 mg/kg of beryllium, as its nitrate salt, caused reduction of foetal and placental weights in rats. In addition several other effects were noted in embryos, including stunted growth and a change in sex ratios.

9 Other effects

According to the ATSDR (2002) review, data on the effects of beryllium on the cardiovascular system, blood, liver and kidneys of humans are fairly limited. The fairly brief account given here is based essentially on that given in the ASTDR (2002) review.

Cardiovascular effects: In some cases of severe CBD, post mortem examination has revealed hypertrophy of the right heart ventricle. It is suggested that this could be due to impaired lung function in the CBD sufferers. In animal experiments, few effects have been recorded in monkeys exposed to acute inhalation of soluble beryllium salts, but some heart enlargement was recorded. In dogs exposed to beryllium oxide or beryllium sulphate, some decreased arterial oxygen tension was observed. In general it seems likely that effects on the cardiovascular system are essentially related to the effects of beryllium on the lungs.

Haematological effects: In workers exposed to beryllium (including a CBD sufferer), few effects have been observed on blood chemistry, blood counts or erythrocyte sedimentation rate. Similarly, in animal experiments acute inhalation exposure has been shown to cause few effects. However, rabbits exposed to beryllium oxide at a concentration of 31 mg/m^3 beryllium for 10 days showed a slight decrease in erythrocyte counts. Experiments with rabbits exposed to very high concentrations of beryllium oxide over longer periods showed decreasing erythrocyte counts and a transient decrease of haemoglobin. Dogs similarly exposed showed similar effects, developing macrocytic anaemia. Similar effects also occurred in rats and rabbits exposed to soluble beryllium salts.

Hepatic effects: Few effects of beryllium inhalation exposure have been observed in humans. After an accidental leak of beryllium chloride dust, no observable effects were noted on the livers of 25 exposed. In a study of 17 workers exposed to beryllium in a fluorescent lamp factory, Hardy and Tabershaw (1946) note that post mortem examination revealed that one had liver necrosis. Few effects have been found in animals, except at lethal concentrations.

Renal effects: In workers suffering from CBD, 10 per cent were found to be suffering from kidney stones. It has also been noted that an excess of calcium in blood and urine frequently occurs in CBD sufferers, however, it has been pointed out that these effects cannot definitely be attributed to beryllium exposure. Ward *et al.* (1992), in his mortality study of workers at seven beryllium processing plants, found that there was an increased incidence of death due to renal failure, renal sclerosis and necrosis. In animals, beryllium inhalation has only been found to have minor effects on the renal system.

Endocrine effects: Examination of the adrenal glands of patients who died from CBD reveal marked effects. Similarly, in animal studies adrenal glands showed marked effects resulting from inhalation.

Body weight effects: Weight loss in workers suffering from acute beryllium disease and CBD have been reported in the literature. Weight loss, which can be severe, has been observed in animals exposed to acute to chronic inhalation of a variety of beryllium-containing materials.

10 Evaluations and recommendations by other organisations

The respiratory system has been shown to be the major pathway for beryllium into the human body. There is therefore an overriding importance to consider beryllium concentrations in ambient air when imposing regulations in industry and so on. Some organisations have produced mandatory or recommended safe concentrations for atmospheric beryllium, with ATSDR (2002) stating that at the time of the review, there was insufficient data to derive an MRL for beryllium. There has been considerable debate on concentrations that constitute safe occupational exposure limits (OEL) for beryllium. Following the identification of CBD in the 1940s, the first OEL was introduced by the U S Atomic Energy Commission in 1949 (Stokinger, 1966), when the eight-hour OEL for beryllium was established at 2.0 μg/m^3. This standard was based on the values used for other toxic metals such as cadmium, mercury and thallium rather than the incidence of CBD, but was subsequently widely adopted.

10.1 Literature values

It became clear that while the OEL of 2.0 μg/m^3 resulted in a decrease of beryllium exposure, it had not provided complete protection for workers and several researchers voiced concerns. Only a few attempts have been made to define a human LOAEL for beryllium and no suitable animal model has been identified. Most experiments with animals receiving respiratory sources of beryllium have involved large doses, and subsequently determined LOAELs have been very much higher than those found in studies on humans (US EPA, 1998; ATSDR, 2002). A small number of studies have identified a human LOAEL, some of which are listed in Table 4.

Table 4. LOAEL values from literature data in US EPA (1998) and ATSDR (2002)

Source of data	Beryllium source	LOAEL
Kreiss *et al*. (1996)	Ceramic manufacture from beryllium oxide	0.55 μg/m^3
Stange *et al*. (1996)	Rocky Flats nuclear weapons facility	1.04 μg/m^3
Cullen *et al*. (1987)	Precious metal refinery – beryllium oxide	0.52 μg/m^3
Cotes *et al*. (1983)*	Beryllium manufacturing plant – beryllium oxide	0.1 μg/m^3

Notes: *- based on a very limited study.

Studies have shown that there is a dose response between beryllium sensitisation and alveolar-deposited beryllium-containing particles of <10 µm (Kent *et al*., 2001), while there is generally no correlation between total atmospheric beryllium concentrations and sensitisation or CBD. Within a beryllium works environment, workers performing different tasks have variable exposure to fine particles, thus those involved in machining or grinding beryllium containing materials are subject to higher concentrations of fine particles (Martyny *et al.,* 2000). The original OEL was based on total atmospheric beryllium, and it has been strongly suggested that the OEL should take account of particle size and surface area (Kolanz *et al*., 2001; Stefaniak *et al*., 2003). Wambash and Tuggle (2000) used the Eisenbud *et al*. (1949) study to statistically suggest an OEL, which they derived to be 0.1µg/m^3. However, Eisenbud (1998), using the earlier Lorain data, derived an OEL of 0.2µg/m^3 as the lowest concentration protecting individuals from CBD.

10.1.1 U.S. Environmental Protection Agency

The study by Eisenbud *et al*. (1949) is the most complete study of non-occupationally exposed populations. In this study, centred around the Lorain processing plant in Ohio, USA, 10,000 residents were evaluated for CBD. In the initial study, 11 cases of CBD were identified along with three more in a follow-up study (Sterner and Eisenbud, 1951). Of all the cases, one was due to dust from contaminated work clothes, while the rest were due to exposure to atmospheric beryllium and all lived within ¾ of a mile (1.21 km) of the plant. It was apparent that a similar percentage of the local population were suffering from CBD to that found in workers from the beryllium plant. It was suggested that this could be due to finer beryllium-containing particles (mainly beryllium oxide) being transported from the factory. The atmospheric beryllium content was estimated to be 0.01 – 0.1 µg/m^3, which is suggested to be a NOAEL (US EPA, 1998). The study by Kreiss (1996) suggested a LOAEL of 0.55 µg/m^3 for workers exposed to beryllium. These studies were used as a basis for the US EPA standard.

Based on these two studies, the US EPA has calculated an Inhalation Reference Concentration, RfD, of 0.02 µg/m^3. From this value a beryllium concentration of 0.1 µg/m^3 was adopted as a NOAEL (US EPA, 1998).

The US EPA (1998) also list regulations from several US states, which are given in Table 5.

Table 5. Regulations for concentrations of beryllium in air for some US states from US EPA (1998)

State	Allowable concentration
North Carolina	4.1 x 10^{-3} µg/m^3
Vermont	1.3 x 10^{-3} µg/m^3
Washington	4.2 x 10^{-4} µg/m^3

10.1.2 American Committee of Governmental Industrial Hygienists (ACGIH)

The ACGIH (2001) document on beryllium recommended a Threshold Limit Value-Time Weighted Average (TLV-TWA) of 2.0 µg m^{-3} beryllium, to protect against operational exposure, but stated that the figure was under review. However, in a recent draft document (ACGIH, 2005) the proposed TLV-TWA is very significantly lower, at 0.02 µg m^{-3} as beryllium, inhalable particulate mass. This is in response to the many studies that have demonstrated that susceptible individuals are at risk at low atmospheric concentrations of beryllium, and that inhalation of fine particulate beryllium substantially increases the risk of developing sensitisation and CBD. However, the draft document is based on total inhalable beryllium, as it is suggested that sensitisation could be caused by deposition of beryllium along the respiratory tract.

In addition the ACGIH (2001) draft document accepts that beryllium is a skin sensitiser and as such could be a factor in development of sensitisation and development of CBD. It recommends that suitable precautions need to be taken to limit dermal exposure in the workplace.

10.1.3 Occupational Safety and Health Administration (OSHA)

The OSHA TWA limit for industrial exposure is still 2 µg m^{-3} (OSHA, 2005).

10.1.4 WHO/IPCMS, Concise International Chemical Assessment Document (CICAD)

No recommendations on exposure levels have been made.

10.2 Lung cancer

As outlined in Section 7, various studies have suggested that exposure to atmospheric beryllium can increase the risk of lung cancer. While the several studies covering this topic have been heavily criticised, it seems likely that such a risk does exist. The International Agency for Research on Cancer has classified beryllium as a Group 1, human carcinogen, defining it as a proven carcinogen (IARC, 1993). The US Department of Health and Human Services (US DHHS, 2003) also lists beryllium and its compounds as known human carcinogens.

On the basis of the existing data on lung cancer Willis and Florig (2002) suggest that an individual exposed to 2 µg/m^3 of beryllium for a 2,000-hour work year and a 40-year working life, the lifetime lung cancer risk would be 0.0005, which is an order of magnitude smaller than that of CBD, for sensitised individuals.

10.2.1 US Environmental Protection Agency

The US EPA (1998) lists beryllium as a Group B1, probable human carcinogen. The USEPA (1998) has estimated the health risk from lung cancer due to continuous exposure to beryllium to be 2.4 x 10^{-3} per ug/m^3. On this basis, the agency has further estimated that an individual inhaling in an atmosphere containing 0.0004 ug/m^3 beryllium throughout life, would theoretically have no more than a one in a million increased chance of lung cancer. An individual spending a lifetime inhaling atmosphere containing 0.04 ug/m^3 beryllium, would theoretically have no more than a one in a thousand increased chance of developing lung cancer.

10.2.2 American Committee of Governmental Industrial Hygienists

ACGIH (2001, 2005) lists beryllium as a confirmed carcinogen. However, the committee suggests (ACGIH, 2001) that as the carcinogenic potency of beryllium is low, exposure to beryllium below the TLV of 2 per ug/m^3 will carry a lung cancer risk significantly below the risk associated with smoking.

11 Key studies

11.1 Non-cancer endpoints

The study of Eisenbud *et al*. (1949) is a key study on ambient air beryllium exposure and CBD, in that it is the most complete study of non-occupationally exposed populations. This study found that genetically predisposed individuals exposed to 0.01 μg/m^3 were at risk of CBD. The studies of Kreiss *et al*. (1996) and Stange *et al.* (1996) identified LOAELs for occupationally exposed populations of 0.55 μg m^{-3} and 1.04 μg m^{-3}, respectively.

Several studies published since the ATSDR (2002) provide good reviews of beryllium sensitisation and CBD. These include Sawyer *et al*. (2002), Maier (2002) and Willis and Florig (2002). Recent works on the genetic reasons for sensitisation and CBD have been provided by McCanlies *et al*. (2003, 2004), Tinkle *et al.* (2003b) and Dotti *et al*. (2004).

A recent study by Newman *et al.* (2005) gives an account of beryllium sensitisation and rate of progression of sensitised individuals to CBD. A very recent study by Rosenman *et al*. (2005) is a case study of a cohort of former workers in a beryllium plant, which closed in 1978.

Finally, Tinkle *et al* (2003a) discuss the problems of skin sensitisation and its potential role in CBD etc.

11.2 Cancer endpoints

The most quoted study on beryllium and lung cancer is that of Ward *et al*. (1992) who assessed lung cancer incidence in beryllium manufacturing plants in Pennsylvania and Ohio. This study, despite criticisms of the methodology, strongly suggests that elevated lung cancer occurs in workers exposed to relatively high concentrations of beryllium. An epidemiological study by Steenland and Ward (1991) is also seen as indicating a causal link between beryllium exposure and lung cancer. Recently, Sanderson *et al*. (2001) provided fairly convincing evidence on beryllium dose and lung cancer incidence.

A recent review by Willis and Florig (2002) suggests that the risk of lung cancer associated with beryllium inhalation is an order of magnitude lower than the risk posed by CBD for genetically susceptible individuals.

12 Preliminary evaluation for EPAQS

The US EPA ambient standard (US EPA, 1998) for the concentration for occupational exposure is 0.1µg m^{-3}.

The ACGIH document (2001) stated that the Threshold Limit Value-Time Weighted Average (TLV-TWA) of 2 µg m^{-3} for beryllium, intended to protect against acute and chronic beryllium disease, was under review. However, in a recent draft document ACGIH (2005), the proposed TLV-TWA is significantly lower at 0.02 µg m^{-3} as beryllium, inhalable particulate mass.

The ACGIH (2005) draft document also suggests that beryllium can sensitise skin and as such it is recommended that care be taken to prevent dermal exposure.

With regard to lung cancer, it is probable that much higher concentrations would be needed to pose a significant risk, as Willis and Florig (2002) have shown that the risk of lung cancer associated with beryllium inhalation is an order of magnitude lower than the risk posed by CBD for genetically susceptible individuals. This is a view also shared by McCanlies *et al.* (2003), who believe that the risk of lung cancer to beryllium exposed workers is dwarfed by the risk of CBD in sensitised individuals. ACGIH (2001) suggest that the TLV-TWA of 2 µg m^{-3} proposed for protection from beryllium diseases would reduce the lung cancer risk of exposed workers to significantly less than that associated with smoking.

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