HSE’s DISEASE REDUCTION PROGRAMME - CANCER PROJECT

Profiling of Occupational Carcinogens

<table>
<thead>
<tr>
<th>Identity</th>
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<tbody>
<tr>
<td>Beryllium metal and beryllium compounds</td>
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<td>Including:</td>
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<tr>
<td>Beryllium metal</td>
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<tr>
<td>Beryllium-aluminium alloy</td>
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<tr>
<td>Beryllium-copper alloy</td>
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<tr>
<td>Beryl</td>
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<tr>
<td>Beryllium chloride</td>
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<tr>
<td>Beryllium fluoride</td>
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<td>Beryllium oxide</td>
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<td>Beryllium hydroxide</td>
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<tr>
<td>Beryllium sulphate</td>
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<tr>
<td>Beryllium sulphate tetrahydrate</td>
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<tr>
<td>Beryllium carbonate basic</td>
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<tr>
<td>Beryllium nitrate</td>
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<tr>
<td>Beryllium nitrate trihydrate</td>
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<td>Beryllium nitrate tetrahydrate</td>
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<td>Beryllium phosphate</td>
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<td>Beryllium silicate</td>
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<td>Zinc beryllium silicate</td>
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Beryllium oxide is also known as beryllium monoxide, Beryllia and Thermalox.

Name: DTG/AJS  Date: 29/07/05 (updated 24 Feb06)
Regulatory history

2005: US occupational exposure limits (OELs). The ACGIH TLV committee proposed reduction in the TLV (8h TWA, inhalable particulate mass) from 0.0002 mg/m³ to 0.00002 mg/m³. This was justified by studies claiming that sensitisation to beryllium and development of chronic beryllium disease may occur in those exposed to lifetime weighted average occupational exposures between 0.000024 – 0.0006 mg/m³.

2005: UK OEL. In line with changes to the OEL framework the Maximum Exposure Limit (MEL) of 0.002 mg/m³ (8 TWA) was converted to a Workplace Exposure Limit (WEL) of 0.002 mg/m³ (8h TWA) as beryllium. A ‘Carc’ notation was also added to the entry for Be and compounds.


2000: HSE published Beryllium and You (IND(G)311). This leaflet was aimed at employees and informed them about the health hazards posed by beryllium and its compounds. It also described precautions that should be taken in the workplace.

1999: US OEL. The ACGIH TLV committee lowered its threshold limit value (TLV) to 0.0002 mg/m³ (8h TWA).

1998: HSE published Guidance Note (EH13), 2nd edition – Beryllium: Health and safety precautions. This provided advice and recommendations on minimising inhalation and dermal exposure to beryllium, its alloys and its compounds. It was aimed particularly at employers and managers of those exposed to beryllium through their work. The importance of regular occupational health surveillance for those exposed amongst high-risk categories (“grinding or melting metallic beryllium and its alloys or handling powders and soluble salts”) was emphasised.

1995: UK OEL. A MEL of 0.002 mg/m³ (8h TWA) as Be was set for beryllium and compounds. The limit justified by evidence for chronic beryllium disease in humans and cancer in animal studies.

1993: IARC classified beryllium and beryllium compounds in Group 1 for carcinogenicity.


1991: EC Dangerous Substances Directive (15th ATP). Beryllium and compounds were classified in category 2 for carcinogenicity.

1989: UK OEL. The Recommended Limit (RL) set in 1984 was withdrawn pending a comprehensive review.

1984: UK OEL. A RL of 0.002 mg/m³ (8-hr TWA) was set.

1980: IARC concluded that there was sufficient evidence for the carcinogenicity of beryllium in the lung and several beryllium compounds in laboratory animals.
Hazard ranking

EU: Carc Cat 2

IARC: Group 1 (carcinogenic to humans)

There remains some controversy over the carcinogenicity of beryllium and its compounds. An analysis that included several US epidemiological studies (inc. Steenland and Ward, 1991, and Ward et al, 1992) led IARC (1993) to conclude that these chemicals where human lung carcinogens. Others have argued that the data are not so convincing, and especially that confounding by personal smoking habits have not been adequately controlled.

There appears to be only 1 epidemiological study (Sanderson et al, 2001) that has attempted to quantify exposure conditions and relate them to lung cancer incidence in workers. This study provides some limited evidence (relatively short exposures to high levels of beryllium) for the high potency of beryllium and compounds.

Beryllium and compounds have not been well studied for carcinogenicity in laboratory animals. However, in spite of methodological limitations, some of the available studies have shown beryllium compounds to induce lung cancer following relatively short periods of exposure. This further points to beryllium and compounds possibly being high potency carcinogens.

Human data:

Sanderson et al., (2001) provide the only study of the relationship between beryllium exposure characteristics and lung cancer. This was a nested-case control study of lung cancer within a cohort of 3,569 male workers employed at a beryllium processing plant in Reading, Pennsylvania, USA. Workers included in the cohort had worked for at least two days between 1940 and 1969. Mortality follow-up was extended through to December 1992. For each case of lung cancer (n=142), 5 controls (n=710) of comparable race and age were selected. Work history records (collated blindly) were linked to a detailed job-exposure matrix to produce personal exposure details for the cases and controls. The majority of the workers included in the study were first employed during the 1940s, and the average age at first employment was 33 and 37 for cases and controls, respectively. Almost two thirds of the cases and half the controls had worked at the plant for < 1year: mean employment 202 days (standard deviation 9.4) for cases and 328 (9.40) for controls. The overall lung cancer mortality rate for the cohort was 1.22 (95% CI, 1.03-1.43). The authors applied 10 and 20 year lag periods in their analyses, to minimise the possibility of lung cancer induction as a result of exposure to carcinogens after the period of beryllium exposure, and found that duration of exposure and cumulative exposure matrices were higher for cases. The ORs for the lagged average exposures, particularly a 10-year lag, were greater than those for the unlagged exposures: 10 year lag < 2 µg/m³ SMR = 1, > 2-20 µg/m³ SMR = 4.07 (p<0.01), > 20 µg/m³ SMR = 4.17 (p<0.01). The mean periods of employment for cases and controls at the plant were reduced considerably when tenure records were lagged for 10 and 20 years. Smoking did not appear to confound exposure-response analyses.

At best, this study supports others that suggest beryllium is a lung carcinogen in humans and provides limited evidence for high potency of beryllium and compounds.

There was considerable uncertainty about exposure levels at the plant during the 1940s and 50s and the possibility of exposure to different lung carcinogens in other jobs during the key exposure period did not seem to be assessed. The relatively short periods of potential exposure to beryllium compounds for workers in this study could be viewed as evidence of high potency.

The Steenland and Ward (1991) study was an extended analysis of mortality among people entered into the US Beryllium Case Registry cohort. The cohort consisted of 689 men and women who were alive at entry into the Registry between July 1952
and the end of 1980. Follow-up was extended through 1988 and comparisons were made with US death rates. Excess mortality was found for all cancers (SMR 1.51; 95 % CI 1.17 – 1.91; 70 observed deaths) due primarily to an excess of lung cancer (SMR 2.00; 95 % CI 1.33 – 2.89; 28 observed deaths). The SMR for lung cancer was greater among cohort members with acute beryllium pneumonitis (SMR 2.32; 95 % CI 1.35 – 3.72; 17 observed deaths) than among those with chronic beryllium disease (SMR 1.57; 95 % CI 0.75 – 2.89; 10 observed deaths) [Note: one death was due to disease of unknown type]. The SMRs for lung cancer varied little by time since first exposure or by duration of exposure. The authors concluded that smoking was unlikely to be a confounding factor in this analysis.

Ward et al., (1992) provided the cohort mortality study of 9225 male workers that was taken for the nested case-control study of Sanderson et al (2001). Workers included in the cohort had worked for at least two days between 1940 and 1969. Mortality follow-up was extended through to 1988 and was analysed using standard modified life-table methods. The SMR for all cancers was 1.06 (95 % CI 0.99 – 1.44) and that for lung cancer 1.26 (95 % CI 1.12 – 1.42). The authors estimated that the contribution of smoking to this was 13 %, i.e. that smoking alone could account for a lung cancer SMR of 1.13 compared with the 1.26 observed. Groups of workers with a high SMR for pneumoconiosis also had an elevated SMR for lung cancer, which may have been due to higher beryllium exposures. Lung cancer SMRs for the total cohort increased with increasing latency, the SMR being statistically significantly increased when latency was > 30 years (latency < 15 years, SMR 0.89, 27 deaths; latency 15 – 30 years, SMR 1.20, 119 deaths; latency > 30 years, SMR 1.46, 134 deaths). Poisson regression analysis, with control for age, race, calendar time and time since first employment, showed an independent effect of decade of hire on lung cancer SMRs. Duration of employment had no effect. This may have reflected poorer working conditions during the earlier periods of the cohort history.

The studies by Steenland and Ward (1991) and Ward et al (1992) provide the strongest available evidence for the carcinogenicity of beryllium and compounds, but are uninformative about potency.

Animal data (HSE, 1993; IARC, 1980; IARC, 1993)

A number of studies demonstrate that inhalation of beryllium oxide dust produces lung tumours in rats. In rats exposed to 0.36 – 252 µg/m$^3$ (as Be), for 1 h/d, 5 d/wk for 4 months, the following lung tumours were reported in surviving animals at 24 months: 0/5, 0/5, 3/12 and 4/10 at 0.36, 7.2, 36 and 252 µg/m$^3$, respectively. No lung tumours were reported in control animals. In a similar study, in rats exposed to 0.8 – 400 µg/m$^3$ (as Be) for 1 h/d, 5 d/wk for 4 months, the following tumour incidence was reported: 3/44, 4/39, 6/26 and 8/21 at 0.8, 4, 30 and 400 µg/m$^3$, respectively. Although these studies have several methodological shortcomings, including the low numbers of rats involved, the relatively short duration of exposure in both cases is viewed as a sign of high potency.

Lung tumours have also been seen in rats (both sexes) exposed by inhalation to several other beryllium compounds. For example, groups of female rats were exposed to 35 µg/m$^3$ (as Be) beryllium sulphate aerosol for 7h/d, 5 d/wk for varying times. Exposure periods were 22, 45 or 68 weeks. Animals were killed when moribund or examined at the end of their natural life. Pulmonary tumours were reported in all exposure groups, the incidence and malignancy dependent on age at initial exposure. For example, pulmonary tumours were reported in 3/16 surviving animals exposed for 22 weeks from 13 months of age and were classified as adenomas; while 13-14 animals showed pulmonary tumours out of 18-23 survivors following exposure for 22 weeks from between 2 – 10 months of age and these tumours occurred in multiple clusters and metastasised to the local lymph nodes.
kidneys and adrenals. No tumours were reported in control animals. Although providing minimal dose response information, this study shows that exposure aerosols of beryllium occurring over less than half a year results in an increase in incidence of lung tumours in rats.

In a similar study, rats were exposed to 35 µg/m$^3$ (as Be) beryllium sulphate aerosol for 7h/d, 5 d/wk for 72 weeks. The first pulmonary tumours were reported after 9 months, while all treated animals examined had pulmonary tumours from 13 months onwards. No tumours were reported in control animals. However, in this study there were large variations in the doses given (34.2 ± 23.7 µg/m$^3$) and rats were reported to have an 'intercurrent respiratory infection', suggesting that the rats were ill throughout the course of the study. A meaningful assessment of potency does not seem possible from this study.

In a number of briefly reported Russian studies, lung tumours in rats were described following inhalation exposure to beryllium as beryllium chloride or beryllium fluoride. Exposure periods were up to 4 months and animals were sacrificed at various points after this. It is not clear when the tumours were first detected. A single inhalation exposure to 1130 or 1920 µg/m$^3$ Be, was claimed to produce lung tumours in 40 – 45% of animals. Exposure to between 0.09 – 80 µg/m$^3$ Be for 1 h/d 5 d/wk for 4 months produced the following lung tumour incidence: 8 tumours in animals exposed to 0.09 or 0.15 µg/m$^3$ Be; one tumour in 34 animals exposed to 0.4 or 0.8 µg/m$^3$ Be; 6 out of 15 rats exposed to 4 or 8 µg/m$^3$ Be had lung tumours; and 11 out of 19 rats exposed to 40 or 80 µg/m$^3$ Be had lung tumours. The tumours were described mainly as adenocarcinoma. No tumours were reported in control animals. Rats exposed to between 0.8 – 400 µg/m$^3$ Be, 1 h/d 5 d/wk for 4 months showed the following tumour incidence: 1 lung tumour out of 41 animals examined at 0.8 µg/m$^3$ Be; 2 lung tumours out of 42 animals examined at 4 µg/m$^3$ Be; 8 lung tumours out of 24 animals examined at 30 µg/m$^3$ Be; and 11 lung tumours out of 19 animals examined at 400 µg/m$^3$ Be. No lung tumours were seen in control animals. Taking this evidence at face value, in spite of the poor reporting, the short exposure periods that resulted in lung cancer may have been indicative of high potency.

Although there are no studies available for beryllium metal, there are data showing that lung tumours are induced in rats that receive beryllium-aluminium dust by intratracheal instillation. Given the non-physiological route of exposure, no conclusions about the potency of beryllium and compounds have been made from these studies.

**Mechanism**

No information on the mechanism by which beryllium may produce lung tumours in humans is available. The mechanism in animals is not well understood: both chronic irritation and genotoxicity could play a role. There are no studies of genotoxicity in lung tissue but there is limited evidence from *in vitro* tests that soluble beryllium compounds can induce gene mutations in mammalian cells. A well-conducted *In vivo* bone marrow micronucleus study in mice after oral dosing with beryllium was negative, while two briefly reported bone marrow micronucleus studies in rats and mice via the oral and intraperitoneal routes, respectively, produced positive results. It is concluded that beryllium and beryllium compounds are genotoxic and, in the absence of information to the contrary, they are regarded as genotoxic carcinogens.

**Additional views about the carcinogenic potency of beryllium and compounds**

Calabrese and Brain (1999) include beryllium as a compound to which "limited occupational exposure" (defined as lasting less than one year) was identified as the causal factor in the development of human cancer. However, it should be noted that
the epidemiology studies cited to support this assertion are those which both IARC and HSE were not able to base firm recommendations upon.

**TD50:** No entry on Gold database.

**Additional hazards listed in the UK Classification & Labelling Approved Supply List**

Beryllium, beryllium oxide, beryllium compounds with the exception of aluminium beryllium silicates, and with those specified elsewhere in Annex 1:

- Acute toxicity (inhalation and oral)
- Repeated toxicity (inhalation)
- Skin, eye and respiratory irritation
- Skin sensitisation

**Provisional Potency Estimate:** Level A

In some studies, relatively short exposure periods have been associated with increased lung cancer risk (mean tenure of occupation among lung cancer cases in epidemiological study was < 1 year; lung tumours in rats after 1 hour/day, 4 months exposure to beryllium oxide dust).

Other factors: biopersistence; high tumour incidence, low latency (in rat studies).

**Toxicology References:**


Occurrence

Beryllium is used in three forms in industry, beryllium metal, beryllia (the oxide of beryllium) and as an addition to certain alloys. Beryllium is a lightweight, strong metal that is steel-grey in colour. Beryllium oxide is a light white powder with a high melting point and thermal conductivity.

Beryllium compounds also exist (sulphate, nitrate, fluoride etc) but these are only found either in the beryllium extraction industry (none in the UK) or possibly in certain analytical procedures. These compounds have no current industrial uses but could arise from chemical treatment of beryllium and its compounds.

The pure metal, copper alloys and beryllium oxide are imported into the UK.

Use

Beryllium oxide as a ceramic, only 3 companies worldwide, one company in the UK employing 24 workers. Company manufactures a high quality product used in the electronics industry. Beryllium oxide also used in rocket combustion liners, electrical insulators and laser microwave tubes.

UK estimates from 2006 indicate that the use of beryllium is increasing. Approximately 51 companies employing approximately 510 employees (assuming an average of 10 worker per company) in the UK manufacture/machine products containing beryllium as an alloy. Evidence suggests a proliferation of industrial uses of beryllium and therefore the potential for greater numbers of workers to be exposed. Beryllium is most often used as an alloy with copper, aluminium, magnesium or nickel and therefore the beryllium content and its hazards may not be obvious to workers generating fumes or dust.

Beryllium/copper alloys used for making springs, electrical contacts, non-sparking tools, aircraft engine parts as well as in gears, precision castings and spot-welding electrodes.

Beryllium/Aluminium alloys used in the aerospace industry in structural components in aircraft and space vehicles. It is also used in inertial guidance systems and as a component in nuclear reactors.

Pure Beryllium used in computer parts, in nuclear weapons and in X-ray windows.
Occupational Exposure

Occupational exposure to beryllium is predominantly from inhalation of dust or fume containing beryllium. This occurs at: beryllium processing plants where the work involves handling beryllium oxide powder and machining beryllium ingots; operations in metal machining shops; and in alloy applications. Recycling of electronic, computers and scrap alloy to recover copper will also result in the potential for beryllium exposure. These processes tend to be enclosed or partially enclosed and extracted. Personal exposure monitoring is routinely carried out and apart from occasional excursions above the limit exposure is controlled below the limit. However, recent evidence appears to suggest that the current occupational exposure limit for beryllium may be inadequate to prevent disease and chronic beryllium disease has been identified in workers with beryllium exposures 20-100 times lower than the OEL.

Worker exposure using beryllium as a ceramic is well controlled and consequently worker exposure is low.

Occupational hygiene priority classification

In view of the increasing use of beryllium, coupled with the high number of workers potentially exposed in the metal machining industry, beryllium should remain a high priority substance for the further work within the DRP carcinogens project.