5. Summary of Data Reported and Evaluation

5.1 Exposure data

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

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

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

5.2 Human carcinogenicity data

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

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

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

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

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

5.3 Animal carcinogenicity data

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

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

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

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

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

5.4 Other relevant data

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

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

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

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

5.5 Evaluation[1]

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

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

Overall evaluation

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

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