The Carcinogenicity of Beryllium

by Marvin Kuschner*

Beryllium, some of its alloys, and a variety of its compounds have induced malignant tumors of the lung and osteogenic sarcoma in experimental animals. Three animal species, monkeys, rabbits, and rats, have been shown to be susceptible.

Beryllium induces morphological transformation in mammalian cells and enhances viral transformation of mammalian cells. It has been shown to decrease fidelity of DNA synthesis.

It has been recognized that exposure to compounds of this metal will, in some individuals, result in a chronic granulomatous disease of the lung. A series of overlapping recent human epidemiological studies have been suggestive of an increase in the incidence of lung cancer in populations occupationally exposed to beryllium. Such studies, together with animal and in vitro studies, argue for the strong presumption of a carcinogenic hazard to man in occupational beryllium exposures.

Recognition of the potential hazards of exposure to compounds of beryllium is of fairly recent origin. As late as 1943, Bulletin No. 181 of the United States Public Health Service attributed lung disease in exposed workers to irritating anions such as fluoride (1). German (2-5), Italian (6, 7) and Russian (8, 9) reports of pulmonary disease following on exposure to beryllium compounds had appeared in the 30's and 40's and these were subsequently amplified by descriptions of the disease clinically, radiologically and pathologically in the United States.

In 1946 Hardy and Tabershaw described the occurrence of “delayed chemical pneumonitis” in 17 workers in a plant manufacturing fluorescent tubes (10). This landmark paper clearly established the clinical and morphological characteristics of berylliosis. The lack of relationship between the incidence of the disease and the level of exposure represented a puzzling feature of berylliosis. In 1951, Sterner and Eisenbud proposed hypersensitivity to beryllium as a mechanism for the granulomatous pulmonary disease and for the lesions evoked by accidental implantation of beryllium in the skin (11). The demonstration by Belman that beryllium combines with proteins in the skin provided a model for understanding the production of a metalloprotein complex that might serve as an antigen in the induction of hypersensitivity (12).

The position of the U.S. Public Health Service was revised with the publication in 1972 of Public Health Service Publication #2173, (13). In addition to summarizing the then-available data on the nature of the disease and recommending environmental limits of exposure and methods of control, the bulletin reviewed the uses of beryllium and the potential sources of industrial exposure. The prospects for human occupational encounter with beryllium are summarized by Fishbein as are the sources and levels of general environmental contamination by the metal (14). This summary emphasizes, as do those coming from the EPA (15, 16), the major contribution to atmospheric pollution made by burning coal and oil. The recommended permissible concentrations have been set at an in-plant concentration not exceeding 2 µg/m³ as an average over an eight-hour day; no exposure greater than 25 µg/m³ for any period of time, however short; plant neighborhood exposures not exceeding average monthly concentrations of 0.01 µg/m³.

In 1946, Gardner and Heslington in a brief note reported, in apparent astonishment, the first instance of a tumor experimentally induced by the administration of beryllium (17). Seven rabbits surviving injection of zinc beryllium silicate for seven or more months all developed osteosarcomas at multiple sites. This observation has been followed by ample confirmation of the ability of beryllium to induce malignant tumors in monkeys, rabbits, and rats. Beryllium’s carcinogenic activity has been demonstrated when in the form of the

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metal, some of its alloys, and a variety of compounds. It has produced lung cancers and osteogenic sarcoma. The lung cancers result from pulmonary instillation or inhalation with consequent direct action on the lung and the bone tumors reflect beryllium's bone seeking propensities (18). Experimental approaches to beryllium carcinogenesis are summarized in Table 1.

It should be noted that the levels of exposure producing tumors of the lung on inhalation in rats and monkeys was 30-40 μg/m³.

In in vitro tests of genotoxic properties, beryllium has been negative as a mutagen in bacterial systems (46, 47). However, beryllium has been shown to induce morphological transformation in mammalian cells and to enhance viral transformation of mammalian cells (48, 49). The testing of metals in in vitro assay is reviewed by Sirover (50) in this symposium. Beryllium's ability to decrease the fidelity of DNA synthesis is reviewed in this symposium by Loeb and Zakour (51).

Epidemiological evidence for an increased risk of cancer in humans occupationally exposed to beryllium is presently uncertain. Four reports appearing between 1967 and 1970 failed to show evidence of carcinogenicity for humans (52-55). Four more recent studies of the same populations all show what appears to be an excess of lung cancer in individuals (white males) exposed to beryllium in the courses of employment (57-59). These studies have been criticized on the following grounds: comparison with lung cancer rates for all U.S. white males may not be appropriate; the straight-line extrapolation of lung cancer death rates from

Table 1. Carcinogenicity of beryllium compounds.

| Year | Species | Compound                        | Route of administration | Tumor                        | Reference |
|------|---------|---------------------------------|-------------------------|------------------------------|-----------|
| 1946 | Rabbit  | Zinc beryllium silicate         | Intravenous             | Osteosarcoma                 | (17)      |
| 1949 | Mouse   | Zinc beryllium silicate         | Intravenous             | "Malignant bone tumors"      | (19)      |
| 1949 | Rabbit  | Zinc beryllium silicate         | Intravenous             | Osteosarcoma                 | (19)      |
| 1950 | Rabbit  | Zinc beryllium silicate         | Intravenous             | Osteosarcoma                 | (22-24)   |
| 1960 | Rabbit  | Beryllium oxide and zinc beryllium silicate | Intravenous | Osteosarcoma                 | (21)      |
| 1960 | Rabbit  | Beryllium oxide                 | Inhalation              | Osteosarcoma                 | (20)      |
| 1963 | Rat     | Beryllium sulfate tetrahydrate  | Inhalation              | Lung cancer (adeno and squamous) | (25) |
| 1964 | Rabbit  | Beryllium phosphate, beryllium oxide | Inhalation             | Osteosarcoma                 | (25)      |
| 1964 | Rabbit  | Zinc beryllium silicate         | Intravenous             | Osteosarcoma                 | (20)      |
| 1964 | Rat     | Beryllium sulfate tetrahydrate  | Inhalation              | Lung cancer (adeno and squamous) | (27)      |
| 1966 | Monkey  | Beryllium oxide                 | Intratracheal           | Pulmonary cancer (anaplastic) | (34)      |
| 1967 | Rat     | Beryllium sulfate tetrahydrate  | Instillation            | Pulmonary cancer (anaplastic) |           |
| 1968 | Rabbit  | Beryllium oxide                 | Intravenous             | Osteosarcoma                 | (26)      |
| 1969 | Rat     | Beryl ore, bertrandite ore      | Inhalation              | Lung cancer (adeno) no tumors | (37)      |
| 1969 | Hamster | Beryl ore, bertrandite ore      | Inhalation              | None                         | (37)      |
| 1969 | Monkey  | Beryl ore, bertrandite ore      | Inhalation              | None                         | (37)      |
| 1969 | Rabbit  | Zinc beryllium silicate, beryllium oxide | Subperiosteal injection | Osteosarcoma                 | (38, 39) |
| 1972 | Rat     | Beryl ore, beryllium oxide      | Intratracheal           | "Pulmonary tumors"           | (40)      |
| 1975 | Rat     | Beryllium fluoride, beryllium chloride | Inhalation             | Lung cancer (adeno and squamous) | (41)      |
| 1975 | Rabbit  | Zinc beryllium silicate         | Intramedullary          | Osteosarcoma                 | (42)      |

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one examines the group in which more than 15 years had elapsed since the onset of employment. Finally it should be recognized that short periods of exposure to a toxicant do not rule out a causal effect between that exposure and tumor induction. This is particularly true when the material in question is durable and may remain for many years, and, in addition, produces a potent competing nonneoplastic disease. One is reminded of the emergence of mesothelioma as a problem in asbestos exposure after severe asbestosis disappeared and the incidence of lung cancer diminished with lower levels of exposure.

The occurrence of a specific cell type of lung cancer in association with occupational exposure might be considered presumptive evidence of a causal relationship. An attempt to examine this the period of 1965-1967 to the later years under study (1968-1975) ignores the increase in death rates from this disease; the short period of exposure for many of the lung cancer patients (the majority in Wagoner’s study were employed for less than 12 months) presents the curious phenomenon of cancer mortality being inversely related to length of exposure; no account can be taken or smoking habits which surely affect the outcomes of comparisons where the excess risk is 1.4 times that of the control population.

These objections are countered by the following elements in the studies in question: Mancuso’s 1980 study (58) compares mortality in the beryllium-exposed workers originally studied in 1979 (56) to a group of workers in the viscose rayon industry rather than to national mortality rates and an excess incidence of lung cancer still holds; the borderline or nonexistent significance of the excess in Wagoner’s study (57), particularly if one substitutes a more correct and higher figure for the expected incidence, becomes more impressive if possibility is inconclusive (60). In Wagoner’s 47 cases of lung cancer deaths in beryllium workers, 27 samples of tissue were available. One proved to be a metastatic pancreatic carcinoma and another an adenocarcinoma of uncertain primary site. Although there was a deficit of epidermoid cancers in this group, the authors point out that there is no reason to expect that the same distribution would have held in the 20 cases for which specimens were not received. Indeed, five of seven cases in which cell types are recorded but in which no material could be examined are epidermoid.

At the present time, a material which produces malignant tumors in three animal species at different sites and for which human epidemiological studies are, at the very least, strongly suggestive of a carcinogenic effect in man, must certainly be regarded with a high degree of suspicion as being a human carcinogen.

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**Table 1. (Cont.)**

| Year | Species | Compound | Route of administration | Tumor | Reference |
|------|---------|----------|-------------------------|-------|-----------|
| 1977 | Rat     | Beryllium sulfate tetrahydrate | Ingestion | ? No greater than controls | (43) |
| 1978 | Rat     | Beryllium oxide | Inhalation | Single lung cancer (adenocarcinoma) | (44) |
| 1979 | Rat     | Beryllium metal, beryllium alloy, passivated beryllium metal, beryllium hydroxide | Intratracheal instillation | Lung cancer (adenocarcinoma and squamous) | (45) |

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