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The Carcinogenicity of Beryllium

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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*).

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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 $\mu g/m^3$ as an average over an eight-hour day; no exposure greater than 25 $\mu g/m^3$ for any period of time, however short; plant neighborhood exposures not exceeding average monthly concentrations of 0.01 $\mu g/m^3$.

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

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 $\mu g/m^3$.

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.[a]

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 and beryllium metal	Intravenous	Osteosarcoma	(*22-24*)
1950	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	(*21*)
1950	Rabbit	Beryllium oxide and zinc beryllium silicate	Intravenous	Osteosarcoma	(*20*)
1951	Rabbit	Beryllium oxide	Inhalation	Osteosarcoma	(*25*)
1953	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung cancer (adeno and squamous)	(*26*)
1954	Rabbit	Beryllium phosphate, beryllium oxide	Inhalation	Osteosarcoma	(*27*)
1954	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	(*28*)
1957	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung cancer (adeno and squamous)	(*29*)
1961	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	(*30*)
1964	Rabbit	Zinc beryllium silicate	Intravenous	Chondrosarcoma	(*31*)
1964	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	(*32*)
1965	Rat	Beryllium sulfate tetrahydrate	Ingestion	? no greater than controls	(*33*)
1966	Monkey	Beryllium oxide	Intratracheal Instillation	Pulmonary cancer (anaplastic)	(*34*)
	Monkey	Beryllium sulfate tetrahydrate	Inhalation	Pulmonary cancer	(*34*)
1967	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung cancer (alveolar-adeno Ca)	(*35*)
1968	Rabbit	Beryllium oxide	Intravenous	Osteosarcoma	(*36*)
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 silicate, beryllium oxide	Subperiosteal injection	Osteosarcoma	(*38*, *39*)
1972	Rat	Beryl ore, beryllium oxide beryllium hydroxide, beryllium metal	Intratracheal	"Pulmonary tumors"	(*40*)
1975	Rat	Beryllium fluoride, beryllium chloride	Inhalation	Lung cancer (adeno and squamous)	(*41*)
1975	Rabbit	Zinc beryllium silicate beryllium chloride	Intramedullary	Osteosarcoma (adeno and squamous)	(*42*)

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 (adeno)	(*44*)
1979	Rat	Beryllium metal, beryllium alloy, passivated beryllium metal, beryllium hydroxide	Intratracheal instillation	Lung cancer (adeno and squamous) "	(*45*)

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 availble. 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.

REFERENCES

1. Hyslop, F., Palmes, E. D., Alford, W. C., Monaco, A. R., and Fairhall, L. T. The Toxicology of Beryllium, Bulletin 181; United States Public Health Serivice, 1943.
2. Weber, H., and Engelhardt, W. E. Anwendung bei der Untersuchungen von Stauben aus der Berylliumgewinnung. Zentralbl. Gewerbehyg. Unfallverhuet 10: 41 (1933).
3. Berkovitz, M., and Israel, B. Changes in the lungs in fluorine beryllium poisoning. Klin. Med. (Moscow) 18: 5: 117 (1940); Brit. J. Ind. Med. 1: 259 (1944).
4. Meyer, H. E. Uber berylliumer Krankungen der Lunge. Beitr. Klin. Tuberk. 98: 388 (1942); Chem. Abstr. 38: 5019 (1944).
5. Wurm, H., and Ruger, H. Untersuchungen zur Frage der beryllium Staubpneumonia. Beitr. Klin. Tuberk. 98: 396 (1942), Chem. Abstr. 38: 5019 (1944).
6. Fabroni, S. M. Pulmonary pathology of beryllium powders. Med. Lavoro, 26: 297 (1935).
7. Menesini, G. Biological action of beryllium carbonate. Rass. Med. Appl. Lav. Ind. 8: 317 (1938).
8. Gelman, I. Poisoning by vapours of beryllium oxyfluoride. J. Ind. Hyg. Toxicol. 18: 371 (1936).
9. Gelman, I. Beryllium (glucinium). Occupational and Health Supplement, International Labour Office, 1938.
10. Hardy, H. L., and Tabershaw, I. R. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. J. Ind. Hyg. Toxicol. 28: 197 (1946).
11. Sterner, J. H., and Eisenbud, M. Epidemiology of beryllium

intoxication. Arch. Ind. Hyg. Occup. Med. 4: 123 (1951).
12. Belman, S. Beryllium binding of epidermal constituents. J. Occup. Med. 11: 175 (1969).
13. U.S. Dept. of Health, Education, and Welfare. The Toxicology of Beryllium. Public Health Service Publications #2173, 1972.
14. Fishbein, L. Sources, transport and alterations of metal compounds: an overview. Environ. Health Perspect. 0: 000 (1981).
15. Drury, J. S., Shriner, C. R., Lewis, E. B., Towill, L. E., and Hammons, A. S. Reviews on the Environmental Effects of Pollutants: VI. Beryllium. ORNL/EIS-87. EPA-600/1-78-028, Oak Ridge National Laboratory, Oak Ridge, Tenn., Nov, 1978.
16. U.S. Environmental Protection Agency. National Inventory of Sources and Emissions: Beryllium. 1968, EPA Report #APTD-1508, Office of Air and Water Programs, Research Triangle Park, N.C., 1971, p. 53.
17. Gardner, L. U., and Heslington, H. F. Osteosarcoma from intravenous beryllium compounds in rabbits. Fed. Proc. 5: 221 (1946).
18. VanCleave, C. D., and Kaylor, C. T. Distribution, retention and elimination of Be in the rat after intratracheal injection. Arch. Ind. Health 11: 375 (1955).
19. Cloudman, A. M., Vining, D., Barkulis, S., and Nickson, J. J. Bone changes observed following intravenous injections of beryllium. Am. J. Pathol. 25: 810 (1949).
20. Dutra, F. R., and Largent, E. J. Osteosarcoma induced by beryllium oxide. Am. J. Pathol. 26: 197 (1950).
21. Hoagland, M. B., Grier, R. S., and Hood, M. B. Beryllium and growth, I. Beryllium-induced osteogenic sarcomata. Cancer Res. 10: 629 (1950).
22. Barnes, J. M. Experimental production of malignant tumors by beryllium. Lancet 1: 463 (1950).
23. Barnes, J. M., Denz, F. A., and Sissons, H. A. Beryllium bone sarcomata in rabbits. Brit. J. Cancer 4: 212 (1950).
24. Sissons, H. A. Bone sarcomas produced experimentally in the rabbit using compounds of beryllium. Acta Unio. Int. Contra Cancrum 7: 171 (1950).
25. Dutra, F. R., Largent, E. J., and Roth, J. L. Osteogenic sarcoma after inhalation of beryllium oxide. Arch. Pathol. 51: 473 (1951).
26. Vorwald, A. J., Pratt, P. C., and Urban, E. J. The production of pulmonary cancer in albino rats exposed by inhalation to an aerosol of beryllium sulfate. Acta Unio. Int. Contra Cancrum 11: 735 (1953).
27. Araki, M., Okada, S., and Fujita, M. Experimental studies on beryllium-induced malignant tumors of rabbits. Gann 45: 449 (1954).
28. Janes, J. M., Higgins, G. M., and Herrick, J. F. Beryllium-induced osteogenic sarcoma in rabbits. J. Bone Jt. Surg. 36B: 543 (1954).
29. Schepers, G. W. H., Durkan, T. M., Delahant, A. B., and Creedon, F. T. The biological action of inhaled beryllium sulfate. Arch. Ind. Health 15: 32 (1957).
30. Kelly, P. J., Janes, J. M., and Peterson, L. F. A. The effect of beryllium on bone. A morphological study of the progressive changes observed in rabbit bone. J. Bone Jt. Surg. 43A: 829 (1961).
31. Higgins, G. M., Levy, B. M., and Yollick, B. L. A transplantable beryllium-induced chondrosarcoma of rabbits. J. Bone Jt. Surg. 46A: 789 (1964).
32. Peterson, L. F. A., Brown, A. L., Jr., and Janes, J. M. The ultrastructure of beryllium-induced osteogenic sarcoma in the rabbit. J. Bone Jt. Surg. 46A: 920 (1964).
33. Schroeder, H. A., and Mitchener, M. Life-term studies in rats: effects of aluminum, barium, beryllium and tungsten. J. Nutr. 105: 421 (1965).
34. Vorwald, A. J., Reeves, A. L., and Urban, E. C. J. Experimental beryllium toxicology. In: Beryllium: Its Industrial Hygiene Aspects, H. E. Stokinger, Ed., Academic Press, New York, 1966, pp. 201-334.
35. Reeves, A. L., Deitch, D., and Vorwald, A. J. Beryllium carcinogenesis. I. Inhalation exposure of rats to beryllium sulfate aerosol. Cancer Res. 27: 439 (1967).
36. Komitowski, D. Experimental beryllium-induced bone tumors as a model of osteogenic sarcoma. Chir. Narzadow. Ruchu. Ortop. Pol. 33: 237 (1968).
37. Wagner, W. D., Groth, D. H., Holtz, J. L., Madden, G. E., and Stokinger, H. E. Comparative chronic inhalation toxicity of beryllium ores, bertrandite and beryl with production of pulmonary tumors by beryl. Toxicol. Appl. Pharmacol. 15: 10 (1969).
38. Tapp, E. Osteogenic sarcoma in rabbits following subperiostal implantation of beryllium. Arch. Pathol. 88: 89 (1969).
39. Tapp, E. Changes in rabbit tibia due to direct implantation of beryllium salts. Arch. Pathol. 88: 521 (1969).
40. Groth, D. H., Scheel, L. D., and MacKay, G. R. Comparative pulmonary effects of beryllium and arsenic compounds in rats. Lab. Invest. 26: 477 (1972).
41. Litvinov, N. N., Bugryshev, P. F., and Kazenashev. V. F. Toxic properties of soluble beryllium compounds based on experimental morphological investigations. Gig. Tr. Prof. Zabol. 7: 34 (1975).
42. Mazabraud, A. Experimental production of osteosarcomas in rabbits by single local injection of beryllium. Bull. Cancer 62: 49 (1975).
43. Morgareidge, K., Cox, G. E., Bailey, D. E., and Gallo, M. A. Chronic oral toxicity of beryllium in the rat. Toxicol. Appl. Pharmacol. 41: 204 (1977).
44. Sanders, C. L., Cannon, W. C., and powers, G. J. Lung carcinogenesis induced by inhaled high-fired oxides of beryllium and plutonium. Health Phys. 35: 193 (1978).
45. Groth, D. H., Homenini, C., and Mackay, G. R. Carcinogenicity of beryllium hydroxide and alloys. Environ. Res. 21: 63 (1980).
46. Rosenkranz, H. S. and Poirier, L. A. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and non-carcinogens in microbial systems. J. Natl. Cancer Inst. 62: 873 (1979).
47. Simmon, V. V. *In vitro* mutagenicity assays of chemical carcinogens and related compounds with *Salmonella typhimurium*. J. Natl. Cancer Inst. 62: 893 (1979).
48. Casto, B. C., Meyers, M., and DiPaolo, J. A. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 39: 193 (1979).
49. DiPaolo, J. A., and Casto, B. C. Quantitative studies of *in-vitro* morphologic transformation of Syrian hamster cells by inorganic metal salts. Cancer Res. 39: 1008 (1979).
50. Sirover, M. A. Effects of metals in *in-vitro* bioassays. Environ. Health Perspect. 40: 163 (1981).
51. Zakour, R. A., Kunkel, T. A., and Loeb, L. A. Metal-induced infidelity of DNA synthesis. Environ. Health Perspect. 40: 197 (1981).
52. Hardy, H. L., Robe, E. W., and Lorch, S. United States Beryllium Case Registry (1952-1966): Review of its method and utility. J. Occup. Med. 9: 271 (1967).
53. Stoeckle, J. D., Hardy, H. L., and Weber, A. L. Chronic beryllium disease: Long-term follow-up of 60 cases and selective review of the literature. Am. J. Med. 46: 545 (1979).
54. Mancuso, T. F., and El-AHar, A. A. Epidemiological study of the beryllium industry: cohort methodology and mortality studies. J. Occup. Med. 11: 422 (1969).

55. Mancuso, T. F. Relation of duration of employment and prior respiratory illness to respiratory cancer among beryllium workers. Environ. Res. 3: 251 (1970).
56. Mancuso, T. F. Occupational lung cancer among beryllium workers. In: "Conference on Occupational Exposures to Fibrous and Particle Dust and Their Extension into the Environment, R. Lemen and J. Dement, Eds., Society for Occupational and Environmental Health, Washington, D.C., 1979.
57. Wagoner, J. K., Infante, P. F., and Bayliss, D. L. Beryllium: an etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease and heart disease among industrially exposed workers. Environ. Res. 21: 15 (1980).
58. Mancuso, T. F. Mortality study of beryllium industry workers' occupational lung cancer. Environ. Res. 21: 48 (1980).
59. Infante, P. F., Wagoner, J. K., and Sprince, N. L. Mortality patterns from lung cancer and non-neoplastic respiratory disease among white males in the beryllium case registry. Environ. Res. 21: 35 (1980).
60. Smith, A. B., and Suzuki, Y. Histopathologic classification of bronchogenic carcinomas among a cohort of workers occupationally exposed to beryllium. Environ. Res. 21: 10 (1980).