ENVIRONMENTAL RESEARCH 21, 56–62 (1980)

Carcinogenicity of Beryllium: Review of the Literature[1]

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Received April 27, 1979

The carcinogenicity of beryllium (Be) is reviewed. At least 17 different senior authors have published 27 different scientific articles which demonstrate the carcinogenicity of 13 different beryllium compounds. Osteogenic sarcomas can be induced in rabbits by the intravenous injection or by the inhalation of Be compounds. Lung cancer can be induced in rats and monkeys by intratracheal injections and inhalation exposures. The first published report on the carcinogenicity of Be was in 1946.

INTRODUCTION

Reviews on the toxicology of beryllium (Be) have been published (Stokinger, 1966; Tabershaw, 1972; Key, 1972). However, the experimental details were not selected to emphasize the carcinogenic aspects of beryllium. In this review, most of the published experiments which demonstrate the carcinogenicity of beryllium and its compounds will be presented.

OSTEOGENIC SARCOMAS

Beryllium compounds were the first nonradioactive chemicals found to cause osteogenic sarcomas in animals. In a search to find the cause of an "unusual incidence of pulmonary sarcoid" in industry, Gardner and Heslington (1946) discovered that zinc beryllium silicate (at one time commonly used in fluorescent light bulbs) and beryllium oxide (intermediate chemical presently used in making many widely used beryllium alloys and ceramics) caused osteogenic sarcomas in rabbits. The phosphor induced cancer in 100% (7/7) of the animals, whereas no tumors were produced by zinc oxide, zinc silicate, or silicic acid. The authors noted that this had never occurred in similar, previous experiments with 65 different minerals. Thus began a new era in carcinogenesis with inorganic compounds.

Since this original discovery, many investigators have reproduced these results with the same and other beryllium compounds, including beryllium metal (Barnes, 1950), beryllium silicate (Barnes *et al.*, 1950), and beryllium phosphate (Araki *et al.*, 1954; Vorwald, 1950).

Although the intravenous route of administration was most commonly used, these tumors were also induced by direct intramedullary injections in bones (Tapp, 1969; Yamaguchi, 1963) and by inhalation exposures (Dutra *et al.*, 1951).

Although specific matched control groups of animals were not used in each experiment, they were used in several (Gardner and Heslington, 1946; Cloudman *et al.*, 1949; Barnes *et al.*, 1950). In intramedullary injection experiments, Tapp

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0013-9351/80/010056-07$02.00/0

(1969) used the contralateral bone for injecting zinc oxide. No tumors arose from this site, whereas 4/12 rabbits developed tumors in the contralateral bone injected with the phosphor zinc beryllium silicate. In addition, Dutra *et al.* (1951) noted that they had not observed osteogenic sarcomas in rabbits in over a 20-year period of experimentation with a variety of other compounds. As previously stated, Gardner and Heslington (1946) made similar observations.

Not only was the observation of the induction of osteogenic sarcomas rather unique, but their incidences were consistently high. This varied from 13 to 100%, with a mean incidence in the combined experiments with intravenously injected zinc beryllium silicate of 66% (40/61) (Table 1). In addition, the latent period was relatively short, usually 10 months, but it varied from 5.5 to 24 months after the last injection in individual animals. There was also no doubt about the malignancy of the neoplasms. Metastases were common, occurring in 40–100% of the animals with primary osteogenic sarcomas in the various experiments.

As might be expected after intravenous injections, the osteogenic sarcomas originated in several different bones, including the humerus, tibia, femur, ilium, ischial tuberosity, lumbar vertebra, scapula, and ribs. Frequently, primary tumors arose in two or more bones in the same animal. Metastases were observed most frequently in the lungs, but also occurred in the liver, kidney, omentum, skin, and lymph nodes (mediastinal, pelvic, and abdominal).

The cell types of these neoplasms were not all the same in each animal or among animals injected with the same compounds. Kelley *et al.* (1961) described the primary tumors as osteoblastic, chondroblastic, and fibroblastic, with all three cell types occurring frequently in the same tumor. These sarcomas were described by Tapp (1969) as chondrosarcomatous or anaplastic, and the metastases were similar in appearance to the primary tumors. Dutra and Largent (1950) noted that the metastases contained bone spicules, and Barnes *et al.* (1950) noted ossifying metastases as well. Dutra *et al.* (1951) described the pulmonary metastases from an osteogenic sarcoma induced by the inhalation of beryllium oxide. They were similar to the primary tumor, i.e., consisted of poorly differentiated cells, masses of hyaline cartilage, and occasional masses of osseous tissue. They were similar in all respects to the osteogenic sarcomas induced by the intravenous injection of beryllium compounds. Based upon these findings, it can be deduced that there was no difficulty in differentiating between metastatic osteogenic sarcoma in the lungs and primary lung neoplasms (adenomas, adenocarcinomas, and epidermoid carcinomas) that were later shown to be induced by the inhalation of beryllium compounds.

Some authors (Janes *et al.*, 1954) believed that the success in inducing cancer was related to the splenic atrophy which occurred after intravenous administration of these compounds. However, the fact that the osteogenic sarcomas were induced by methods that did not produce splenic atrophy (inhalation and intramedullary injections) negated that hypothesis.

Although intravenous doses were frequently relatively high (up to 700 mg Be), as little as 7.0 mg of Be given intravenously (Hoagland *et al.*, 1950) and 0.144 mg Be given by intramedullary injections (Tapp, 1969) as the phosphor to rabbits produced the osteogenic sarcomas. In general, the BeO was less potent a carcinogen than the fluorescent phosphor.

TABLE 1
OSTEOGENIC SARCOMAS IN RABBITS[a]

Compound	Dose of compound (g)	Dose of beryllium (mg)	Route of injection	No. of animals with tumors	Incidence of tumors	Incidence of metastases	Reference
ZnBeSiOx	1	UN	iv	7	7/7 (100%)	3/7 (43%)	
BeO	1	360	iv	1	UN	UN	Gardner and Heslington, 1946
ZnBeSiOx	UN	17	iv	4	4/5 (80%)	3/4 (75%)	
ZnBeSiOx	UN	0.264	iv (M)	>1	UN	UN	Cloudman *et al.*, 1949
ZnMnBeSiOx	0.45–0.85	3.7–7.0	iv	3	≅3/6 (50%)		
ZnMnBeSiOx	0.2	10–12.6	iv	3	≅3/4 (75%)	5/7 (71%)	Hoagland *et al.*, 1950
BeO	UN	360	iv	1	≅1/9 (11%)		
Be metal	0.04	40	iv	2	2/5 (40%)	UN	Barnes *et al.*, 1950
ZnBeSiOx	1–2.1	7.2–15	iv	6	6/13 (46%)	4/6 (67%)	
BeSiOx	1–1.2	UN	iv	1	1/8 (13%)	None	Barnes *et al.*, 1950
ZnBeSiOx	UN	64–90	iv	2	2/3 (67%)	2/2 (100%)	
BeO	UN	360–700	iv	6	6/6 (100%)	6/6 (100%)	Dutra and Largent, 1950
ZnBeSiOx	1	12	iv	5	5/10 (50%)	>2/5 (>40%)	Janes *et al.*, 1954
ZnBeSiOx	1	12	iv	10	10/13 (77%)	UN	Kelly *et al.*, 1961
BeO	1	360	iv	3	UN	2/3 (66%)	Komitowski, 1967
Be phosphate	0.103	UN	iv	1	UN	UN	Vorwald, 1950
BeO	0.22–0.4	79–144	IMD	7	7/9 (78%)	UN	
BeO	0.42–0.6	151–216	IMD	11	11/11 (100%)	UN	Yamaguchi, 1963
$ZnBeSiO_3$	0.02	0.144	IMD	4	4/12 (33%)	3/4 (75%)	Tapp, 1969
BeO	Inhalation 6 mg Be/m^3			1	≅1/6 (≅17%)	1/1 (100%)	Dutra *et al.*, 1951
Totals for ZnBeSiOx + ZnMnBeSiOx			iv	40	40/61 (66%)	≅18/30 (60%)	

[a] UN, unknown; IMD, intramedullary; ZnBeSiOx, zinc beryllium silicate; (M), mouse; ZnMnBeSiOx, zinc manganese beryllium silicate; BeO, beryllium oxide.

Dutra *et al.* (1951) found that the bones in animals that developed neoplasms contained 3–49 μg Be/g bone and that the primary tumors contained 0.007–0.93 μg Be/g tumor tissue. They and other authors believed that most of the beryllium in the bone was in reticuloendothelial cells in the marrow, since the particles were seen there by light microscopy. No separate chemical analyses were performed on the marrow alone.

LUNG CANCER

Soon after beryllium was discovered to induce osteosarcomas, Vorwald (1953) presented the first evidence which indicted beryllium as a pulmonary carcinogen. Four out of six rats that had survived for more than 1 year of intermittent inhalation exposures to $BeSO_4$ (33 μg Be/m^3) developed pulmonary adenocarcinomas. Metastases to tracheobronchial lymph nodes were seen in one rat. Although the number of animals in the specific control group was not stated, no lung tumors were found in that group or in hundreds of rats that had been exposed to a variety of other aerosols previously.

The first evidence confirming Vorwald's results was presented by Schepers (1955). Lung cancer was found in 39% (51/131) of rats exposed by inhalation to $BeSO_4$, for 6 months and autopsied at various times up to 18 months postexposure. Ten percent of the tumors metastasized. Both adenocarcinomas and squamous cell carcinomas were induced. Of considerable interest were the facts that the neoplasms developed after a relatively brief exposure period (6 months) and the peak incidence of lung cancer (55%) occurred 10–12 months after termination of exposures.

In 1957, Schepers *et al.* published similar data with more experimental details. Fifty-two exposed rats were autopsied at intervals from 7 to 24 months after initiation of a 6-month period of intermittent inhalation exposures to $BeSO_4$ (35 μg Be/m^3). Seventy-four lung neoplasms were identified after microscopic examination of single midcoronal sections of each lung. The maximum average number of lung neoplasms per animal was 2.5. Although the number of animals with lung tumors was not stated, the calculated number of animals so affected would be about 30 (74/2.5). The estimated incidence of lung tumors in the exposed rats was, therefore, 58% (30/52). Metastases were again noted to occur, and the primary neoplasms were successfully transplanted. A total of 81 control rats autopsied at intervals from 7 to 24 months of age did not exhibit any lung neoplasms. In a later paper, Schepers (1961) noted that the lung cancers induced by this method metastasized to adrenals, kidneys, liver, pancreas, and brain.

Again, in 1967, Reeves *et al.* confirmed that $BeSO_4$ was a pulmonary carcinogen in rats. Male and female rats exposed to 35 μg Be/m^3 (7 hr/day, 5 days/week) and controls were autopsied monthly over a period of 82 weeks. The total duration of exposure was 72 weeks. The first lung tumor was seen after 9 months of exposure and 43/43 (100%) of rats autopsied after 13 months of exposure had pulmonary adenocarcinomas. No lung neoplasms were seen in equal numbers of controls.

The inhalation of beryl ore (source of commerical beryllium for many years) containing 4% Be also caused pulmonary adenomas, adenocarcinomas, and epidermoid carcinomas in rats (Wagner *et al.*, 1969), whereas another beryllium

ore (bertrandite) with a lower beryllium content (1.4%) did not. The inhalation of beryllium fluoride, zinc manganese beryllium silicate, and beryllium phosphate have also been claimed to have produced lung cancer in rats (Schepers, 1961).

The first inhalation experiment with beryllium in monkeys was reported by Schepers (1964). Rhesus monkeys (*Macaca mulatta*) were exposed for 7–30 days to relatively high concentrations of BeF_2, $BeSO_4$, or beryllium phosphate. The most striking findings were alveolar epithelialization and metaplasia in lungs of animals exposed for 8–10 days and autopsied 7–82 days later, and a small tumor (3 mm in diameter) in the one monkey autopsied 82 days postexposure. This proved to be an indicator of the results that were to be obtained by Vorwald (1968). He found lung cancer in eight of nine rhesus monkeys that had survived 6 or more years of intermittent inhalation exposures to $BeSO_4$. The exposures to the affected monkeys varied from 1178 to 4070 hr to 35 μg Be/m^3 of air. The neoplasms were described as generally anaplastic with epidermoid and adenomatous characteristics. They all metastasized to the mediastinal lymph nodes and some to the bone, adrenals, and liver.

Intratracheal injection experiments have also proven useful in identifying carcinogenic beryllium compounds.

One lung tumor was produced by the intratracheal injection of BeO in rats in Vorwald's (1953) original work. The induction of lung cancer with metastases in monkeys after intrabronchial implantation and/or injection of beryllium oxide was also reported by Vorwald *et al.* (1966). Intratracheal injections of $Be(OH)_2$ were found to produce pulmonary metaplasia and cancer in rats (Groth *et al.*, 1972, 1979).

The most detailed studies with intratracheal injections with beryllium oxide were reported by Spencer *et al.* (1968, 1972). Several different experiments were performed in an effort to determine the role that surface area, solubility, and other physicochemical properties played on the carcinogenicity of beryllium oxide. Beryllium hydroxide was heated at 500, 1100, or 1600°C to provide three different beryllium oxides with slightly different physicochemical properties. These samples were injected intratracheally into rats in short- and long-term experiments. Although all three samples were found to be carcinogenic, there was a difference in tumor incidence. Fifty-one percent (23/45) of the rats developed pulmonary adenocarcinomas after single injections of 50 mg/kg of 500°C BeO, whereas 16% (3/19) and 11% (3/28) developed the same lesions when treated in the same manner with 1100°C BeO and 1600°C BeO, respectively. Results of later experiments (Spencer *et al.*, 1972) demonstrated that a BeO rocket exhaust product was almost as potent a carcinogen as the 500°C BeO. In that experiment, metastases to mediastinal lymph nodes were also observed.

In a series of experiments designed to compare the chronic effects of intratracheally injected beryllium alloys and intermetallics, Groth *et al.* (1979) found that Be metal, passivated Be metal, and a BeAl alloy caused pulmonary neoplasms. Although no tumors were produced with a 4% BeCu alloy and several other alloys and intermetallics, the dose of Be, duration of experiments, and numbers of anmials used were not sufficient to rule out the possibility of a carcinogenic effect from those compounds.

DISCUSSION

The history of the investigation of the carcinogenic effects of beryllium compounds has been relatively unique. Beryllium compounds were the first nonradioactive chemicals that were found to cause osteogenic sarcomas and the first to produce lung cancer by inhalation in animals (and possibly the first to produce lung neoplasms by intratracheal injections).

It can be safely stated that no other metal has been tested by as many different investigators and in as many different compounds in chronic aminal experiments as has beryllium. Eleven different senior authors have published 13 articles showing that osteogenic sarcomas can be produced by the intravenous injection of beryllium compounds in rabbits. Six different senior authors have published 14 articles and concluded that pulmonary neoplasms could be produced by inhalation exposures to and/or intratracheal injections of beryllium compounds in rats. In addition, lung cancer has been produced in monkeys. The following beryllium-containing compounds and materials have been shown to be carcinogenic: The phosphors—zinc beryllium silicate and zinc manganese beryllium silicate, beryllium silicate, BeO (fired at 500, 1100, or 1600°C), $Be(OH)_2$, beryllium phosphate, Be metal, BeA1 alloy, passivated Be metal, beryl ore, $BeSO_4$, and Be rocket exhaust. In addition, BeF_2 has been stated to be carcinogenic (Schepers, 1961).

In view of the overwhelming evidence, it is safe to conclude that Be is a carcinogen in laboratory animals, and that all beryllium-containing compounds should be considered potential carcinogens.

ACKNOWLEDGMENTS

The author wishes to thank Roberta Andrews for providing the source materials and Patricia Walker and Sylvia Shokler for typing the manuscript.

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