3. Studies of Cancer in Experimental Animals

3.1 Beryllium ores

Inhalation exposure

(*a*) *Rat*

Groups of 60 and 33 male Charles River, caesarian-derived rats and 30 Greenacres Controlled Flora rats (more than four weeks old) were exposed by inhalation to **beryl ore** (geometric mean particle diameter, 0.64 μm) or **bertrandite ore** (geometric mean particle diameter, 0.27 μm) as 15 mg/m^3 dust (the threshold limit value for inert dust in 1968) for 6 h per day on five days a week for up to 17 months. A third group, serving as controls, was housed in an inhalation chamber without exposure. The bertrandite ore atmosphere in the inhalation chamber contained 210 μg/m^3 beryllium, and the beryl ore atmosphere contained 620 μg/m^3 beryllium (for chemical composition, see Table 17). The death rates of the animals exposed to the two ores exceeded that of controls by 13%. Of the animals killed after 12 months of exposure, 5/11 treated with beryl ore had foci of squamous metaplasia or small epidermoid tumours. Of those killed at 17 months, 18/19 had lung tumours (18 bronchiolar alveolar-cell tumours, 7 adenomas, 9 adenocarcinomas and 4 epidermoid tumours). No metastasis was observed. In the group treated with bertrandite ore, granulomatous lesions and some atypical proliferations in the lung were observed, but no bronchiolar alveolar-cell tumour or other lung tumour was found. Controls had no neoplastic or granulomatous pulmonary lesion (Wagner *et al.*, 1969). [The Working Group noted the high crystalline silica content of the bertrandite ore and the incomplete reporting of the study.]

(*b*) *Hamster*

Groups of 48 and 17 male Syrian golden hamsters (more than four weeks old) were exposed by inhalation to **beryl ore** (geometric mean particle diameter, 0.64 μm) or **bertrandite ore** (geometric mean particle diameter, 0.27 μm) as 15 mg/m^3 dust for 6 h per day, five days a week for up to 17 months. A third group, serving as controls, was housed in an inhalation chamber without exposure. The bertrandite ore atmosphere in the inhalation chamber contained 210 μg/m^3 beryllium, and the beryl ore atmosphere contained 620 μg/m^3 (for chemical composition, see Table 17). The mortality of the animals exposed to the two ores exceeded that of controls by 25%. Atypical proliferations, first seen at 12 months in both groups of exposed animals, and lesions considered by the authors to be bronchiolar alveolar-cell tumours, except for their size, occurred. The lesions in the beryl-exposed animals were reported to become larger and more adenomatous after 17 months. The control hamsters had no pulmonary lesion (Wagner *et al.*, 1969). [The Working Group noted the incomplete reporting of the study.]

(*c*) *Monkey*

Groups of 12 and 4 male squirrel monkeys (*Saimiri sciurea*) (more than four weeks old) were exposed by inhalation to **beryl ore** (geometric mean particle diameter, 0.64 μm) or **bertrandite ore** (geometric mean particle diameter, 0.27 μm) as 15 mg/m^3 dust for 6 h per

day, five days a week for up to 23 months. A third group, serving as controls, was housed in an inhalation chamber without exposure. The bertrandite ore atmosphere in the inhalation chamber contained 210 μg/m^3 beryllium, and the beryl ore atmosphere contained 620 μg/m^3 (for chemical composition, see Table 17). The death rates of the animals exposed to the two ores exceeded that of controls by 11%. No tumour was found. Aggregates of dust-laden macrophages, lymphocytes and plasma cells were observed near respiratory bronchioles and small blood vessels in the lungs of exposed animals. Control monkeys had no similar change (Wagner *et al.*, 1969). [The Working Group noted the incomplete reporting and the limited duration of the study.]

Table 17. Chemical composition (of constituents representing > 0.1%) of representative bertrandite and beryl ore samples

Chemical constituent	Analysis by weight (%)	
	Bertrandite	Beryl ore
Be[a]	1.4	4.14
Al_2O_3	9.8	18.1
SiO_2	63.9[b]	
SiO_2 (as silicates)		63.6
SiO_2 (as quartz)		1.9
Fe_2O_3	1.8	1.1
MnO_2	1.8	1.0
CaF_2	8.3	
CaO	0.2	
MgO	2.3	1.1
K_2O	1.2	
Na_2O	1.5	0.5
ZnO	0.7	
CO_2	0.2	
NiO		0.5

Modified from Wagner *et al.* (1969)

[a][Probably as the oxide]

[b]23.5% of the mineral constituents were crystalline quartz and 23.5%, cristobalite (crystalline silica); the remainder was other silicates.

3.2 Beryllium metal and alloys

3.2.1 *Intratracheal instillation*

Rat: Twelve groups of 35 female Wistar rats, three months old, were treated with a single intratracheal instillation of 0.5 or 2.5 mg **beryllium metal** (100% Be), **passivated beryllium metal** (99% Be, 0.26% Cr [as chromate]), **beryllium–aluminium alloy** (62% Be, 38% Al), **beryllium–copper alloy** (4% Be, 96% Cu), **beryllium–copper–cobalt alloy** (2.4% Be, 0.4%

Co, 96% Cu) or **beryllium–nickel alloy** (2.2% Be, 97.8% Ni), with geometric mean particle sizes of 1–2 μm, suspended in 0.4 ml isotonic saline, followed by 0.2 ml saline. Forty control animals were instilled with 0.6 ml saline. The rats were killed when moribund or 18 months after instillation. The first lung neoplasm appeared 8–10 months after instillation. Lung neoplasms, mostly adenocarcinomas and adenomas, were found in 2/21 rats treated with the low dose and in 9/16 rats given the high dose of beryllium metal, in 7/20 animals treated with the low dose and in 9/26 treated with the high dose of passivated beryllium metal, and in 1/21 treated with the low dose and in 4/24 given the high dose of beryllium–aluminium alloy. No lung tumour occurred in 39 controls or in the groups treated with other alloys. The incidence of lung neoplasms was significantly ($p < 0.008$) increased over that in controls (using Fisher's exact test, one-tailed) in the groups that received 2.5 mg beryllium metal or 0.5 mg and 2.5 mg passivated beryllium metal (Groth *et al.*, 1980). [The Working Group noted the low beryllium content of the beryllium–copper alloy, the beryllium–copper–cobalt alloy and the beryllium–nickel alloy.]

3.2.2 *Intravenous injection*

Rabbit: In a study reported as a letter to the Editor, 24 young rabbits [sex and strain unspecified] received a series of intravenous injections of a washed suspension of finely divided **beryllium metal** in water (total dose, 40 mg/animal). Nine animals had died with liver necrosis within seven days, and 10 more died with this condition during the next month. Two of the surviving five rabbits died from pulmonary infections, two developed characteristic bone sarcomata, and a single rabbit survived (Barnes, 1950).

3.3 Beryllium compounds

3.3.1 *Oral administration*

Rat: **Beryllium sulfate** was administered to 52 male and 52 female Long–Evans rats (BLU:LE) in the drinking-water at a concentration of 5 ppm [5 mg/L] from weaning until natural death. The water also contained 5 ppm chromium[III] acetate, 50 ppm zinc acetate and 5 ppm copper acetate; 10 ppm manganese chloride and 1 ppm cobalt chloride; and 1 ppm sodium molybdate. An equal number of animals treated with water served as controls. The life span of the treated rats did not differ significantly from that of controls, but 20–30% of rats in each group died from pneumonia. No significant difference in tumour incidence was observed between treated and control groups (Schroeder & Mitchener, 1975). [The Working Group noted that the dose was too low for an evaluation of carcinogenicity.]

3.3.2 *Inhalation*

(*a*) *Rat*

Twenty-seven male and female albino Wistar rats, weighing 140–210 g, and 109 male and female Sherman rats, weighing 80–110 g, were exposed by inhalation to **beryllium sulfate tetrahydrate** aerosol to give a concentration of 1 μg/ft^3 Be [35.8 μg/m^3], for 8 h per day on 5.5 days a week for 180 days. Control groups of 69 male and female Wistar and 70 male and female Sherman rats were maintained in normal air. In the 52 rats that survived the

treatment, were transferred to 'normal air' and observed for periods of up to 18 months, 76 lung tumours were found, eight with metastases. The tumours included 18 adenomas, 5 squamous carcinomas, 24 acinous adenocarcinomas, 11 papillary adenocarcinomas and 7 alveolar-cell adenocarcinomas. None of the 139 control rats had lung tumours (Schepers *et al.*, 1957). [The Working Group noted the incomplete reporting of the study.]

A group of 75 male and 75 female Sprague–Dawley CD rats, six weeks of age, were exposed by inhalation to **beryllium sulfate tetrahydrate** aerosol for 7 h per day on five days a week for 72 weeks at a mean atmospheric concentration of 34.25 ± 23.66 μg/m^3 Be (average particle diameter, 0.118 μm). An equal number of control animals was exposed to an aerosol of distilled water. Subgroups of animals were killed each month up to the 56th week of exposure; 87% of all animals survived to their scheduled sacrifices. The first lung tumour was observed after nine months of exposure. All of the 43 rats that survived 13 months or more after the beginning of treatment had tumours, and all of the 56 tumours studied histologically were reported to be alveolar adenocarcinomas. No lung tumour was found in the control group (Reeves *et al.*, 1967). [The Working Group noted the incomplete reporting of the study.]

Groups of 30–50 female albino rats, weighing 155–160 g, received **beryllium oxide** or **beryllium chloride** by inhalation at concentrations of 0.8, 4, 30 or 400 μg/m^3 for 1 h per day on five days a week for four months. A group of 160 females served as controls. Only malignant epithelial lung tumours were considered: these occurred in 3/44, 4/39, 6/26 and 8/21 rats treated with beryllium oxide and in 1/44, 2/42, 8/24 and 11/19 treated with beryllium chloride, but in none of the controls (Litvinov *et al.* 1984) [The Working Group noted the incomplete reporting of the study.]

(*b*) *Rabbit*

Three groups of rabbits [sex, strain and age unspecified] were exposed by inhalation to aerosols of **beryllium oxide** (average particle diameter, 0.285 μm; range, 0.11–1.25) at doses of 1 (five rabbits), 6 (six rabbits) or 30 (eight rabbits) μg/L Be for 5 h per day on five days a week for 9–13 months. No control group was available. An osteogenic sarcoma in the left pubis with widespread visceral metastases was observed in one rabbit that had been exposed to 6 μg/L Be for 235 days over 11 months (Dutra *et al.*, 1951). [The Working Group noted the small number of animals and the short duration of exposure.]

(*c*) *Monkey*

In a study reported as an abstract, 16 rhesus monkeys (*Macaca mulatta*) were exposed daily by inhalation 'for a long period of time' to **beryllium sulfate** aerosol at a concentration of 35 μg/m^3 Be. Primary anaplastic pulmonary tumours with adenomatous and epidermoid patterns were observed in three monkeys between six months and eight years after the beginning of exposure (Vorwald, 1967).

3.3.3 *Intratracheal instillation*

(*a*) *Rat*

A group of 35 female Wistar-derived rats, three months old, received single intratracheal instillations of 50 μg Be as **beryllium hydroxide** suspended in distilled water,

followed 10 months later by a second instillation of 25 μg. A group of 35 controls received a single intratracheal instillation of 2.5 mg chrysotile asbestos. Both materials were suspended in 0.4 ml distilled water, and the instillation was followed by 0.2 ml distilled water. Of the beryllium hydroxide-treated rats sacrificed at 19 months of age, 13/25 had pulmonary tumours (six adenomas and seven adenocarcinomas); one rat had both an epidermoid carcinoma and an adenocarcinoma. The lungs of all of the animals instilled with chrysotile had small and occasionally larger scars; adenomas occurred in two rats and an adenocarcinoma in a third. Metaplastic foci were found in the lungs of 5% of the chrysotile-treated group, whereas in 90% of the animals instilled with beryllium most of the normal lung tissue was replaced by metaplastic foci and tumours (Groth *et al.*, 1980). [The Working Group noted the lack of an appropriate control group.]

Two groups of 30 male Wistar rats, 10 weeks of age, were instilled intratracheally with **beryllium oxide** (low-temperature fired, 900 °C; 1 mg as Be) or arsenic trioxide (1 mg as As) once a week for 15 weeks. A group of 16 rats served as untreated controls. All rats in the beryllium-treated group, 19 in the arsenic-treated group and all of the controls survived the treatment period and were observed for life. Two malignant (one squamous-cell carcinoma and one adenocarcinoma) and four benign lung adenomas (three suspected of malignancy) were found in rats treated with beryllium, and one malignant lung tumour (a squamous-cell carcinoma) was found in those treated with arsenic; no lung tumour was observed in the control group (Ishinishi *et al.*, 1980).

Eight groups of inbred albino rats [initial number and sex unspecified], weighing 140–150 g, received single intratracheal instillations of **high-temperature fired beryllium oxide** (2000 °C) or **low-temperature fired beryllium oxide** (600 °C) at doses of 0.036, 0.36, 3.6 and 18 mg/kg bw. A group of 300 untreated rats served as controls. All animals were observed for life. Malignant epithelial lung tumours occurred in 0/76, 0/84, 2/77 and 2/103 rats treated with the high-temperature fired beryllium oxide and in 3/69, 7/81, 18/79 and 8/26 rats treated with the low-temperature fired compound. None were found in 104 controls (Litvinov *et al.*, 1983).

(*b*) *Monkey*

In a study reported as an abstract, a group of 20 rhesus monkeys (*Macaca mulatta*) received an intrabronchial intubation and/or a bronchomural injection [unspecified] of **beryllium oxide** particulates suspended in sterile physiological saline. The first bronchogenic tumour was detected about 4.5 years after first treatment. In the course of the following year, two additional monkeys developed tumours, which were highly anaplastic, with adenomatous and epidermoid patterns (Vorwald, 1967).

3.3.4 *Intravenous injection*

(*a*) *Mouse*

In a study reported as an abstract, three groups of mice received 20–22 intravenous injections (two/week) of either **zinc beryllium silicate** (8.36 mg Zn, 0.264 mg Be), zinc silicate (2.8 mg Zn) or **beryllium oxide** (1.54 mg Be). A fourth group was untreated. 'Some' mice given zinc beryllium silicate were reported to have developed malignant bone tumours (Cloudman *et al.*, 1949).

(*b*) *Rabbit*

In a study reported as an abstract, rabbits received synthetic **zinc beryllium silicate** and its ingredients, **beryllium oxide**, zinc oxide, silicic acid and zinc silicate, intravenously in 20 doses totalling 1 g of particles 3 μm or smaller, over a six-week period. All of the seven rabbits given zinc beryllium silicate which survived the injections for seven months or more developed malignant osteosarcomas, four with visceral metastases. One rabbit killed one year after injection of beryllium oxide had a malignant osteosarcoma. Such tumours were not induced by administration of 65 other minerals in the same way (Gardner & Heslington, 1946).

In a study reported as an abstract, three groups of rabbits received 20–22 intravenous injections (two/week) of either **zinc beryllium silicate** (550 mg Zn, 17 mg Be), zinc silicate (390 mg Zn) or **beryllium oxide** (390 mg Be). A fourth group was untreated. Four of five rabbits given zinc beryllium silicate which survived over one year from the start of injections had bone tumours, three with metastases (Cloudman *et al.*, 1949).

Six groups comprising 67 rabbits of different breeds and sexes were injected intravenously twice a week with various samples of **zinc beryllium silicate** (67% ZnO, 28% SiO_2, 2% BeO and 3% MnO; or 67% ZnO, 31% SiO_2 and 2% BeO), **beryllium silicate** or zinc silicate, with particle sizes of 5 μm or less as a 1 ml suspension in water at the dose schedule indicated in Table 18. Bone sarcomas developed in 7/21 rabbits injected with beryllium silicates that survived for 30 weeks or more. The earliest evidence of malignant change was observed at 32 weeks, and the latest tumour occurred 83 weeks after the last injection. No tumour was found in any of the animals injected with zinc silicate only (Barnes *et al.*, 1950). [The Working Group noted the poor survival.]

Table 18. Results of experiments in rabbits with beryllium silicates

Material injected	Conc. of suspension (%)	No. of injections	Total amount injected (g)	Initial no./group	No. of survivors	No. with osteosarcomas
Zinc beryllium silicate	10	10	1.0	10	3	0
Zinc beryllium silicate	30	6	2.1	12	3	2
Zinc beryllium silicate	10	10	1.0	12	11	4
Beryllium silicate	20	6	1.2	11	3	1
Beryllium silicate	10	10	1.0	12	8	0
Zinc silicate	20	6	1.2	10	8	0

From Barnes *et al.* (1950)

Young, adult, male and female white rabbits [number unspecified] were given intravenous injections of either a highly purified **beryllium oxide** or a **calcined phosphor** containing beryllium oxide, zinc oxide and silica mixed in a molar ratio of 1:1:1, as 1% suspensions in physiological saline. The particles of the powders were smaller than 1 μm. The beryllium oxide-treated group received a total of 360–700 mg Be/rabbit in 20–26 injections, and the phosphor group received 64–90 mg Be/rabbit in 17–25 injections. The compounds were given three times a week over approximately six to nine weeks. One year or more after the first injection, six animals given beryllium oxide and three given calcined phosphor were

still alive. The first tumour was found 11.5 months after the start of the experiment. Osteosarcomas were found in all six beryllium oxide-treated rabbits (two were reported after the paper had been submitted for publication); some were metastases and some were multiple primary tumours. Osteosarcomas were found in 2/3 rabbits given the phosphor. About 50 untreated rabbits kept for similar or longer periods developed no malignant tumour (Dutra & Largent, 1950). [The Working Group noted the small group sizes, the limited reporting and the incomplete observations.]

A group of 13 female and 11 male rabbits of unselected strains, with an average initial body weight of 5.5 lbs [2.5 kg], received intravenous injections of insoluble beryllium compounds under sterile conditions at a dose of 5 ml at one-day or four-day intervals, in an attempt to administer a total of 1 g of the powder. Five animals received **beryllium phosphate**; six rabbits received a **zinc beryllium silicate** containing 60% ZnO, 30% SiO_2, 2% MnO and 2.3% BeO; four received another zinc beryllium silicate containing 14% **beryllium oxide** and 48% zinc oxide; and nine rabbits received **beryllium oxide** from different sources. Except for the beryllium phosphate, which was administered in a 0.1% suspension in saline, all substances were injected as 1% suspensions in saline. Eight animals died of various causes within three months of the start of treatment, and eight more rabbits died at 14–28 months from infectious diseases. Seven of the eight surviving rabbits developed osteogenic sarcomas: three in the group treated with zinc beryllium silicate containing 2.3% BeO, three in the group treated with zinc beryllium silicate containing 14% BeO and one treated with beryllium oxide. One animal that received 100 mg beryllium phosphate was still alive 2.5 years after injection (Hoagland *et al.*, 1950). [The Working Group noted the small group size and the lack of appropriate controls.]

Osteosarcomas were found in 2/4 rabbits within 18 months after a single intravenous injection of 1 g **beryllium phosphate**; no tumour was found in three rabbits that received 1 g **beryllium oxide**. Of animals injected with beryllium oxide mixed with zinc oxide, manganese oxide and/or silicon oxide, 9/31 developed osteosarcomas (Araki *et al.*, 1954). [The Working Group noted the small number of animals, the lack of an appropriate control group and the incomplete reporting.]

Ten adult, male rabbits received two intravenous injections per week for 10 weeks of 5 ml of a 1% suspension of **zinc beryllium silicate** containing 3.36% **beryllium oxide** (total dose, 1 g zinc beryllium silicate or 33.6 mg beryllium oxide). Five rabbits developed osteogenic sarcomas 9–11 months after the injection period (Janes *et al.*, 1954). [The Working Group noted the lack of an appropriate control group and the small group size.]

Fourteen rabbits were injected intravenously with 5 ml of a 1% suspension of **zinc beryllium silicate** (size of particles, 1–3 μm) in physiological saline twice a week for 10 weeks (total dose, 1 g zinc beryllium silicate). The animals died or were killed 28–57 weeks after the last injection. Osteogenic sarcomas appeared in 10/14 rabbits 30–52 weeks after the last injection (Kelly *et al.*, 1961). [The Working Group noted the lack of an appropriate control group and the small group size.]

Osteosarcomas were induced in 3/20 rabbits 15–18 months after single intravenous injections of **beryllium oxide** (total dose, 1 g/rabbit) as a 1% suspension in saline (Komitowski, 1968). [The Working Group noted the lack of an appropriate control group.]

Sixty rabbits, six months of age on average, were treated intravenously with a 1% **beryllium oxide** suspension in 5 ml physiological saline, once a week for 25 weeks. Of the 29 animals that survived until the end of the experiment, 21 developed sarcomas (Fodor, 1977). [The Working Group noted the lack of an appropriate control group and the incomplete reporting.]

3.3.5 *Intraperitoneal injection*

Mouse: In a screening assay based on the accelerated induction of lung adenomas in a strain highly susceptible to development of this neoplasm, three groups of 20 male A/J mice, five to six weeks old, were injected intraperitoneally three times a week for eight weeks with **beryllium sulfate tetrahydrate** (purity $\geq$ 99%) suspended in distilled water at doses of 0.02, 0.05 or 0.1 (maximum tolerated dose) mg/mouse per injection. An equal number of animals were treated with the vehicle only and served as controls. The authors stated that beryllium sulfate produced a significant (χ^2 analysis) increase in lung tumour incidence at total doses of 1.2 and 2.4 mg/mouse with no significant increase in lung tumour multiplicity (Ashby *et al.*, 1990). [The Working Group noted that the increases were not significant using Fisher's exact test.]

3.3.6 *Implantation and/or injection into bone*

Rabbit: Of 55 rabbits that received 1–43 injections of 10 mg **beryllium oxide** as a 1% suspension in isotonic saline into the marrow of the right femur twice weekly (20 mg/week), one developed a chondroma, three developed osteomas, 15 developed chondrosarcomas and seven developed osteochondrosarcomas. The average time between the last injection and the appearance of a tumour was 85 days. The period of observation was one to two years (Yamaguchi, 1963).

A group of 12 rabbits of mixed breeds and sexes, six weeks old, received 20 mg **zinc beryllium silicate powder** (particle diameter, $\leq$ 5 μm), suspended in 0.5 ml of water, as a single intramedullary injection into the upper end of the right tibia. A similar suspension of **zinc oxide** was injected into the left tibia as a control. All rabbits survived the injections for at least 12 months; four animals died of intercurrent infections. Osteogenic sarcomas were found in four rabbits at 12–15 months; three metastasized. The remaining four animals were killed at 15–20 months with no clinical or radiological evidence of tumours. No effect was seen with zinc oxide (Tapp, 1966).

Three groups of six rabbits of mixed breeds and sexes, six to eight weeks old, received implants of 10 mg **zinc beryllium silicate**, **beryllium oxide** or **beryllium silicate** under the periosteum of the upper end of the right tibia. Three animals from each group also received implants of zinc oxide or zinc silicate in a similar procedure into the left tibia and served as controls. Nine animals were killed between 2 and 18 months; the remaining animals lived for 25 months. Four of the animals developed central osteogenic sarcomas between 10 and 25 months after implantation; two occurred in animals treated with beryllium and metastasized, one occurred in an animal given zinc beryllium silicate and metastasized, and one occurred in an animal given beryllium silicate. No tumour occurred in the left tibia of the animals implanted with zinc oxide or zinc silicate (Tapp, 1969).

After intramedullary administration of **beryllium oxide** [purity, dose and dose schedule unspecified] (particle size, ~4 μm) in gelatin into the femur, 5/20 rabbits developed osteogenic sarcomas with lung metastases during an observation period of 24 months. The first tumour was observed 13 months after injection (Komitowski, 1974). [The Working Group noted the lack of an appropriate control group and the incomplete reporting.]

Rabbits were given intramedullary implantations of **beryllium carbonate** (173 rabbits), **beryllium acetate** (18 rabbits), **beryllium acetylacetonate** (10 rabbits), **beryllium laurate** (3 rabbits) or **beryllium stearate** (3 rabbits). Thirty animals given beryllium carbonate developed osteosarcomas 10–17 months after the first treatment; the tumours were detected radiologically between 10 and 21 months and confirmed histologically. One rabbit given beryllium acetylacetonate that survived 13 months developed an osteosarcoma (Matsuura, 1974). [The Working Group noted the incomplete reporting and the small numbers of animals in groups other than the group treated with beryllium carbonate.]

A group of 65 Fauve de Bourgogne rabbits [sex unspecified], 15–20 weeks old, received single intraosseous injections of 0.5 ml of a suspension prepared from 1 g **zinc beryllium silicate** in 15 ml distilled water and gelatin (33 mg Be) into the tibial or femoral metaphysis. Of the 65 rabbits that survived more than four months after the injection, 45 developed osteogenic sarcomas. Radiographic examination indicated that the first sarcomatous changes occurred after three months (Mazabraud, 1975). [The Working Group noted the lack of an appropriate control group.]

Three groups of 10 male rabbits [strain unspecified], six weeks of age, received implants of pellets of hydroxypropylcellulose mixed with **beryllium oxide** into the distal metaphysis of the right femur as follows: Group 1, into the internal callus one week after production of an artificial fracture at a dose of 300 mg; Group 2, into the bone-marrow cavity at a dose of 300 mg; and Group 3, into the bone-marrow cavity at a dose of 50 mg. A further group of 10 rabbits served as untreated controls. At 56 weeks, osteosarcomas had developed in 10/10 rabbits in Group 1, in 7/10 rabbits in Group 2 and in 1/10 rabbits in Group 3. Tumours appeared significantly earlier in Group 1 than in the other groups, and 80% of animals with osteosarcomas had lung metastases (Hiruma, 1991).

3.3.7 *Administration with known carcinogens*

Mouse: Five groups of 40 female and 40 male SENCAR mice, seven to nine weeks old, received a single intraperitoneal injection of 0, 0.01, 0.1, 1.0, 5.0 or 10.0 μg/mouse **beryllium sulfate** [purity unspecified]) in saline. One week after treatment, each animal received dermal applications of 2 μg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) twice a week for 26 weeks. A positive control group received 50.5 μg/mouse benzo[*a*]pyrene followed by the TPA treatment. About 95% of the animals survived the treatment. Beryllium sulfate did not induce a significant number of mouse skin papillomas (Nesnow *et al.* 1985).