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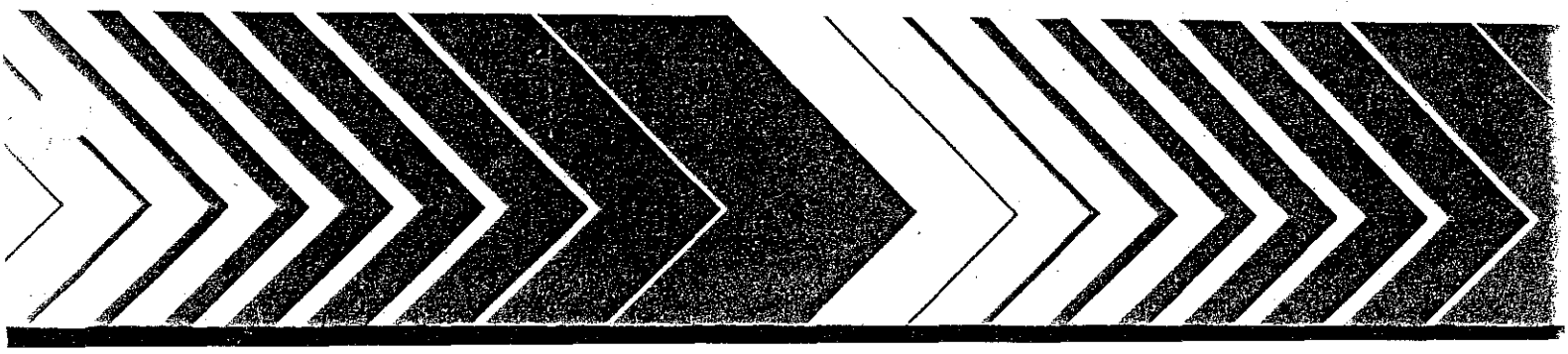
Health Assessment Document for Beryllium



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Health Assessment Document for Beryllium

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Research Triangle Park, North Carolina 27711

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New cases of chronic beryllium disease are still being reported due to the fact that, in some instances, the occupational standards have been exceeded. In industries where the average exposure generally has been below 2 $\mu g/m^3$, there have been very few new cases of chronic beryllium disease.

There have also been a large number of "neighborhood" cases of beryllium disease. Neighborhood cases are those in which chronic beryllium disease occurs in people living in the vicinity of beryllium-emitting plants. The air concentrations of beryllium in such areas at the time when the disease occurred have probably been around 0.1 $\mu g/m^3$, but considerable exposure via dust transferred to homes on workclothes likely contributed to the occurrence of the disease. No new "neighborhood" cases of beryllium disease have occurred since standards of 0.01 $\mu g/m^3$ were set for the ambient air and the practice of washing workers' clothes in the plants was initiated. Presently, ambient air levels are generally below 1 ng/m^3.

2.3.3 Dermatological Effects of Beryllium Exposure

Contact dermatitis and some other dermatological effects of beryllium have been documented in occupationally exposed persons, but there are no data indicating that such reactions have occurred, or may occur, in the general population.

2.3.4 Teratogenic and Reproductive Effects of Beryllium Exposure

Available information on the teratogenic or reproductive effects of beryllium exposure is limited to three animal studies. The information from these studies is not sufficient to determine whether beryllium compounds have the potential to produce adverse reproductive or teratogenic effects. Further studies are needed in this area.

2.4 MUTAGENIC EFFECTS OF BERYLLIUM EXPOSURE

Beryllium has been tested for its ability to cause gene mutations in *Salmonella typhimurium*, *Escherichia coli*, yeast, cultured human lymphocytes, and Syrian hamster embryo cells; DNA damage in *Escherichia coli*; and unscheduled DNA synthesis in rat hepatocytes.

Beryllium sulfate and beryllium chloride have been shown to be nonmutagenic in all bacterial and yeast gene mutation assays. However, this may be

due to the fact that bacterial and yeast systems generally are not sensitive to metal mutagens. In contrast, gene mutation studies in cultured mammalian cells, Chinese hamster V79 cells, and Chinese hamster ovary (CHO) cells have yielded positive mutagenic responses of beryllium. Similarly, chromosomal aberration and sister-chromatid exchange studies in cultured human lymphocytes and Syrian hamster embryo cells have also resulted in positive mutagenic responses of beryllium. In DNA damage and repair assays, beryllium was negative in pol, rat hepatocyte, and mitotic recombination assays, but was weakly positive in the rec assay. Based on available information, beryllium appears to have the potential to cause mutations.

2.5 CARCINOGENIC EFFECTS OF BERYLLIUM EXPOSURE

2.5.1 Animal Studies

Experimental beryllium carcinogenesis has been induced by intravenous or intramedullary injection of rabbits and by inhalation exposure or by intratracheal injection of rats and monkeys. With one possible exception, beryllium carcinogenesis has not been induced by ingestion. Carcinogenic responses have been induced by a variety of forms of beryllium including beryllium sulfate, phosphate, oxide, and beryl ore. The carcinogenic evidence in mice (intravenously injected or exposed via inhalation) and guinea pigs and hamsters (exposed via inhalation) is equivocal.

Osteosarcomas are the predominant types of tumors induced in rabbits. These tumors are highly invasive, metastasize readily, and are judged to be histologically similar to human osteosarcomas. In rats, pulmonary adenomas and/or carcinomas of questionable malignancy have been obtained, although pathological end points have not been well documented in many cases.

Although, individually, many of the reported animal studies have methodological and reporting limitations compared to current standards for bioassays, collectively the studies provide reasonable evidence for carcinogenicity. Responses have been noted in multiple species at multiple sites and, in some cases, afford evidence of a dose response. On this basis, using EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) to classify the weight of evidence for carcinogenicity in experimental animals, there is "sufficient" evidence to conclude that beryllium is carcinogenic in animals. Since positive responses were seen for a variety of beryllium compounds, all forms of beryllium are considered to be carcinogenic.

2.5.2 Human Studies

Epidemiologic studies provide equivocal conclusions on the carcinogenicity of beryllium and beryllium compounds. Early epidemiologic studies of beryllium exposed workers (see IARC, 1972, 1980; Bayliss et al., 1971; Bayliss and Lainhart, 1972) do not report positive evidence for increased cancer incidence. However, recent studies do report a significantly increased risk of lung cancer in exposed workers. The absence of beryllium exposure levels and a demonstrated concern about possible confounding factors within the workplace make the reported positive correlations between beryllium exposure and increased risk of cancer difficult to substantiate. This relegates the reported statistically significant increases of lung cancer to, at best, an elevated incidence that is not statistically significant. Because of these limitations, the EPA (U.S. EPA, 1986) considers the available epidemiologic evidence to be "inadequate" to support or refute the existence of a carcinogenic hazard for humans exposed to beryllium.

This designation of the epidemiologic data as "inadequate" differs from that of the International Agency for Research on Cancer (IARC, 1980) which concluded that the epidemiologic data provides "limited" evidence for the carcinogenicity of beryllium. In the EPA evaluation, more recent unpublished tabulations and analysis of the earlier study cohorts that correct for errors in the data base and the National Institute for Occupational Safety and Health (NIOSH) Life-Table program were included. Use of this newer data provides a basis to change the weight-of-evidence conclusion for the human data.

2.5.3 Qualitative Carcinogenicity Conclusions

Using the EPA weight-of-evidence criteria for evaluating both human and animal evidence, beryllium is most appropriately classified in Group B2, indicating that, on the strength of animal studies, beryllium should be considered a probable human carcinogen. This category is reserved for chemicals having "sufficient" evidence for carcinogenicity in animal studies and "inadequate" evidence in human studies. In this particular case, the animal evidence demonstrates that all beryllium species should be regarded as probably being carcinogenic for humans.

2.6 HUMAN HEALTH RISK ASSESSMENT OF BERYLLIUM

2.6.1 Exposure Aspects

In the general U.S. population, the dietary intake of beryllium is probably less than 1 μg a day, and due to its chemical properties, very little is available in the gut for absorption. Approximately half of the absorbed beryllium enters the skeleton.

For most people, the daily amount of beryllium inhaled is only a few nanograms. However, it is likely that much of this is retained in the lungs. The available data indicate that the beryllium lung burden in the average adult ranges from 1 to 10 μg. Since beryllium occurs in cigarettes, it is possible that smokers will inhale and retain more beryllium than nonsmokers. Unfortunately, the data on beryllium concentrations in mainstream smoke are, at present, uncertain.

2.6.2 Relevant Health Effects

Occupational exposure to various beryllium compounds has been associated with acute respiratory disease and chronic beryllium disease (in the form of granulomatous interstitial pneumonitis). Some systemic effects have also been noted and a hypersensitization component probably plays a major role in the manifestation of these effects. In the past, chronic beryllium disease was found in members of the general population living near beryllium-emitting plants, but past exposures were relatively high compared to present levels of beryllium in the ambient air. Contaminated workclothes brought home for washing contributed to these exposures. No "neighborhood" cases of chronic beryllium disease have been reported in the past several years.

Numerous animal studies have been performed to determine whether or not beryllium and beryllium-containing substances are carcinogenic. Although some of these studies have limitations, the overall evidence from animal studies should be classified as "sufficient" using EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986). IARC (1980) has also concluded that the evidence from animal studies is "sufficient." Human studies on beryllium carcinogenicity have deficiencies that limit any definitive conclusion that a true association between beryllium exposure and cancer exists. Nevertheless, it is possible that a portion of the excess cancer risks reported in these studies may, in fact, be due to beryllium exposure. Although IARC concluded that beryllium and its

compounds should be classified as having "limited" human evidence of carcinogenicity, the U.S. Environmental Protection Agency's Carcinogen Assessment Group (CAG) has concluded that the human evidence is "inadequate."

2.6.3 Dose-Effect and Dose-Response Relationships of Beryllium

As previously stated, beryllium can act upon the lung in two ways, either through a direct toxic effect on pulmonary tissue or through hypersensitization. Even if reliable and detailed exposure data were available, it would still be difficult to establish dose-effect and dose-response relationships due to this hypersensitization factor. No adverse effects have been noted in industries complying with the 2 $\mu g/m^3$ standard set by the Occupational Safety and Health Administration (OSHA); therefore, it appears that this level of beryllium in air provides good protection with regard to respiratory effects. It is unknown whether exposures to the maximum permissible peak standard (25 $\mu g/m^3$) can cause delayed effects.

From available data, the CAG has discussed the estimation of carcinogenic unit risks for inhalation exposure to beryllium. The quantitative aspect of carcinogen risk assessment is included here because it may be of use in setting regulatory priorities and in evaluating the adequacy of technology-based controls and other aspects of the regulatory decision-making process. However, the methodologic uncertainties associated with estimating cancer risks to humans at low levels of exposure should be recognized. The linear extrapolation procedures used (see Section 7.3) typically provide a rough but plausible estimate of the upper limit of risk--that is, it is not likely that the true risk would be much higher than the estimated risk, but it could be considerably lower. In the case of beryllium, due to the uncertainty introduced by specific characteristics of the data base which may be best thought of as affecting the confidence in the upper-limit estimates, the unit risk estimates presented below may be most appropriately viewed as sensitivity analyses. These risk estimates should not be regarded, therefore, as accurate representations of true cancer risks. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-limit risks and sensitivity analyses are found to be useful.

Both animal and human studies have been used to examine the carcinogenic potency of beryllium. For quantitative risk assessment purposes the animal data present some difficult analytical problems because of weaknesses in the

design and the reporting of the studies. Despite the weaknesses of the individual studies, however, there is little doubt that beryllium induces cancer in laboratory animals.

An additional difficulty in the use of animal data for quantitative assessment is due to the fact that, not only did many of the animal studies utilize different forms of beryllium than those commonly present in the ambient environment, but the carcinogenic response varied with the beryllium compound used. Moreover, the form most common in ambient air is beryllium oxide and, although all the animal studies were deficient in some respects, the ones utilizing beryllium oxide were more deficient, as a group, than those utilizing beryllium salts. Nevertheless, it was felt that the quantitative analysis should focus upon the form of beryllium humans are most likely to be exposed to.

While the available beryllium oxide studies were individually weak, a correlation of estimates from several data sets would be expected to increase confidence in the results. Potency factors were thus calculated using data from eight beryllium oxide animal studies. The results were reasonably consistent and the geometric mean of all eight potency factors was $2.1 \times 10^{-3}/(\mu g/m^3)$, which agreed quite well with the potency factor derived from the human epidemiologic data.

The question of beryllium potency by ingestion is highly uncertain and debatable due to the equivocal or negative results from ingestion studies. From a weight-of-evidence point of view, the potential for human carcinogenicity by this route cannot be dismissed. For practical purposes, however, the potency of beryllium via ingestion must be considered as largely unknown.

Even though the epidemiologic studies have been judged to be qualitatively inadequate to assess the potential of carcinogenicity for humans, these studies can be analyzed to determine the largest plausible risk that is consistent with the available epidemiologic data. This upper bound is a risk estimate and can be used to evaluate the reasonableness of estimates derived from animal studies. Information from the epidemiologic study by Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been combined to estimate a plausible upper bound for incremental cancer risk associated with exposure to air contaminated with beryllium oxide. The epidemiologic data, while being useful for estimating the cancer potency of beryllium, nevertheless, also has interpretative limitations because of the uncertainties regarding exposure levels. In the occupational exposure studies upon which the risk analysis is based, the narrowest range for median exposure

that could be obtained on the basis of available information was 100 to 1,000 $\mu g/m^3$. Furthermore, an assumption was made that the ratio of exposure duration to years at risk ranged from 0.25 to 1.0. The geometric mean of the potency factors derived using these assumptions equals $2.4 \times 10^{-3}/(\mu g/m^3)$.

The unit risks from the beryllium oxide animal data sets are best viewed as demonstrating a consistency of response, as opposed to a collection of individually reliable upper-bound risk values. Within the consistency range, sensitivity is shown relating to the beryllium species tested, and for beryllium oxide, perhaps to firing temperature. Because of the need to assume exposure levels, the risk estimate derived from the human epidemiology data is, in effect, also the result of a sensitivity analysis which shows a consistency of response.

With these noted caveats, the CAG feels that a recommendation for a specific upper-bound estimate of risk is warranted, even though it does evolve from less than ideal data, in order to provide a crude measure of the potential for public health impact if, in fact, beryllium is assumed to be a human carcinogen. Taken together, the notable comparability of the animal and human based estimates for beryllium oxide encourages one to consider these estimates as being of some utility. Given the correlation of animal and human estimates, the upper-bound incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium oxide, after rounding to one significant figure, is 2×10^{-3}.

There are two types of uncertainty associated with this value, one involving the typical concern about upper-limit values (i.e. the true risk is not likely to be higher than this value and may be lower) and a second uncertainty relating to the use of dosimetry assumptions in the risk modelling which may result in either an over- or underestimation of the recommended upper-limit value. The utility of the beryllium oxide risk value in risk management analysis should be judged with these uncertainties in mind. Hence, whereas one might use these estimates to screen for a possible public hazard, one should exercise much greater caution in using these values for an assessment of individual cancer risk. If the form of beryllium present includes more than a small fraction of beryllium salts, then the beryllium oxide risk value may underestimate the upper limit and the animal based estimates for beryllium sulfate or other salts should be used. These estimates have the typical upper-limit uncertainty relating to the true risk. The incremental upper-limit of $2 \times 10^{-3}/(\mu g/m^3)$ places beryllium oxide in the third quartile of 59 suspect carcinogens evaluated by the CAG.

2.6.4 Populations at Risk

In terms of exposure, persons engaged in handling beryllium in occupational environments obviously comprise individuals at highest risk. With regard to the population at large, there may be a small risk for people living near beryllium-emitting industries. However, the risk for such individuals may not be from ambient air levels of beryllium, but rather from beryllium-contaminated dust within the household. There are no data that allow an estimate of the number of people that may be at such risk, but it is reasonable to assume that it is a very small group. It should be noted that no new "neighborhood" cases of beryllium disease have been reported since the 1940s.

6. MUTAGENIC EFFECTS OF BERYLLIUM

Beryllium has been tested for its ability to cause genetic damage in both prokaryotic and eukaryotic organisms. The prokaryotic studies include gene mutations and DNA damage in bacteria. The eukaryotic studies include DNA damage and gene mutations in yeast and cultured mammalian cells, and studies of chromosomal aberrations and sister-chromatid exchanges in mammalian cells in vitro. The available literature indicates that beryllium has the potential to cause gene mutations, chromosomal aberrations, and sister-chromatid exchange in cultured mammalian somatic cells.

6.1 GENE MUTATIONS IN BACTERIA AND YEAST

The studies on beryllium-induced gene mutations in bacteria and yeast are summarized in Table 6-1.

6.1.1 Salmonella Assay

Beryllium has been tested for its ability to cause reverse mutations in Salmonella typhimurium (Simmon, 1979a; Rosenkranz and Poirier, 1979).

Simmon (1979a) found that beryllium sulfate was not mutagenic in Salmonella strains TA1535, TA1536, TA1537, TA98, and TA100. Agar-incorporation assay, with and without S-9 metabolic activation, was employed. The highest concentration of beryllium sulfate tested was 250 µg/plate (12.5 µg Be). No mutagenic response was obtained in any of the above strains.

Beryllium sulfate was also not mutagenic in Salmonella typhimurium strains TA1535 and TA1538, both in the presence and absence of the S-9 activation system (Rosenkranz and Poirier, 1979). The two concentrations of the test compound used were 25 µg/plate and 250 µg/plate. No significant differences in the mutation frequencies between the experimental and the control plates were noted.

TABLE 6-1. MUTAGENICITY TESTING OF BERYLLIUM: GENE MUTATIONS IN BACTERIA AND IN YEAST

Test System	Strain	Concentration of Test Compounds as Be	S-9 Activation System	Results	Comments	Reference
Salmonella typhimurium	TA1535 TA1536 TA1537 TA100 TA98	Maximum of 12.5 µg/plate	±	Reported negative in all strains	1. Only highest concentration used.	Simmon (1979a)
Salmonella typhimurium *Saccharomyces cerevisiae*	TA1530 TA1538 TA1535 D_3	Unknown [Given either as i.m. injections (25 mg/kg) or by gavage (1200 mg/kg beryllium sulfate)]	Host-mediated assay in mice	Reported negative in all strains by both routes of exposure		Simmon et al. (1979)
Salmonella typhimurium	TA1535 TA1538	1.25 µg/plate 12.5 µg/plate	±	Reported negative		Rosenkranz and Poirier (1979)
Escherichia coli	WP2	0.9-90 µg/plate		Reported negative		Ishizawa (1979)

6.1.2 Host-Mediated Assay

Negative mutagenic response of beryllium sulfate was obtained in the host-mediated assay (Simmon et al., 1979). Several procedures were used. In all procedures the tester strain was injected intraperitoneally and the beryllium sulfate was given orally or by intramuscular injection. Four hours later, the Salmonella or Saccharomyces tester strain was recovered from the peritoneal cavity and plated to determine the number of mutants (Salmonella) or recombinants (Saccharomyces) and the number of recovered microorganisms. Simultaneous experiments were conducted with control (untreated) mice. Using 25 mg/kg given intramuscularly, beryllium sulfate was not mutagenic with tester strain TA1530 or TA1538. Using 1200 mg/kg given orally, beryllium sulfate was not mutagenic in TA1535 and did not significantly increase the recombination frequency in S. cerevisiae D3.

6.1.3 Escherichia coli WP2 Assay

A negative mutagenic response in the Escherichia coli WP2 system was obtained with beryllium concentrations ranging from 0.1 to 10 µmol/plate (10.5-105 µg Be/plate) (Ishizawa, 1979). These results should not be taken as proof, however, that beryllium is not mutagenic. The standard test system may be insensitive for the detection of metal mutagens because of the large amount of magnesium salts, citrate, and phosphate in the minimal medium (McCann et al., 1975). Bacteria appear to be selective in which metal ions are internalized. More research is needed to select a suitable strain of bacteria to detect metal-induced mutagenesis in these prokaryotic systems.

6.2 GENE MUTATIONS IN CULTURED MAMMALIAN CELLS

The ability of various beryllium compounds to cause gene mutations in cultured mammalian cells has been investigated by Miyaki et al. (1979) and Hsie et al. (1979a,b) (Table 6-2).

Miyaki et al. (1979) demonstrated the induction of 8-azaguanine-resistant mutants by beryllium chloride in the Chinese hamster V79 cells. Beryllium chloride at concentrations of 2 and 3 mM (18 and 27 µg Be/ml, respectively) induced 35.01 ± 1.4 and 36.5 ± 1.7 mutant colonies per 10^6 survivors. These values were approximately six times higher than the control value of 5.8 ± 0.8 colonies per 10^6 survivors. The cell survival rates were 56.9 percent at 2 mM

TABLE 6-2. MUTAGENICITY TESTING OF BERYLLIUM: GENE MUTATIONS IN MAMMALIAN CELLS IN VITRO

Test System	Strain	Concentration of Test Compounds as Be	S-9 Activation System	Results	Comments	Reference
Chinese hamster	V79 cells; resistance to 8-azaguanine	18 µg/ml 27 µg/ml	None	Reported positive 6.0- to 6.3-fold increase	1. 99 percent pure. 2. No dose response.	Miyaki et al. (1979)
Chinese hamster	CHO cells; resistance to 8-azaguanine	Not stated	±	Reported mutagenic and weakly mutagenic	1. No details. 2. The authors noted variable results with noncarcinogens such as calcium.	Hsie et al. (1979a,b)

concentration and 39.4 percent at 3 mM. Analysis of mutant colonies revealed that they were deficient in the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT) activity indicating that the mutation had occurred at the HGPRT locus.

Hsie et al. (1979a,b) also reported that beryllium sulfate induced 8-azaguanine-resistant mutants in Chinese hamster ovary (CHO) cells. However, they did not provide details about the concentrations of the test compound and the number of mutants induced per 10^6 survivors.

These studies indicate that beryllium has the ability to cause gene mutations in cultured mammalian cells.

6.3 CHROMOSOMAL ABERRATIONS

Beryllium sulfate was tested for its clastogenic potential in cultured human lymphocytes and Syrian hamster embryo cells (Larramendy et al., 1981) (Table 6-3). Cultured human lymphocytes (24-hours old) were exposed to a single concentration, 2.82×10^{-5}M (0.25 µg Be/ml), of beryllium sulfate, and chromosome preparations were made 48 hours after the treatment. A minimum of 200 metaphases were scored for chromosomal aberrations. In cultures treated with beryllium, there were 19 cells (9.5 percent) with chromosomal aberrations, or 0.10 ± 0.02 aberration per metaphase. In the nontreated control cells, only 3 cells (1.5 percent) had chromosomal aberrations. This sixfold increase in the aberration frequency clearly indicates that beryllium sulfate is clastogenic in cultured human lymphocytes. A beryllium concentration of 2.82×10^{-5}M was selected because it induced a maximum number of sister-chromatid exchanges in human lymphocytes in another experiment reported by the same authors (see Section 6.4).

In the Syrian hamster embryo cells the results were even more dramatic. This same concentration of beryllium sulfate induced aberrations in 38 out of 200 cells (19 percent) 24 hours after the treatment. The number of aberrations per metaphase was 0.12 ± 0.03. In control cells, only 3 cells (1.5 percent) had aberrations, or 0.01 ± 0.01 aberration per cell. In these studies, chromosomal gaps were also considered as aberrations. Even if the gaps were not included as true aberrations, the aberration frequency was still far above the control level, indicating that beryllium sulfate has clastogenic potential in cultured mammalian cells.

TABLE 6-3. MUTAGENICITY TESTING OF BERYLLIUM: MAMMALIAN IN VITRO CYTOGENETICS TESTS

Test System	Strain	Concentration of Test Compounds as Be	S-9 Activation System	Results	Comments	Reference
Chromosomal aberrations	Human lymphocytes	0.25 µg/ml	--	Reported positive	1. 6x above background level. 2. Primarily breaks.	Larramendy et al. (1981)
Chromosomal aberrations	Syrian hamster embryo cells	0.25 µg/ml	--	Reported positive	1. 12x above background level. 2. Primarily breaks and gaps.	Larramendy et al. (1981)
Sister chromatid exchanges	Human lymphocytes	0.05 µg/ml 0.125 µg/ml 0.25 µg/ml	--	Reported positive	1. Less than two-fold increase. 2. Insufficient evidence for a positive conclusion.	Larramendy et al. (1981)
Sister chromatid exchanges	Syrian hamster embryo cells	0.05 µg/ml 0.125 µg/ml 0.25 µg/ml	--	Reported positive	1. Less than two-fold increase. 2. Insufficient evidence for a positive conclusion.	Larramendy et al. (1981)

6.4 SISTER CHROMATID EXCHANGES

Larramendy et al. (1981) also studied the potential of beryllium to induce sister chromatid exchanges (Table 6-3). Both cultured human lymphocytes and Syrian hamster embryo cells were used in these studies.

After 24 hours of cultivation, lymphocytes were exposed to increasing concentrations of beryllium sulfate (0.05, 0.125, and 0.25 µg Be/ml) followed by 10 µg BrdUrd/ml medium. Cultures were incubated for an additional 48 hours and chromosome preparations were made and stained for sister-chromatid exchange analysis. At least 30 metaphases were scored for each concentration of the test compound. The background sister-chromatid exchange level was 11.30 ± 0.60. According to these investigators, there was a dose-dependent increase in sister-chromatid exchanges, i.e. 17.75 ± 1.10, 18.15 ± 1.79, and 20.70 ± 1.01, respectively, for the above concentrations.

In the Syrian hamster embryo cells, the same concentrations of beryllium sulfate induced 16.75 ± 1.52, 18.40 ± 1.49, and 20.50 ± 0.98 sister-chromatid exchanges. The background sister-chromatid exchange frequency was 11.55 ± 0.84. The sister-chromatid exchange assay has been extensively used in mutagenicity testing because of its sensitivity to many chemicals.

The authors stated that the results of the sister-chromatid exchange studies in human lymphocytes and Syrian hamster embryo cells demonstrated a dose-response relationship. However, in these studies, the increase was less than twofold and fell within a plateau region. Thus, the dose-response relationship suggested by the authors may be somewhat tenuous. Further experimentation to confirm the study results are advisable.

6.5 OTHER TESTS OF GENOTOXIC POTENTIAL

6.5.1 The Rec Assay

Kanematsu et al. (1980) found that beryllium sulfate was weakly mutagenic in the rec assay. Bacillus subtilis strains H17 (rec$^+$) and M75 (rec$^-$) were streaked onto agar plates. An aqueous solution (0.05 ml) of 0.01 M (4.5 µg Be/plate) beryllium sulfate was added to a filter paper disk (10-mm diameter) placed on the plates at the starting point of the streak. Plates were first cold incubated (4°C) for 24 hours and then incubated at 37°C overnight. Inhibition of growth due to DNA damage was measured in both the wild-type H17 (rec$^+$) and the sensitive-type (rec$^-$) strains. The difference in growth

inhibition between the wild-type strain and the sensitive strain was 4 mm, which was considered to indicate a weak mutagenic response. Similar results were also obtained by Kada et al. (1980).

6.5.2 Pol Assay

Beryllium was tested for mutagenicity in the pol assay using Escherichia coli (Rosenkranz and Poirier, 1979; Rosenkranz and Leifer, 1980). This assay is based on the fact that cells deficient in DNA repair mechanisms are more sensitive than normal cells to the growth-inhibiting properties of mutagenic agents. Escherichia coli strains pol A^+ (normal) and pol A^- (DNA polymerase I-deficient) were grown on agar plates, and filter disks impregnated with 250 µg of beryllium sulfate were placed in the middle of each agar plate and incubated at 37°C for 7 to 12 hours. Experiments were conducted both in the presence and absence of an S-9 activation system. There was no difference in the diameter of the zones of growth in either strain. Positive and negative controls were used for comparison. The shortcomings of this assay are that (1) conclusions can be drawn only when measurable zones of growth inhibition occur; (2) it is possible that the test chemical may not be able to penetrate the test organisms; and (3) insufficient diffusion of chemicals from the disk can occur because of low solubility or large molecular size.

6.5.3 Hepatocyte Primary Culture/DNA Repair Test

DNA damage and repair, as reflected by unscheduled DNA synthesis (incorporation of tritiated thymidine), was examined for beryllium sulfate by Williams et al. (1982). Rat primary hepatocyte cultures were exposed to 0.1, 1, and 10 mg/ml of beryllium sulfate with 10 µCi/ml of tritiated thymidine and incubated for 18 to 20 hours. Following incubation, autoradiographs of cells were prepared. A minimum of 20 nuclei was counted for each concentration and the uptake of radioactive label was measured as grain counts in each nucleus. The compound was considered positive when the nuclear grain count was five grains per nucleus above the control value. The compound was considered negative in the assay if the nuclear grain count was less than five at the highest nontoxic dose. Cytotoxicity was determined by the morphology of the cells. According to the authors, beryllium sulfate did not induce a statistically greater grain count at any of the concentrations. Benzo(a)pyrene was employed as a positive compound.

6.5.4 Beryllium-Induced DNA Cell Binding

Kubinski et al. (1981) reported that beryllium induces DNA protein complexes (adducts) that can be measured. Escherichia coli cells and Ehrlich ascitis cells were exposed to radioactive DNA in the presence of 30 μM of beryllium. Methyl methanesulfonate (MMS) was used as a positive control. The negative control consisted of cells only and radioactive DNA. The radioactive DNA bound to cell membrane proteins was measured, and, like MMS, beryllium induced positive results. However, the significance of beryllium-induced DNA binding to cell membranes is not clear in terms of its ability to induce mutations.

6.5.5 Mitotic Recombination In Yeast

Beryllium sulfate did not induce mitotic recombination in the yeast Saccharomyces cerevisiae D_3 (Simmon, 1979b). The S. cerevisiae strain D_3 is a heterozygote with mutations in ade 2 and his 8 of chromosome XV. When grown on a medium containing adenine, cells homozygous for the ade 2 mutation produce a red pigment. These homozygous mutants can be generated from the heterozygotes by mitotic recombination induced by mutagenic compounds. A single concentration (0.5 percent) of beryllium induced 10 mutant colonies per 10^5 survivors, while in the control the mutant frequency was 6 colonies per 10^5. In the mitotic recombination assay, there must be a threefold increase in the mutant frequency of experimental over the control in order to be considered a positive mutagenic response. The negative mutagenic response of beryllium may be due to an inability of beryllium to penetrate yeast cells.

6.5.6 Biochemical Evidence of Genotoxicity

Several in vitro experiments of the genotoxic potential of beryllium have been reported. In one study, in vitro exposure of rat liver cells to beryllium resulted in its binding to phosphorylated non-histone proteins (Parker and Stevens, 1979). Perry et al. (1982) found that exposure of cultured rat hepatosomal cells to beryllium reduced the glucocorticoid induction of tyrosine transaminase activity. In a DNA fidelity assay, beryllium increased the misincorporation of nucleotide bases in the daughter strand of DNA synthesized in vitro from polynucleotide templates (Zakour et al., 1981). Beryllium has also been investigated for its effects on the transcription of calf thymus DNA and phage T_4 DNA by RNA polymerase (from E. coli) under controlled conditions.

Beryllium inhibited overall transcription but increased RNA chain initiation, indicating the interaction of the metal with the DNA template (Niyogi et al., 1981).

6.5.7 Mutagenicity Studies in Whole Animals

Information on the mutagenicity of beryllium compounds in whole animal organisms, such as Drosophila and mammals, is not available in the literature. Such studies would be highly valuable for assessing the in vivo effects of beryllium compounds, in particular to learn whether or not they induce mutations in germ cells. Metals such as cadmium and methyl mercury have been implicated in the induction of aneuploidy (numerical chromosomal aberrations) in female rodent germ cells. Aneuploidy is generally induced as a result of malfunctioning of the spindle apparatus. Such studies with beryllium compounds would yield valuable information.

7. CARCINOGENIC EFFECTS OF BERYLLIUM

The purpose of this section is to evaluate the carcinogenic potential of beryllium, and on the assumption that beryllium is a human carcinogen, to estimate its potency relative to other known carcinogens, as well as its impact on human health.

The estimation of the carcinogenic potential of beryllium relies on animal bioassays and epidemiological studies. However, studies on the mutagenicity, DNA interaction, and metabolism of beryllium are also important for the qualitative and quantitative assessment of its carcinogenicity. Because the latter are specifically dealt with elsewhere in this document, this section focuses on animal and epidemiological studies as well as the dose-response (i.e., quantitative) aspects of beryllium carcinogenicity. Summary and conclusions sections highlight the most significant aspects of beryllium carcinogenicity.

7.1 ANIMAL STUDIES

Numerous animal studies have been performed to determine whether or not beryllium and beryllium-containing substances are carcinogenic. In these studies, metallic beryllium, salts of beryllium, and beryllium-containing alloys and ores were administered by various routes. In the discussions that follow, the studies are grouped according to the route of administration.

7.1.1 Inhalation Studies

The first report of pulmonary tumors after exposure to beryllium by inhalation was made by Vorwald (1953). Four of 8 female rats exposed to beryllium sulfate ($BeSO_4$) aerosol (at 33 µg Be/m^3, 7 hrs/d, 5.5 d/wk) for one year developed primary pulmonary adenocarcinomas. The rate was 80 percent (4/5) for animals necropsied after 420 days of exposure. This study was presented in a paper read before a meeting of the American Cancer Society, but was never published; an abstract of the presentation was printed two years later (Vorwald et al., 1955).

Schepers et al. (1957) updated the Vorwald study to include 115 rats, 78 of which survived to planned necropsy. Tumors were counted after the animals had been exposed for 6 months to beryllium sulfate aerosol followed by up to 18 months in normal air. The total number of tumors (76) -- not the number of tumor-bearing animals -- was counted. Eight histologic variants of neoplasms were observed. Intrathoracic metastases were also noted, and transplantation was successful in several cases. No lung tumors were reported among controls.

During the late 1950s and early 1960s, both Schepers and Vorwald continued their experiments. Unfortunately, because these studies were never published, details are often lacking, although some of the results have been alluded to in subsequent reviews (Schepers, 1961; Vorwald et al., 1966). It can be surmised that Schepers observed 35 to 60 tumors in 170 rats (21 to 35 percent) exposed to beryllium phosphate at a concentration of 32 to 35 μg Be/m^3, and 7 tumors in 40 animals (17.5 percent) at 227 μg Be/m^3. After exposure to beryllium fluoride, he obtained a tumor rate of 10 to 20 in 200 animals (5 to 10 percent) exposed to 9 μg Be/m^3. With zinc beryllium manganese silicate ($ZnBeMnSiO_3$), a fluorescent phosphor in use at that time, the tumor rate was 4 to 20 in 220 animals (2 to 9 percent) exposed to 0.85 to 1.25 mg Be/m^3 (Table 7-1). No tumors were observed in similarly exposed rabbits or guinea pigs.

In all but one of his inhalation experiments, Vorwald exposed rats to beryllium sulfate aerosol at concentrations ranging from 2.8 to 180 μg Be/m^3 at exposure schedules of 3 to 24 months. In one experiment, beryllium oxide was used at 9 mg/m^3 (temperature of firing not given). Pulmonary lesions believed to be adenocarcinomas were found in all groups at frequencies ranging from 20 to 100 percent. Weak correlations were observed between tumor rate and exposure concentrations, and between tumor rate and exposure length (Table 7-1). No metastases were observed, and serial homotransplants were unsuccessful.

Reeves et al. (1967) exposed 150 Sprague Dawley rats of both sexes and an equal number of controls to beryllium sulfate aerosol, with a mean particle diameter of 0.2 μ, at a mean concentration of 34.25 ± 23.66 μg Be/m^3 for 35 hours a week. Sacrifices were conducted quarterly. The first lung tumors were seen at 9 months, and by 13 months all 43 animals necropsied had pulmonary adenocarcinomas. Similar results were reported by Reeves and Deitch (1969) two years later for another animal group. In the latter study, 225 female Charles River CD rats of various ages were exposed (35 hrs/wk) to 35.66 ± 13.77 μg Be/m^3 with a mean particle size of 0.21 μm (Figure 7-1). Five groups were

TABLE 7-1. PULMONARY CARCINOMA FROM INHALATION EXPOSURE TO BERYLLIUM

Compound	Species	Atmospheric concentration $\mu g/m^3$ as Be	Weekly exposure time (hours)	Duration of exposure (months)	Incidence of pulmonary carcinoma	Reference
$BeSO_4$	Rats	33-35	33-38	12-14	4 in 8	Vorwald (1953)
		33-35	33-38	13-18	17 in 17	Vorwald et al. (1955)
		32-35	44	6-9	58 in 136	Schepers et al. (1957)
		55	33-38	3-18	55 in 74	Vorwald (1962)
		180	33-38	12	11 in 27	Vorwald (1962)
		18	33-38	3-22	72 in 103	Vorwald (1962)
		18	33-38	8-21	31 in 63	Vorwald (1962)
		18	33-38	9-24	47 in 90	Vorwald (1962)
		18	33-38	11-16	9 in 21	Vorwald (1962)
		1.8-2.0	33-38	8-21	25 in 50	Vorwald (1962)
		1.8-2.0	33-38	9-24	43 in 95	Vorwald (1962)
		1.8-2.0	33-38	13-16	3 in 15	Vorwald (1962)
		21-42	33-38	18	Almost all	Vorwald et al. (1966)
		2.8	33-38	18	13 in 21	Vorwald et al. (1966)
		34	35	13	43 in 43	Reeves et al. (1967)
		36	35	3	19 in 22	Reeves and Deitch (1969)
		36	35	6	33 in 33	Reeves and Deitch (1969)
		36	35	9	15 in 15	Reeves and Deitch (1969)
		36	35	12	21 in 21	Reeves and Deitch (1969)
		36	35	18	13 in 15	Reeves and Deitch (1969)
	Monkeys	35-200	42	8	0 in 4	Schepers (1964)
		38.8	15	36+	8 in 11	Vorwald (1968)

(continued on the following page)

TABLE 7-1. (continued)

Compound	Species	Atmospheric concentration $\mu g/m^3$ as Be	Weekly exposure time (hours)	Duration of exposure (months)	Incidence of pulmonary carcinoma	Reference
$BeSO_4$	Guinea pigs	35	NR	12	0	Schepers (1961)
		36	35	12	2 in 20	Schepers (1971)
		3.7-30.4	35	18-24	0 in 58	Reeves et al. (1972)
		~15	35	18-24	0 in 110	Reeves (1976)
$BeHPO_4$	Rats	32-35	NR	1-12	35-60 in 170[a]	Schepers (1961)
		227	NR	1-12	7 in 40[a]	Schepers (1961)
	Monkeys	200	42	8	0 in 4	Schepers (1964)
		1100	42	8	1 in 4	Schepers (1964)
		8300	42	8	0 in 4	Schepers (1964)
BeF_2	Rats	9	NR	6-15	10-12 in 200	Schepers (1961)
	Monkeys	180	42	8	0 in 4	Schepers (1964)
$ZnBeMnSiO_3$	Rats	700	NR	9	4-20 in 220[a]	Schepers (1961)
	Rabbits	700	NR	24	0	Schepers (1961)
	Guinea pigs	700	NR	22	0	Schepers (1961)
Beryl ore	Rats	620	30	17+	18 in 19	Wagner et al. (1969)
	Hamsters	620	30	17+	0 in 48	Wagner et al. (1969)
	Monkeys	620	30	17+	0 in 12	Wagner et al. (1969)
Betrandite ore	Rats	210	30	17+	0 in 30-60	Wagner et al. (1969)
	Hamsters	210	30	17+	0 in 48	Wagner et al. (1969)
	Monkeys	210	30	17+	0 in 12	Wagner et al. (1969)

[a]Number of tumors per number of animals exposed.

NR: Not reported.

Source: Adapted from Reeves (1978).

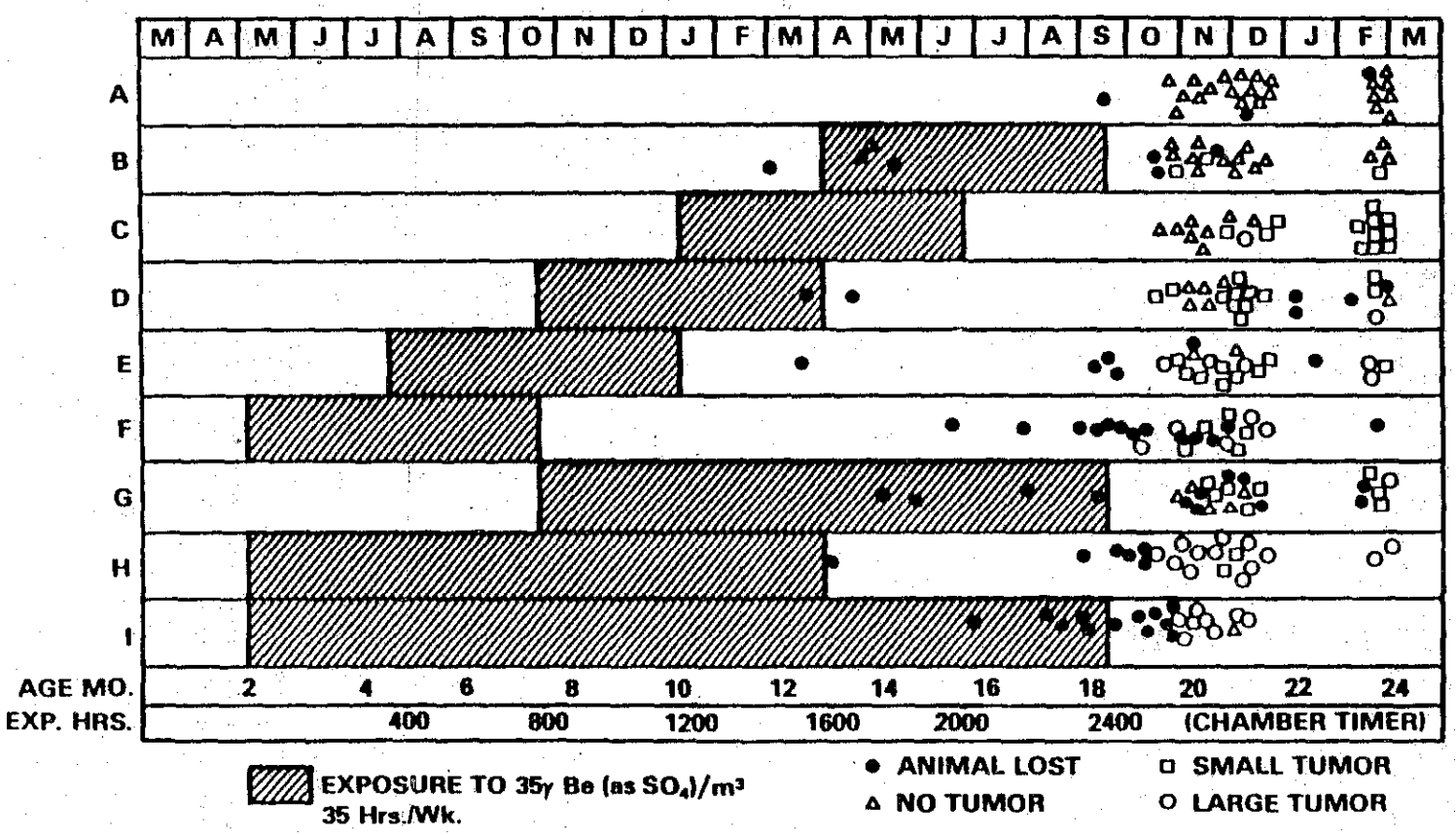

Figure 7-1. Pulmonary tumor incidence in female rats, 1965-1967.

Source: Reeves and Deitch (1969).

exposed for 800 hours, two groups for 1600 hours, and one group for 2400 hours. It was found that tumor yield depended not on length of exposure but on age at exposure. Rats exposed at an early age for only 3 months had essentially the same tumor frequency (19/22; 86 percent) as rats exposed for the full 18 months (13/15; 86 percent), whereas rats receiving the 3-month exposure later in life had substantially reduced tumor counts (3-10/20-25; 15 to 40 percent). Generally, an incubation time of at least 9 months after commencement of exposure was required to produce actual tumors. Epithelial hyperplasia of the alveolar surfaces commenced after about 1 month, progressed to metaplasia by 5 to 6 months, and to anaplasia by 7 to 8 months. In guinea pigs, 18 months of exposure (35 hrs/wk) to three different concentrations of beryllium sulfate (3.7 ± 1.5 μg Be/m^3, 16.6 ± 8.7 μg Be/m^3, and 30.4 ± 10.7 μg Be/m^3) produced only alveolar hyperplasia/metaplasia (associated with diffuse interstitial pneumonitis) in 23 of 144 animals. No tumors were seen. The rate of hyperplasia/metaplasia in unexposed controls was 3/55 (Reeves et al., 1971, 1972; Reeves and Krivanek, 1974). Schepers (1971) reported the occurrence of lung tumors in 2 of 20 guinea pigs exposed to beryllium sulfate (at 36 μg Be/m^3, 35 hrs/wk) for one year. While these results are suggestive of a positive effect when compared to the very low background incidence of tumors in guinea pigs, very little detail was given in the report to reach definitive conclusions.

Sanders et al. (1978) exposed female Wistar rats to aerosols of medium-fired (1000°C) beryllium oxide, with a mass median diameter of 1.1 ± 0.17 μm. A single nose-only exposure of 30 to 180 minutes duration was used. Exposure concentrations were not reported, but initial alveolar deposition of beryllium for three exposure groups averaged 0.9 ± 0.3 μg, 16.0 ± 15.0 μg and 57.0 ± 17.0 μg. The animals were held from 625 to 661 days. Of the animals surviving to termination, no tumors were seen in 50 controls, 30 low-dose, or 43 medium-dose rats. One of 29 rats in the high-dose group developed an adenocarcinoma.

Wagner et al. (1969) exposed Charles River CD rats, Golden Syrian hamsters, and squirrel monkeys (Saimiri sciurea) to aerosols of beryl ore and bertrandite ore at what was then regarded as the "nuisance limit" for all dusts (15 mg/m^3). At this particle concentration, the beryllium content of the aerosols was 620 and 210 μg Be/m^3 for beryl and bertrandite, respectively. The geometric mean diameter for bertrandite was 0.27 μ (σ 2.4) and for beryl was 0.64 μ (σ 2.5). Exposure was for 6 hours/day, 5 days/week, for 17 months. Of the 19 rats exposed to beryl dust, 18 had bronchiolar or alveolar cell tumors, 7 of which

were judged to be adenomas, 9 adenocarcinomas, and 2 epidermoid tumors. Metastases were not observed, and transplants were not attempted. No indisputable tumors were found in either hamsters or squirrel monkeys exposed to beryl dust, although atypical proliferations were seen in the hamsters which, according to the authors, "could be considered alveolar cell tumors except for their size." There were no indisputable tumors in any of the animals exposed to bertrandite dust. However, granulomatous lesions were seen in each species and "atypical proliferations" of the cells lining the respiratory bronchioles and alveoli were seen in the rats and hamsters.

Schepers (1964) found that among 20 female rhesus monkeys (Macaca mulata) exposed for eight months, 6 hours/day, by inhalation to beryllium sulfate ($BeSO_4$), beryllium phosphate ($BeHPO_4$), or beryllium fluoride (BeF_2) (concentrations ranging from 0.035 to 8.3 mg Be/m^3; particle size not reported), only one animal had a small (3 mm) pulmonary neoplasm which appeared to be an alveolar carcinoma. The animal was exposed to beryllium phosphate at a concentration of 1.1 mg Be/m^3. The tumor was discovered on day 82 of exposure; however, its association with the beryllium exposure was judged uncertain. Unfortunately, the eight-month exposure period used in the study was probably insufficient to induce lung cancer in any of the monkeys.

Vorwald (1968) reported the outcome of a chamber study using rhesus monkeys, about 18 months of age, exposed to beryllium sulfate (particle size not reported) at a mean atmospheric concentration of 38.8 μg Be/m^3. The animals were exposed for 6 hours/day, 5 days/week initially, but exposures were intermittent with fewer exposures as the animals aged. The average exposure time for the duration of the experiment was 15 hours/week. The animals were held for a lifetime. Four animals, two males and two females, died within six months of the start of exposure. Three additional females died after approximately one to four years. None of these seven animals developed lung tumors. The remaining 9 animals survived approximately 6 to 10 years. Three of the four surviving females and all five of the males developed pulmonary tumors.

The pathology varied among animals. In some monkeys, the tumor was in the nature of a gross mass, predominantly situated in either the hilar area, or in the more peripheral portions of the lung. In other cases, small and large tumors were scattered irregularly throughout the pulmonary region. The histopathology was generally very anaplastic, but various adenomatous patterns often predominated among areas with epidermal characteristics. Extensive metastases

to the mediastinal lymph nodes were seen, and in some animals there were metastases to the bone, liver, and adrenals. No control animals were kept in this experiment.

Dutra et al. (1951) exposed 5, 6, and 8 rabbits to beryllium oxide aerosol (degree of firing unidentified) at 1, 6, and 30 mg Be/m^3 (mean particle diameter 0.235 μ), respectively, on a 25-hour-per-week schedule for 9 to 13 months. One rabbit in the group exposed to 6 mg Be/m^3 developed osteosarcoma of the pubic bone, with extension into the contiguous musculature. Scattered tumors which were judged to be metastases of the osteogenic sarcoma were seen in the lungs and spleen. The lungs also exhibited extensive emphysema, interstitial fibrosis, and lymphocytic infiltration. Rabbits in the other groups remained free of malignancies.

7.1.2 Intratracheal Injection Studies

Intratracheal administration of beryllium compounds was used as a substitute for inhalation in experiments by Vorwald (1950, 1953, 1968), Van Cleave and Kaylor (1955), Spencer et al. (1965), Kuznetsov et al. (1974), Ishinishi et al. (1980), and Groth et al. (1980). The fate and effects of beryllium compounds deposited by intratracheal injection are not necessarily the same as those for identical compounds deposited by inhalation. Intratracheal injection produces an unnatural deposition pattern in the lungs and permits the entry of larger particles that normally would be filtered out in the upper respiratory tract. Dusts, therefore, frequently show longer pulmonary half-times after intratracheal injection than after inhalation.

Vorwald (1953) found one lung tumor among eight female rats after intratracheal injection of 338 μg beryllium (as beryllium oxide) and one "sarcoma" among eight male rats (site unidentified) after intratracheal injection of 33.8 μg beryllium as sulfate (Table 7-2). The induction of lung cancer with intrathoracic metastases in rhesus monkeys following intrabronchial injection and/or bronchomural implantation of "pure" beryllium oxide (firing temperature unknown) has been mentioned in a review, but without reference to any original publication (Vorwald et al., 1966).

Groth et al. (1980) intratracheally injected rats with dusts of beryllium metal, passivated beryllium metal (with <1 percent chromium), and various beryllium alloys, as well as beryllium hydroxide. Lung tumors were observed after injection of beryllium metal, passivated beryllium metal, and a

TABLE 7-2. PULMONARY CARCINOMA FROM EXPOSURE TO BERYLLIUM VIA INTRATRACHEAL INSTILLATION

Compound	Species	Total dose (mg)	Incidence of pulmonary carcinoma	Reference
$ZnBeMnSiO_3$	Rabbits, rats, and guinea pigs	0.46	0	Vorwald (1950)
		2.3-6.9	0	Vorwald (1950)
		3.4	0	Vorwald (1950)
Be Stearate	Rabbits, rats, and guinea pigs	5.0	0	Vorwald (1950)
Be(OH)	Rabbits, rats, and guinea pigs	31	0	Vorwald (1950)
Be Metal	Rabbits, rats, and guinea pigs	54	0	Vorwald (1950)
Be O	Rabbits, rats, and guinea pigs	75	0	Vorwald (1950)
	Rats	.338	1 in 4	Vorwald (1953)
	Monkeys	18-90+	3 in 20	Vorwald (1968)

Source: Adapted from Reeves (1978).

beryllium-aluminum alloy (containing 62 percent beryllium), but not after injection of other beryllium alloys in which the beryllium concentration was less than four percent. The injection of beryllium hydroxide into 25 rats yielded 13 cases of neoplasia, of which six were judged to be adenomas and seven adenocarcinomas (Table 7-3). The remaining animals had various degrees of metaplasia, which were regarded as precancerous lesions. Several of the tumors were successfully transplanted.

The most detailed studies of intratracheal injections of beryllium were reported by Spencer et al. (1965, 1968, 1972). High-fired (1600°C), medium-fired (1100°C), and low-fired (500°C) specimens of beryllium oxide were injected into rats. The rates of pulmonary adenocarcinomas were 3/28, 3/19, and 23/45 (11, 16, and 51 percent) in the three groups, respectively. None were seen in controls.

Ishinishi et al. (1980) intratracheally injected 30 male Wistar rats with beryllium oxide (calcined at 900°C) in 15 weekly doses of 1 mg each. Of 29 animals examined 1.5 years later, six (21 percent) had lung tumors, i.e. one squamous cell carcinoma, one adenocarcinoma, three adenomas, and one malignant lymphoma. The adenomas had "strong histological architectures [of] suspected malignancy" (Tables 7-4 and 7-5). The malignant lymphoma was found not only in the lung, but also in the hilar lymph nodes and in the abdominal cavity, with the primary site remaining undetermined. Six extrapulmonary lymphosarcomas, fibrosarcomas, or other tumors were found in further injected animals but in only one of the 16 control animals. The frequency of clearly malignant primary pulmonary tumors in this experiment was 2/29, or 7 percent.

7.1.3 Intravenous Injection Studies

In 1946, Gardner and Heslington, in a search to find the cause of an "unusual incidence of pulmonary sarcoid" in the fluorescent light tube industry, injected zinc beryllium silicate ($ZnBeSiO_3$) into rabbits. They found osteosarcomas of the long bones in all seven animals which survived the treatment for seven or more months. Because this was the first instance of experimental carcinogenesis by an inorganic substance, it evoked great interest. Beryllium was clearly implicated as the causative agent because zinc oxide, zinc silicate, or silicic acid did not cause osteosarcomas in a second set of trials, whereas beryllium oxide (firing temperature unknown) did. Guinea pigs and rats, when similarly treated with both zinc beryllium silicate and beryllium oxide, failed

TABLE 7-3. BERYLLIUM ALLOYS--LUNG NEOPLASMS

Compounds	Dose of compound (mg)	Dose of Be (mg)	Total no. rats autopsied	Autopsy intervals and lung neoplasm frequencies (months)					P value[a]
				1	2-7	8-10	11-13	16-19	
Be metal	2.5	2.5	16	0/5[b]	-	-	3/5	6/6	<0.0001
Be metal	0.5	0.5	21	0/5	0/3	0/5	0/5	2/3	0.011
Passivated Be metal	2.5	2.5	26	0/5	0/2	1/5	4/10	4/4	<0.0001
Passivated Be metal	0.5	0.5	20	0/5	0/1	0/3	-	7/11	0.0001
BeAl alloy	2.5	1.55	24	0/5	0/3	2/5	0/5	2/6	0.043
BeAl alloy	0.5	0.3	21	0/5	-	0/1	0/6	1/9	0.30
4% BeCu alloy	2.5	0.1	28	0/5	0/1	0/5	0/6	0/11	
4% BeCu alloy	0.5	0.02	24	0/5	0/2	-	0/4	0/13	
2.2% BeNi alloy	2.5	0.056	28	0/5	0/1	0/5	0/5	0/12	
2.2% BeNi alloy	0.5	0.011	27	0/5	0/2	-	0/5	0/15	
2.4% BeCuCo alloy	2.5	0.06	33	0/5	0/3	0/5	0/5	0/15	
2.4% BeCuCo alloy	0.5	0.012	30	0/5	0/2	-	0/5	0/18	
Saline	-	-	39	0/5	0/3	0/5	0/5	0/21	

[a]P value (Fisher's one-tailed test) when the lung neoplasm frequency in exposed groups is compared with the lung neoplasm frequency in the saline control group at the autopsy period of 16-19 months. Because of multiple comparisons with the control group, the individual P value must be 0.008 or less to be significant.

[b]Number of rats with a lung neoplasm divided by total number of rats autopsied at the specified interval.

Source: Groth et al. (1980).

TABLE 7-4. LUNG TUMOR INCIDENCE IN RATS AMONG BeO, As_2O_3 AND CONTROL GROUPS

Group	Sex	Number of rats surviving after 15 instillations	Average	Range	Malignant tumor	Benign tumor
BeO (1 mg)[a]	M	30/30	545	99-791	2+(1)[b]	4
As_2O_3 (1 mg)[a]	M	19/30	546	98-820	1	0
Control	M	16	398	1-617	0	0

[a]Amount of one instillation Be or As.

[b]Unknown which is primary tumor or metastasis.

Source: Ishinishi et al. (1980).

TABLE 7-5. HISTOLOGICAL CLASSIFICATION OF LUNG TUMORS AND OTHER PATHOLOGICAL CHANGES

			Malignant tumors (A) Benign tumors (B)				All tumors (A + B) [tumor incidence rates]	Squamous cell meta-plasia	Osseous metaplasia	Other site tumors except the lung tumor
Group	Sex	No. of rats	Squamous cell carcinoma	Adeno-carcinoma	Malignant lymphoma	Ade-noma				
BeO (1 mg as Be)	M	29[a]	1[b]	1[c]	(1)[d]	4(3)[e]	20.6%	2	1	6[f]
As_2O_3 (a mg as As)	M	18[a]	1	0	0	0	5.6%	5	2	3[g]
Control	M	16	0	0	0	0	0	1	0	1

[a]One rat was not histopathologically observed because of cannibalism.

[b]Coexistence of squamous cell carcinoma and adenocarcinoma.

[c]Coexistence of adenocarcinoma and adenoma.

[d]Malignant lymphoma in the left lobule of the lung, the lymphatic nodules in the pulmonary hilus, and in the abdominal cavity.

[e]Three of four adenomas have strong histological architectures of suspected malignancy.

[f]Lymphosarcoma or fibrosarcomas (except one).

[g]Mesothelioma in peritoneum, liver and mesentery.

Source: Ishinishi et al. (1980).

to respond. The dose of beryllium within the two compounds injected (beryllium oxide and zinc beryllium silicate) was 360 and 60 mg, respectively, and was given in 20 divided doses during a 6-week period.

This basic experiment was repeated many times by several investigators (Tables 7-6 and 7-7). Cloudman et al. (1949) produced osteosarcomas in four out of five rabbits receiving a total dose of 17 mg beryllium (as zinc beryllium silicate). Mice were also injected with "some" tumors being produced (counts not stated). In this experiment, "substantially 100 percent beryllium oxide by spectrographic standards" (degree of firing not stated, total dose 1.54-390 mg beryllium) produced no tumors. Nash (1950) produced five cases of osteosarcomas in 28 rabbits injected with zinc beryllium silicate phosphor. The minimum effective dose appeared to be 200 mg zinc beryllium silicate (12 mg beryllium). Dutra and Largent (1950) produced osteosarcomas in rabbits with both zinc beryllium silicate (2/3) and beryllium oxide (6/6), and reported a successful transplant in the anterior chamber of the eye of a guinea pig. Barnes et al. (1950) produced six cases of osteosarcomas among 17 rabbits injected with zinc beryllium silicate and one case of osteosarcoma among 11 rabbits injected with beryllium silicate. The tumors were multicentric in origin, and blood-borne metastases were common. Hoagland et al. (1950) injected rabbits with two samples of zinc beryllium silicate phosphor, containing 2.3 and 14 percent beryllium oxide, and produced osteosarcomas in 3/6 and 3/4 rabbits, respectively. With uncompounded beryllium oxide, the tumor rate was 1/8. The osteosarcomas appeared to be highly invasive, but could not be transplanted. Beryllium phosphate produced no tumors.

Araki et al. (1954) injected 35 rabbits with zinc beryllium manganese silicate, zinc beryllium silicate, or beryllium phosphate. The rate of osteosarcoma formation was 6/24, 2/7, and 2/4 in the three groups, respectively. There were no tumors among three rabbits injected with beryllium oxide (firing temperature unstated) or among two uninjected controls. There was also a primary thyroid tumor in the group injected with zinc beryllium manganese silicate. Liver cirrhosis and splenic fibrosis were also observed. Transplant experiments were all negative.

Several experiments reported from the Mayo Foundation confirmed the carcinogenic effects of intravenous beryllium on bone (Janes et al., 1954, 1956; Kelly et al., 1961). Twenty-two of 31 rabbits receiving zinc beryllium silicate (total dose 12 mg Be) developed osteosarcomas. New bone formation was observed in the medullary cavities of the long bones before the malignant changes became

TABLE 7-6. 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
$ZnBeSiO_3$	1	UN	i.v.	7	7/7 (100%)	3/7 (43%)	
BeO	1	360	i.v.	1	UN	UN	Gardner and Heslington (1946)
$ZnBeSiO_3$	UN	17	i.v.	4	4/5 (80%)	3/4 (75%)	
$ZnBeSiO_3$	UN	0.264	i.v.(M)	1	UN	UN	Cloudman et al. (1949)
$ZnMnBeSiO_3$	0.45-0.85	3.7-7.0	i.v.	3	≧ 3/6 (50%)		
$ZnMnBeSiO_3$	0.2	10-12.6	i.v.	3	≧ 3/4 (75%)	5/7 (71%)	Hoagland et al. (1950)
BeO	UN	360	i.v.	1	≧ 1/9 (11%		
Be metal	0.04	40	i.v.	2	2/5 (40%)	UN	Barnes et al. (1950)
$ZnBeSiO_3$	1-2.1	7.2-15	i.v.	6	6/13 (46%)	4/6 (67%)	
$BeSiO_3$	1-1.2	UN	i.v.	1	1/8 (13%)	None	Barnes et al. (1950)
$ZnBeSiO_3$	UN	64-90	i.v.	2	2/3 (67%)	2/2 (100%)	
BeO	UN	360-700	i.v.	6	6/6 (100%)	6/6 (100%)	Dutra and Largent (1950)
$ZnBeSiO_3$	1	12	i.v.	5	5/10 (50%)	>2/5 (40%)	Janes et al. (1954)
$ZnBeSiO_3$	1	12	i.v.	10	10/13 (77%)	UN	Kelly et al. (1961)
BeO	1	360	i.v.	3	UN	2/3 (66%)	Komitowski (1968)
Be phosphate	0.103	UN	i.v.	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 $ZnBeSiO_3$ + $ZnMnBeSiO_3$			i.v.	40	40/61 (66%)	≧ 18/30(60%)	

[a]UN = unknown; IMD = intramedullary; $ZnBeSiO_3$ = zinc beryllium silicate; (M) = mouse; $ZnMnBeSiO_3$ = zinc manganese beryllium silicate; BeO = beryllium oxide.

Source: Groth (1980).

TABLE 7-7. OSTEOSARCOMA FROM BERYLLIUM

Compound	Species	Total dose (mg Be)	Mode of administration	Incidence of osteosarcoma	Reference
$ZnBeSiO_3$	Rats	60	i.v. in 20 doses	0	Gardner and Heslington (1946)
	Guinea pigs	60	i.v. in 20 doses	0	Gardner and Heslington (1946)
	Mice	0.26	i.v. in 20-22 doses	"some"	Cloudman et al. (1949)
	Rabbits	60	i.v. in 20 doses	7 in 7	Gardner and Heslington (1946)
		7.2	i.v. in 6-10 doses	4 in 14	Barnes et al. (1950)
		16	i.v. in 6-10 doses	2 in 3	Barnes et al. (1950)
		12+	i.v. repeated	5 in 28	Nash (1950)
		64-90	i.v. in 17-25 doses	2 in 3	Dutra and Largent (1950)
		12	i.v. in 20 doses	5 in 10	Janes et al. (1954)
		12	i.v. in 20 doses	10 in 14	Kelly et al. (1961)
		3300	i.v. in 20 doses	"many"	Higgins et al. (1964)
		17	i.v. in 20 doses	4 in 5	Cloudman et al. (1949)
	Splenectomized rabbits	12	i.v. in 20 doses	7 in 7	Janes et al. (1956)
ZnBe silicate (BeO = 2.3%)	Rabbits	3-7	i.v. in 30 doses	3 in 6	Hoagland et al. (1950)
ZnBe silicate (BeO = 14%)	Rabbits	10-12	i.v. in 30 doses	3 in 4	Hoagland et al. (1950)

(continued on the following page)

TABLE 7-7. (continued)

Compound	Species	Total dose (mg Be)	Mode of administration	Incidence of osteosarcoma	Reference
BeO	Rats	360	i.v. in 20 doses	0	Gardner and Heslington (1946)
	Guinea pigs	360	i.v. in 20 doses	0	Gardner and Heslington (1946)
	Mice	0.55	i.v. in 20-22 doses	0	Cloudman et al. (1949)
	Rabbits	140	i.v. in 20-22 doses	0	Cloudman et al. (1949)
		180	i.v. in 6-10 doses	1 in 11	Barnes et al. (1950)
		360	i.v. in 1-30 doses	1 in 8	Hoagland et al. (1950)
		360-700	i.v. in 20-26 doses	6 in 6	Dutra and Largent (1950)
		360	i.v. in 20-22 doses	1 in 7	Gardner and Heslington (1946)
		1	Inhalation, 25h/wk, 9-18 mo.	0 in 5	Dutra et al. (1951)
		6	Inhalation, 25h/wk, 9-18 mo.	1 in 6	Dutra et al. (1951)
		30	Inhalation, 25h/wk, 9-18 mo.	0 in 8	Dutra et al. (1951)
Be phosphate	Rabbits	130?	i.v. in 1-30 doses	0 in 5	Hoagland et al. (1950)

Source: Adapted from Reeves (1978)

apparent. Of particular interest was the observation of splenic atrophy only in those animals which developed bone tumors. Following splenectomy, the incidence of bone tumor or new bone formation in the medullary cavity was 100 percent, whereas the incidence of these developments in non-splenectomized rabbits receiving identical doses of beryllium was only 50 percent. The results suggest that a well-functioning spleen may serve as protection against beryllium carcinogenesis in the rabbit. Tibial chondrosarcomas were also produced, and successful transplants to the anterior chambers of the eyes of rabbits were performed (Higgins et al., 1964).

7.1.4 Intramedullary Injection Studies

Beryllium oxide or zinc beryllium silicate was directly introduced into the medullary cavity of bones of rabbits by Yamaguchi (1963), Tapp (1969), and Fodor (1977). Osteosarcomas, chondrosarcomas, and presarcomatous changes (irregular bone formation) were observed. In the Yamaguchi study, twenty to 30 injections (20 mg beryllium oxide per injection) gave the highest frequency of tumor formation (11 of 13 animals). The tumors developed directly from the medullary bone, and were sometimes preceded by fibrosis. Tumors metastasized to the liver, kidney, lymph nodes, and particularly the lung. Tumors developed in 9 of 16 animals receiving 11 to 20 injections and 1 of 14 animals given 1 to 10 injections.

7.1.5 Intracutaneous Injection Studies

Neither the intracutaneous injection of beryllium sulfate, nor the accidental introduction of insoluble beryllium compounds (beryllium oxide, beryllium phosphate, beryllium-containing fluorescent phosphors) into the skin have been found to produce tumors (Van Ordstrand et al., 1945; Reeves and Krivanek, 1974). The lesions that were produced were cutaneous granulomas, or, in the case of extensive injury, necrotizing granulomatous ulcerations.

In the immunotoxicologic experiments of Reeves et al. (1971, 1972) beryllium sulfate was administered intracutaneously in doses of 5 µg beryllium, but there was no evidence that measurable amounts of beryllium left the sites of administration.

7.1.6 The Percutaneous Route of Exposure

No neoplasms have been observed following percutaneous administration of beryllium compounds in any species. However, eczematous contact dermatitis has been noted in humans who have worked with soluble compounds of beryllium (Van Ordstrand et al., 1945). Curtis (1951) studied the allergic etiology of these reactions and developed a beryllium patch test. In 1955, Sneddon reported that a patient with a positive beryllium patch test developed a sarcoid-like granuloma at the test site. Granulomatous ulcerations followed if insoluble beryllium compounds became imbedded in the skin. Using pigs, Dutra et al. (1951) were able to produce beryllium-induced cutaneous granulomas that resembled the human lesions. There is no record that any of these lesions underwent malignant degeneration. The fact that no neoplasms were observed could be explained by the virtual impenetrability of intact skin by beryllium (see Section 4.1.3).

7.1.7 Dietary Route of Exposure

With one exception, no known neoplasms have been observed following beryllium exposure by the dietary route in any species. Guyatt et al. (1933), Jacobson (1933), and Kay and Skill (1934) produced rickets in young rats fed beryllium carbonate at 0.1 to 0.5 percent dietary level. This result is attributable to the precipitation of beryllium phosphate in the intestine, leading to phosphate deprivation. Using similar dietary concentrations of beryllium, Sols and Dierssen (1951) observed a decrease in the intestinal absorption of glucose, which has been attributed to the inhibition of alkaline phosphatase (Du Bois et al., 1949). At intake levels of 0.16 to 5 ppm beryllium sulfate in the diet, no toxic effects of any kind were found (Reeves, 1965; Schroeder and Mitchener, 1975a,b).

In a study by Morgareidge et al. (1977, abstract), a significant increase in reticulum cell sarcomas were found in male rats exposed to 5 or 50, but not 500 ppm beryllium in the diet. The lack of response at the high dose, the lack of response in earlier studies using much greater doses, and the results of intravenous injection studies showing beryllium accumulation in the bones along with induction of osteosarcomas, but no tumors at other sites, render the results highly equivocal.

If insoluble beryllium dusts (beryllium, beryllium alloys, beryllium oxide, beryllium phosphate, or beryllium ores) are ingested, the bulk of these substances will pass through the gastrointestinal tract unabsorbed. Depending

on the size of the particles, and, in the case of beryllium oxide, on the firing temperature, a minor proportion of these dusts could become dissolved in gastric juices, and traces of the resultant beryllium chloride could be absorbed from the stomach. Upon entry into the intestine, any dissolved beryllium would become precipitated again, mainly as beryllium phosphate (Reeves, 1965).

In most mammalian species, alimentary absorption of soluble beryllium salts [beryllium fluoride (BeF_2), beryllium chloride ($BeCl_2$), beryllium sulfate ($BeSO_4$), and beryllium nitrate ($Be[NO_3]_2$)] is minor. Researchers have observed that 80 percent or more of an oral beryllium intake of 0.6 to 6.6 µg/day passes unabsorbed through the gastrointestinal tract of rats (Reeves, 1965; Furchner et al., 1973; Schroeder and Mitchener, 1975a,b). Upon entering the alkaline milieu of the intestine, beryllium forms a precipitate that is excreted with the feces. There is some evidence that increasing the intake concentration does not increase the amount absorbed from the intestine because the latter is governed by the solubility of the intestinal precipitates rather than by the total amount of beryllium present.

7.1.8 Tumor Type, Species Specificity, Carcinogenic Forms, and Dose-Response

7.1.8.1 Tumor Type and Proof of Malignancy. Pulmonary neoplasms found in rats after beryllium exposure have been classified as adenocarcinomas, showing a predominantly alveolar pattern. Reeves et al. (1967) distinguished four histological variants, including focal columnar, focal squamous, focal vacuolar, and focal mucigenous. Schepers et al. (1957) distinguished several more, including some adenomas judged to be nonmalignant. Wagner et al. (1969) and Groth et al. (1980) found that about half of the tumors they produced with beryllium were benign adenomas. The diagnosis of pathological lesions is complicated, and requires special expertise. The histological differentiation between adenomas and adenocarcinomas is not always well defined and may also have species-related peculiarities, so that different conclusions on the same specimen may sometimes be reached by pathologists. This is especially true when pathologists have been trained in human rather than veterinary medicine. It is also noteworthy that neoplasia in the lungs of rats was invariably associated with the purulent lesions of chronic murine pneumonia, which itself was exacerbated by inhalation of the acidic beryllium sulfate aerosol.

Metastases, as well as successful transplants, were claimed by Schepers et al. (1957). In the rat experiments of Vorwald, neither was claimed, but later reports have been ambiguous on these points (Vorwald et al., 1966; see also Lesser, 1977). In the monkey experiments of Vorwald (1968), which lacked controls, extensive metastases to the mediastinal lymph nodes and sometimes to the bones, liver, and adrenals were reported. Groth et al. (1980) performed successful transplants in experiments with intratracheal administration of beryllium metal and beryllium alloy, but metastasis to the mediastinal lymph node was observed in only one animal.

The nature of the neoplasms produced by the intravenous or intramedullary administration of beryllium in rabbits is much more certain. The osteosarcomal or chondrosarcomal character of these neoplasms has not been challenged, and metastases to all parts of the body have been observed. Transplant results have been equivocal, however. Successful transplants to the anterior chamber of the eye were reported by Dutra and Largent (1950) and Higgins et al. (1964), whereas failure with transplants was expressly admitted by Hoagland et al. (1950) and Araki et al. (1954). It is possible that the degree of malignancy of the bone tumors depends on the type of compound used in the injection.

7.1.8.2 Species Specificity and Immunobiology. Pulmonary tumors were produced after inhalation exposure and sometimes after intratracheal injection in rats (Vorwald, 1953; Vorwald et al., 1955; Schepers et al., 1957; Schepers, 1961; Vorwald et al., 1966; Reeves et al., 1967; Reeves and Deitch, 1969; Spencer et al., 1965, 1968, 1972; Wagner et al., 1969; Groth et al., 1980; Ishinishi et al., 1980) and in monkeys (Schepers, 1964; Vorwald et al., 1966; Vorwald, 1968; but see Wagner et al., 1969 for negative evidence). No pulmonary tumors were produced in rabbits (Vorwald, 1950). The evidence for hamsters (Wagner et al., 1969), and guinea pigs (Vorwald, 1950; Schepers, 1961, 1971; Reeves et al., 1972), while generally negative, was suggestive of a positive effect in some cases.

Bone tumors were produced by intravenous or intramedullary injection in rabbits (Gardner and Heslington, 1946; Dutra and Largent, 1950; Barnes et al., 1950; Hoagland et al., 1950; Araki et al., 1954; Janes et al., 1954, 1956; Kelly et al., 1961; Yamaguchi, 1963; Higgins et al., 1964; Tapp, 1969; Fodor, 1977). The single report claiming osteosarcomas in mice (Cloudman et al., 1949) needs confirmation, as does the report of osteosarcomas in rabbits after inhalation exposure (Dutra et al., 1951). Bone tumors were not observed in rats or guinea pigs.

It would appear from these data that (1) pulmonary tumors can be obtained with beryllium in rats and in monkeys, possibly in hamsters and guinea pigs, but not in rabbits, and (2) that bone tumors can be obtained with beryllium in rabbits and perhaps in mice, but not in rats or guinea pigs. The negative evidence with guinea pigs involves both the intravenous injection (Gardner and Heslington, 1946; Vorwald, 1950) and inhalation (Schepers, 1961; Reeves et al., 1972) of beryllium at levels that were definitely carcinogenic in rabbits and rats, respectively. However, in the later inhalation studies of Schepers (1971), there was suggestive evidence for the induction of lung cancer in guinea pigs.

This apparent species specificity, which might operate with other types of carcinogenesis as well (guinea pigs are generally regarded as poor models for cancer induction), has remained largely unexplored. It is certainly noteworthy that guinea pigs develop cutaneous hypersensitivity to beryllium, whereas rats do not (Reeves, 1978). In rabbits, the spleen has been found to be involved in the neoplastic response to intravenous beryllium. Gardner and Heslington (1946) observed prompt splenic atrophy in beryllium-injected rabbits, while Janes et al. (1954) found that splenic atrophy afflicted only those animals that developed the osteosarcomas. In later work, Janes et al. (1956) increased the yield of osteosarcomas in beryllium-injected rabbits twofold by performing splenectomy. These studies suggest that some form of cellular immunity, with immunocompetent cells arising from the spleen, may be a factor in determining whether beryllium is neoplastic. Various species, or perhaps individual members of a species, may have resistance to beryllium-induced cancer according to their immunocompetence.

7.1.8.3 Carcinogenic Forms and Dose-Response Relationships. There is insufficient evidence to implicate any specific chemical form of beryllium as the exclusive carcinogenic entity. Ionic beryllium changes to beryllium hydroxide upon inhalation, and both forms have caused pulmonary tumors in rats when inhaled (ionic beryllium) or injected intratracheally (beryllium hydroxide) (Vorwald, 1953; Schepers et al., 1957; Reeves et al., 1967; Groth et al., 1980). There is reason to believe that beryllium hydroxide particles can change to a much less soluble crystalline form upon aging (Gilbert and Garrett, 1956). Beryllium oxide, when directly introduced into the lungs of rats, showed a remarkable pattern of carcinogenicity, clearly indicating that firing

temperature had a definite influence on the tumor yield and that only "low-fired" (500°C) beryllium oxide was highly carcinogenic (Spencer et al., 1968, 1972). Sanders et al. (1978) observed only one lung tumor among 184 rats exposed to "medium-fired" (1000°C) beryllium oxide. Frequently, no tumors are obtained with beryllium oxide; however, in early studies, the type of beryllium oxide to which the animals were exposed was not generally identified (Cloudman et al., 1949; Dutra and Largent, 1950; Hoagland et al., 1950; Araki et al., 1954; Vorwald et al., 1966).

Experiments attempting to establish a dose-response relationship with intravenous beryllium are limited. Nash (1950) suggested 12 mg beryllium per rabbit was the minimum effective total dose to produce osteosarcomas. In the experiments of Hoagland et al. (1950), the frequency of osteosarcomas increased from 50 to 75 percent as beryllium oxide content of a fluorescent phosphor was increased from 2.3 to 14 percent. Barnes et al. (1950) could increase the rate of rabbit osteosarcomas from 4/14 (29 percent) to 2/3 (67 percent) by doubling the dose of intravenous zinc beryllium silicate from 7.5 to 15 mg. However, in the inhalation experiment of Dutra et al. (1951) and in the intramedullary experiments of Yamaguchi (1963), no clear-cut relation between dose and tumor yield was found.

Vorwald et al. (1966), citing results of their own unpublished studies, claimed that "almost 100 percent of a large number of rats" developed lung cancer after 18 months of exposure to 42 or 21 μg Be/m^3 (as sulfate). After exposure to 2.8 μg Be/m^3 (as sulfate), their reported rate of lung cancer was 13/21 (62 percent). These figures came under considerable scrutiny during the beryllium hearings at the Occupational Safety and Health Administration (Lesser, 1977). It was pointed out that these experiments were poorly controlled and that the exposure data of 2.8 μg Be/m^3 deserved no confidence. Wagner et al. (1969) obtained pulmonary tumors in rats with beryl ore (beryllium content 4.14 percent) but not with bertrandite ore (beryllium content 1.4 percent). Similarly, Groth et al. (1980) obtained pulmonary tumors with beryllium metal, beryllium hydroxide, and a beryllium-aluminum alloy, with beryllium content ranging from 62 to 100 percent. They obtained no tumors with other alloys, ranging in beryllium content from 2.2 to 40 percent. Thus, the evidence points to the existence of a definable dose-response relationship in experimental beryllium carcinogenesis.

Reeves (1978) examined this relationship by the probit method. For the induction of osteosarcomas in rabbits following intravenous injection of zinc beryllium silicate, the median effective total dose per animal was 11.0 mg beryllium. The dose-response curve intersected the 1 percent incidence level at 3.8 mg, the 0.1 percent incidence level at 2.7 mg, and the 0.01 percent incidence level at 2.0 mg. For the induction of pulmonary carcinoma in rats after inhalation of beryllium sulfate (a 35-hr/wk chamber exposure lasting 3 or more months), the median effective concentration was 18.0 μg Be/m^3, and the curve intersected the 1 percent incidence level at 12.0 μg Be/m^3, the 0.1 percent incidence level at 10.5 μg Be/m^3, and the 0.01 percent incidence level at 9.0 μg Be/m^3. Obviously, these estimates are subject to considerable uncertainty.

7.1.9 Summary of Animal Studies

The results of the studies that have been reviewed in this section are summarized in Table 7-8.

Tumors have been successfully induced by intravenous or intramedullary injection of beryllium into rabbits and, possibly, mice, and by inhalation exposure or intratracheal injection into rats, monkeys, and possibly guinea pigs. With one possible exception, attempts to induce tumorigenesis by the dietary route have proven unsuccessful. This failure to induce tumors is probably attributable to minimal absorption resulting from the precipitation of beryllium compounds in the intestine. Guinea pigs and hamsters appear to have a low degree of susceptibility to beryllium carcinogenesis. This species specificity appears to be connected with immunocompetence.

In rabbits, osteosarcomas and chondrosarcomas have been obtained. The tumors are highly invasive and metastasize readily, but transplant with variable success. They have been judged to be histologically similar to corresponding human tumors. In rats, pulmonary adenomas and/or adenocarcinomas have been obtained. The tumors are less invasive, and their metastatic and transplant potential are variable. They appear to be histologically associated with the purulent lesions of chronic murine pneumonia.

There is some evidence that the carcinogenicity of beryllium oxides is inversely related to their firing temperature, with only the "low-fired" (500°C) variety presenting a substantial hazard. Limited dose-response evidence indicates that approximately 2.0 mg beryllium (as beryllium oxide) is

TABLE 7-8. CARCINOGENICITY OF BERYLLIUM COMPOUNDS

Year	Species	Compound	Route of Administration	Tumor	Reference
1946	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Gardner and Heslington
1949	Mouse	Zinc beryllium silicate	Intravenous	"Malignant bone tumors"	Cloudman et al.
1949	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Cloudman et al.
1950	Rabbit	Zinc beryllium silicate and beryllium metal	Intravenous	Osteosarcoma	Barnes et al.
1950	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Hoagland et al.
1950	Rabbit	Beryllium oxide and zinc beryllium silicate	Intravenous	Osteosarcoma	Dutra and Largent
1951	Rabbit	Beryllium oxide	Inhalation	Osteosarcoma	Dutra et al.
1953	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung cancer (adeno and squamous)	Vorwald
1954	Rabbit	Beryllium phosphate Beryllium oxide	Intravenous	Osteosarcoma	Araki et al.
1954	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Janes et al.
1957	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung cancer (adeno and squamous)	Schepers et al.
1961	Rabbit	Zinc beryllium silicate	Intravenous	Osteosarcoma	Kelly et al.
1964	Rabbit	Zinc beryllium silicate	Intravenous	Chondrosarcoma	Higgins et al.

(continued on the following page)

TABLE 7-8. (continued)

Year	Species	Compound	Route of Administration	Tumor	Reference
1966	Monkey	Beryllium oxide	Intratracheal instillation	Pulmonary cancer (anaplastic)	Vorwald et al.
1966	Monkey	Beryllium sulfate tetrahydrate	Inhalation	Pulmonary cancer	Vorwald et al.
1967	Rat	Beryllium sulfate tetrahydrate	Inhalation	Lung cancer (alveolar-adeno)	Reeves et al.
1968	Rabbit	Beryllium oxide	Intravenous	Osteosarcoma	Komitowski
1969	Rat	Beryl ore Bertrandite ore	Inhalation	Lung cancer (adeno) No tumors	Wagner et al.
1969	Hamster	Beryl ore Bertrandite ore	Inhalation	None None	Wagner et al.
1969	Monkey	Beryl ore Bertrandite ore	Inhalation	None None	Wagner et al.
1969	Rabbit	Zinc beryllium silicate Beryllium silicate Beryllium oxide	Subperiosteal injection	Osteosarcoma Osteosarcoma Osteosarcoma	Tapp
1971	Rat	Beryllium hydroxide	Intratracheal	Pulmonary tumors	Groth and Mackay
1975a,b	Rat	Beryllium sulfate tetrahydrate	Ingestion	Tumor incidence no greater than controls	Schroeder and Mitchener
1975	Rat	Beryllium fluoride Beryllium chloride	Inhalation	Lung cancer (adeno and squamous)	Litvinov et al.

(continued on the following page)

TABLE 7-8. (continued)

Year	Species	Compound	Route of Administration	Tumor	Reference
1975	Rabbit	Zinc beryllium silicate	Intramedullary	Osteosarcoma	Mazabrau
1977	Rat	Beryllium sulfate tetrahydrate	Ingestion	Reticulum cell sarcoma significant increase with low dose only	Morgareidge et al.
1978	Rat	Beryllium oxide	Inhalation	Single lung cancer (adeno)	Sanders et al.
1980	Rat	Beryllium metal Beryllium alloy Passivated beryllium metal Beryllium hydroxide	Intratracheal instillation	Lung cancer (adeno and squamous) " "	Groth et al.
1980	Rat	Beryllium oxide	Intratracheal instillation	Lung cancer (squamous, adeno, lympho)	Ishinishi et al.

Source: Adapted from Kuschner (1981).

the minimum intravenous dose for production of osteosarcomas in rabbits, and approximately 10 μg Be/m^3 (as sulfate) is the minimum atmospheric concentration for the production of adenocarcinomas in rats.

Although some studies involving beryllium clearly have limitations, the combined data, using EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) to classify weight of evidence for carcinogenicity in experimental animals, suggest there is "sufficient evidence" to conclude that beryllium and beryllium compounds are carcinogenic in animals.

7.2 EPIDEMIOLOGIC STUDIES

7.2.1 Bayliss et al. (1971)

The first in a series of government-sponsored studies of cancer in workers exposed to beryllium was conducted by Bayliss et al. (1971). This cohort mortality study consisted originally of 10,356 former and current employees of the beryllium-processing industry (the Brush Beryllium Company of Ohio, presently Brush Wellman, Inc. and Kawecki-Berylco Industries of Pennsylvania, presently Cabot Corporation). Some 2153 workers were excluded because of insufficient data. Records consisted only of names of workers and approximate years of employment of workers employed at the Brush Beryllium Company prior to 1942. Company employment records provided no additional information despite an intensive search. These lists were prepared by a former Brush Beryllium Company physician, now deceased. After further removal of 1130 females, the cohort totaled 6818 males. In this group, 777 members died during the period from January 1, 1942 to the cutoff date, December 31, 1967. This was less than the 842.4 expected deaths based upon U.S. male death rates--a shortfall attributable to the "healthy worker effect." No elevated risk of lung cancer (International Classification of Diseases [ICD] 160-164) was evident overall (36 observed versus 34.06 expected). No significant excess risk of lung cancer was found to exist in relation to length of employment, beginning date of employment, or kind of employment (office versus production), nor were significant risks of other forms of cancer evident from these data.

This study suffers from several deficiencies. Over 2000 individuals had to be eliminated from the cohort because birth date, race, and sex were not available. The authors indicated that this reduction in the size of the study necessitated the elimination of some 251 deaths, and represented a loss of over 20 percent of the cohort and 25 percent of the known deaths, a circumstance that had the potential for introducing considerable bias into the results.

be a tendency on the part of the authors to overemphasize the positive nature of their results and minimize the contribution of qualifying factors. A list of these problems is presented in Table 7-14. If the errors detailed in the preceding paragraphs were corrected and proper consideration given to addressing the problems described above, the finding of a significant excess risk would probably no longer be apparent, although the possibility, nevertheless, remains that a portion of the remaining excess lung cancer risk may be partially due to beryllium exposure.

The International Agency for Research on Cancer (IARC) has concluded that beryllium and its compounds should be classified as "limited" with respect to the human epidemiologic evidence of carcinogenicity. This can be explained by the fact that IARC uses only published information to weigh the carcinogenic evidence for any given substance. In the case of beryllium, more recent tabulations and analyses of the major study cohorts than those found in the published reports were available to CAG. These tabulations included some corrections to the data base and were prepared using the more accurate updated NIOSH life-table program. Thus, based upon the analysis of this newer information, CAG regards the epidemiologic evidence of beryllium carcinogenicity in beryllium-exposed workers as inadequate.

7.3 QUANTITATIVE ESTIMATION

This quantitative section deals only with estimation of the unit risk for beryllium as a potential carcinogen in air, and compares the potency of beryllium to other carcinogens that have been evaluated by the CAG. In the Ambient Water Quality Criteria Document for Beryllium, (U.S. EPA, 1980) an upper-limit potency estimate for ingestion was derived from the Schroeder and Mitchener (1975a) drinking water study. The value derived in the water document may have been overly conservative, however, since negative results at much greater doses have been obtained in earlier studies. In the only ingestion study in which a significant tumor response was reported (Morgareidge et al., 1977, abstract), the results were considered to be equivocal for reasons discussed in Section 7.1.7. Moreover, this study was only published in abstract form. Because no study is available in which tumor induction was definitively shown, a potency estimate for beryllium via the ingestion route was not derived in this document.

TABLE 7-14. PROBLEMS WITH BERYLLIUM COHORT STUDIES

Bayliss et al. (1971)	A. Loss of 2000 individuals because of insufficient data. B. No latency considerations. C. Combined study populations of several plants from two companies.
Bayliss and Lainhart (1972)	A. Includes clerical and administrative personnel with no exposure. B. No independent assessment plant employment files. C. Latency after 20 years not assessed.
Bayliss and Wagoner (1977) and Wagoner et al. (1980)	A. Cigarette smoking a possible confounder. B. Underestimate of expected lung cancer deaths in comparison population by 11 percent. C. Inclusion of 1 lung cancer victim who did not fit definition for inclusion. D. Loss of 295 individuals from study cohort. E. Exposure to potential carcinogens prior and post beryllium employment.
Mancuso and El-Attar (1969)	A. Unidentified comparison population. B. Internal rates based on small numbers. C. Tremendous variability and impossible to test significance. D. No smoking consideration as possible confounder.
Mancuso (1970)	A. Internal rates based on small numbers. B. Inappropriate comparison (age group 15-24 left out of comparison). C. No consideration of smoking as a possible confounder. D. No consideration of latency. E. Exposure to potential carcinogens prior and post beryllium employment.
Mancuso (1979)	A. Underestimate of expected lung cancer deaths in comparison population by 11 percent. B. No consideration of smoking as a possible confounder. C. Incomplete delineation of cohort from use of Social Security Quarterly Earnings reports. D. Exposure to potential carcinogens prior and post beryllium employment.
Mancuso (1980)	A. No consideration of latent effects. B. Probable lack of age adjustment. C. No consideration of effects of smoking. D. No description of origin or makeup of comparison cohort except for age. E. Underestimate of expected lung cancer deaths in comparison population by 11 percent.

The unit risk for an air pollutant is defined as the incremental lifetime cancer risk to humans from daily exposure to a concentration of 1 $\mu g/m^3$ of the pollutant in air by inhalation. The unit risk estimate for beryllium represents an extrapolation below the dose range of experimental data. There is currently no solid scientific basis for any mathematical extrapolation model that relates exposure to cancer risk at the extremely low concentrations, including the unit concentration given above, that must be dealt with in evaluating environmental hazards. For practical reasons, the correspondingly low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. Low-dose extrapolation must, therefore, be based on current understanding of the mechanisms of carcinogenesis.

At the present time, the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is based in part on the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that a quantal response characteristic of mutagenesis is associated with a linear (at low doses) nonthreshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at high doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear (at low doses) nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). Some supporting evidence also exists from animal experiments (e.g. the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the nonthreshold model, which is linear at low doses, has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. The risk estimates made with such a model should be regarded as conservative, representing a plausible upper limit for the risk, i.e. the true risk is not likely to be higher than the estimate, but it could be lower.

For several reasons, the unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution and elimination of carcinogens, as well as species differences in target-site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans as compared to animals on a mg/surface area basis is virtually without experimental verification with respect to the carcinogenic response. Finally, genetic constitution, diet, living environment, activity patterns, and other cultural factors are quite varied among different human populations.

The unit risk estimate can give a rough indication of the relative potency of a given agent as compared with other carcinogens. Such estimates are, of course, more reliable when the comparisons are based on studies in which the test species, strain, sex, and routes of exposure are similar.

The quantitative aspect of carcinogen risk assessment is addressed here because of its possible value in the regulatory decision-making process, for example, in setting regulatory priorities, evaluating the adequacy of technology-based controls, and so forth. However, the imprecision of presently available technology for estimating cancer risks to humans at low levels of exposure should be recognized. At best, the linear-extrapolation model used here provides a rough but plausible estimate of the upper limit of risk--that is, with this model it is not likely that true risk would be much more than the estimated risk, but it could be considerably lower. The risk estimates presented in subsequent sections should not be regarded, therefore, as accurate representations of the true cancer risks, even when the exposures involved are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper-risk limits is found to be useful.

7.3.1 Procedures for the Determination of Unit Risk

7.3.1.1 Low-Dose Extrapolation Model. Two dose-response models, which are derivatives of the theory of multistage carcinogenesis, are used to calculate the unit risk of beryllium on the basis of animal data. The selection of these two models is dictated by the nature of the data available for quantitative risk assessment. The first model, a multistage model that allows for a time-

dependent dose pattern, was developed by Crump and Howe (1984), and uses the theory of multistage carcinogenesis developed by Armitage and Doll (1961). The Armitage-Doll multistage model assumes that a cell is capable of generating a neoplasm when it has undergone k changes in a certain order. The rate, r_i, of the i^{th} change is assumed to be linearly related to D(t), the dose at age t, i.e. $r_i = a_i + b_i D(t)$, where a_i is the background rate, and b_i is the proportionality constant for the dose. It can be shown that the probability of cancer by age t is given by

$$P(t) = 1 - \exp[-H(t)]$$

where

$$H(t) = \int_0^t \int_0^{u_k} \cdots \int_0^{u_2} \{[a_1 + b_1 D(u_1)] \cdots [(a_k + b_k D(u_k)]\}\, du_1 \cdots du_k$$

is the cumulative incidence rate by time t.

When H(t) or the risk of cancer is small, P(t) is approximately equal to H(t). When only one stage is dose-related, all proportionality constants are zero except for the proportionality constant for the dose-related stage.

This model will be applied to the data in Reeves and Deitch (1969) where the dose D(t) is constant for t in an interval $[s_1, s_2]$ and is zero elsewhere. Under this particular exposure pattern and the assumption that only a single stage is dose-related, the term H(t) can be written as the sum of two components $H_1(t)$ and $H_2(t)$ where $H_1(t) = a_1 \cdot a_2 \cdots a_k\, t^k/k!$ represents the background cumulative incidence and $H_2(t)$ is the incremental cumulative incidence due to exposure. Three special cases of H_2 which are often used to interpret a given set of data are given below.

$$H_2(t) = \begin{cases} 0 & t < s_1 \\ \dfrac{db_1(\pi a_i)}{k!\, a_1} \times (t - s_1)^k & s_1 \le t < s_2 \\ (t - s_1)^k - (t - s_2)^k & s_2 \le t \end{cases}$$

if the first stage is affected (t = 1),

$$H_2(t) = \frac{db_1(\pi a_i)}{k!\, a_{k-1}} \times \begin{cases} 0 & t < s_1 \\ t^k - s_1^{k-1}[kt - (k-1)s_1] & s_1 \le t < s_2 \\ s_2^{k-1}[kt - (k-1)s_2] - s_1^{k-1}[kt - (k-1)s_1] & s_2 \le t \end{cases}$$

if the penultimate stage is affected (r = k - 1), and

$$H_2(t) = \frac{db_1(\pi a_i)}{k!\, a_k} \times \begin{cases} 0 & t < s_1 \\ t^k - s_1^k & s_1 \le t < s_2 \\ s_2^k - s_1^k & s_2 \le t \end{cases}$$

if the last stage is affected (r = k).

A computer program, ADOLL1-83, has been developed by Crump and Howe (1984) to implement the computational aspect of the model. In this program, the model is generalized to include tumor induction time I by replacing the time factor t by t-I. The best-fit model is identified as the one that has the maximum likelihood among various models with different numbers of stages and the stage affected by the exposure.

The second model used to calculate the carcinogenic potency of beryllium is the one-hit model with zero background rate. This model is used because all the experiments, except that of Reeves and Deitch (1969), had only one data point and did not have a control group. The slope, b, of the one-hit model, P(d) = 1 - exp(-bxd), is calculated by the formula

$$b = [-Ln(1-P)]/d$$

Since the background rate is zero, the least-square estimate b, as calculated above, is also a maximum-likelihood estimate.

7.3.1.2 Selection of Data. For some chemicals, several studies in different animal species, strains, and sexes, each run at several doses and different routes of exposure, are available. A choice must be made as to which of the data sets from several studies to use in the model. It may also be appropriate to correct for metabolism differences between species and for absorption factors via different routes of administration. The procedures used in evaluating these data are consistent with the approach of making a maximum-likelihood risk estimate. They are as follows:

1. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is significantly higher statistically than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the set of data having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers A_1, A_2, ..., A_m, is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$$

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

7.3.1.3 Calculation of Human Equivalent Dosages. Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species unless adequate evidence is presented to the

contrary. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere, the exposure in mg/day per two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner.

Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e. during l_e), and

W = average weight of the experimental animal during the exposure period.

Then, the lifetime exposure is

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

7.3.1.3.1 Inhalation exposure. Often it is necessary to convert given exposures into mg/day. When exposure is via inhalation, the calculation of dose can be considered for two cases. In the first case the carcinogen is a poorly water-soluble gas which reaches equilibrium between the air breathed and the body compartments. After equilibrium is reached, the uptake of such gases is expected to be proportional to the metabolic rate, which is itself a function of surface area and is thus not limited by the respiratory exchange rate. In the second case, in which the carcinogen is in the form of either a completely water-soluble gas, or an aerosol, uptake is respiration limited. This form will be considered here. For aerosols, the dose in mg/day can be expressed as: $m = I \times C \times de$, where I equals the respiratory exchange rate in m^3/day, C equals mg/m^3 of the agent, and de equals the deposition fraction. Particle clearance rates may also influence the bioavailable dose, but such information is seldom available for the same types of particles in both humans and laboratory animals.

The inhalation rates, I, for various species can be calculated from the observations of the Federation of American Societies for Experimental Biology (FASEB, 1974) that 25-g mice breathe 34.5 liters/day and 113-g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

Respiratory values for most other laboratory species are also reported by the Federation of American Societies for Experimental Biology (1974). For humans, the value of 20 m^3/day* is adopted as a standard breathing rate (International Commission on Radiological Protection, 1977). The equivalent human concentration [C_h] can be derived from the experimental air concentration by the following formula

$$C_h = \frac{C_a I_a\ (W_h/W_a)2/3}{I_h}$$

where a and h refer to animals and humans, respectively. An adjustment for deposition efficiency can also be made if adequate data are available. The equivalent human dose can be determined by

$$d = \frac{C_h \times I_h}{W_h}$$

7.3.1.4 Calculation of the Unit Risk from Animal Studies. The risk associated with d mg/$kg^{2/3}$/day is obtained from GLOBAL86 (Howe et al., 1986), and for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of X = 1. This value is estimated by finding the number of

*From "Recommendation of the International Commission on Radiological Protection," page 9. The average breathing rate is 10^7 cm^3 per 8-hour workday and 2×10^7 cm^3 in 24 hours.

$mg/kg^{2/3}/day$ that corresponds to one unit of X, and substituting this value into the above relationship. Thus, for example, if X is in units of $\mu g/m^3$ in the air, then for case 1, $d = 0.29 \times 70^{1/3} \times 10^{-3}$ $mg/kg^{2/3}/day$, and for case 2, $d = 1$, when $\mu g/m^3$ is the unit used to compute parameters in animal experiments.

Note that an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures, and then to increase the j^{th} polynomial coefficient by an amount

$$(W_h/W_a)^{j/3} \quad j = 1, 2, \ldots, k,$$

and to use mg/kg equivalents for the unit risk values.

7.3.1.4.1 Adjustments for less than life span duration of experiment. If the duration of experiment L_e is less than the natural life span of the test animal L, the slope q_1^*, or more generally the exponent g(d), is increased by multiplying by a factor $(L/L_e)^3$. We assume that if the average dose d is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. The age-specific rates for humans increase at least by the second power of the age and often by a considerably higher power, as demonstrated by Doll (1971). Thus, it is expected that the cumulative tumor rate would increase by at least the third power of age. Using this fact, it is assumed that the slope q_1^*, or more generally the exponent g(d), would also increase by at least the third power of age. As a result, if the slope q_1^* [or g(d)] is calculated at age L_e, it is expected that if the experiment had been continued for the full life span L at the given average exposure, the slope q_1^* [or g(d)] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox (1972) and the time-to-tumor model considered by Daffer et al. (1980), where the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp [-f(t) \times g(d)]$$

7.3.1.5 Model for Estimation of Unit Risk Based on Human Data. If human epidemiologic studies and sufficiently valid exposure information are available for a compound, they are always used in some way. If they show a carcinogenic effect, the data are analyzed to give an estimate of the linear dependence of cancer rates on lifetime average dose, which is equivalent to the factor B_H.

If they show no carcinogenic effect when positive animal evidence is available, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study. An upper limit to the cancer incidence is calculated, assuming hypothetically that the true incidence is below the level of detection in the cohort studied, which is determined largely by the cohort size. Whenever possible, human data are used in preference to animal bioassay data.

Very little information exists that permits extrapolation from high-exposure occupational studies to exposures at low environmental levels. However, if a number of simplifying assumptions are made, it is possible to construct a crude dose-response model whose parameters can be estimated using vital statistics, epidemiologic studies, and estimates of worker exposures.

In human studies, the response is measured in terms of the relative risk of the exposed cohort of individuals as compared with the control group. The mathematical model employed for low-dose extrapolation assumes that for low exposures the lifetime probability of death from cancer, P_0, may be represented by the linear equation

$$P_0 = A + B_H x$$

where A is the lifetime probability in the absence of the agent, and x is the average lifetime exposure to environmental levels in units such as ppm. The factor B_H is the increased probability of cancer associated with each unit increase of x, the agent in air.

If it is assumed that R, the relative risk of cancer for exposed workers as compared to the general population, is independent of length of exposure or age at exposure, and depends only upon average lifetime exposure, it follows that

$$R = \frac{P}{P_0} = \frac{A + B_H (x_1 + x_2)}{A + B_H x_1}$$

or

$$RP_0 = A + B_H (x_1 + x_2)$$

where x_1 = lifetime average daily exposure to the agent for the general population, x_2 = lifetime average daily exposure to the agent in the occupational setting, and P_0 = lifetime probability of dying of cancer with no or negligible exposure.

Substituting $P_0 = A + B_H (x_1)$ and rearranging gives

$$B_H = P_0 (R - 1)/x_2$$

To use this model, estimates of R and x_2 must be obtained from epidemiologic studies. The value P_0 is derived by means of the life-table methodology from the age- and cause-specific death rates for the general population found in U.S. vital statistics tables.

7.3.2 Estimation of the Carcinogenic Risk of Beryllium

In extrapolating from animal data, the equivalent human dose may be influenced by a variety of factors. An important variable for inhalation studies is measurement (or estimation) of ventilation. Since it has been shown that ventilatory exchange rates generally vary with metabolic rate (McMahon et al., 1977), it could be assumed that human and animal equivalent concentrations are the same. As described in Section 7.3.1.3.1, however, a more conservative approach is made. Resting values are used for estimated animal respiration, while 20 m^3/day is assumed for humans, a rate well above resting values. Based on this method, the human equivalent concentration is only 38 percent that of a 350 gram rat. Such a method is reasonable, however, since 20 m^3/day is based upon normal 24-hour activity levels. Animal inhalation exposures, on the other hand, are most often conducted during the time period when the animals are normally inactive, or sleeping, with accompanying low levels of respiration.

The efficiency of deposition may also influence the equivalent human dose. For most particles in the respirable size range the fraction deposited in the alveoli and smaller conducting airways would be predicted to be somewhat less in rats than in humans (Raabe et al., 1977; Lippman, 1977; Schlesinger, 1985). At submicron sizes the differences decrease and may disappear at very small particle sizes. Among these studies, deposition varied greatly within species due to breathing patterns and experimental techniques. For many studies, the standard of the means overlapped for humans and rats exposed to

comparable particle sizes. Due to the variability in deposition efficiency, an adjustment in dose based on this variable was not incorporated into the quantitative assessment of risk. As more data become available, however, such adjustment should be carried out. Oberdoerster (personal communication) has developed methodology to adjust for both deposition efficiency and lung surface area. This method is outlined in Section 7.3.2.1.

Retention of particles can be an important factor for determining dose to the lung, since the degree of solubilization and absorption is related to residence time. Humans normally clear inhaled particulate matter more slowly than small laboratory animals and thus might be expected to absorb a greater percentage of a deposited dose (Pepelko, 1987). Rhoads and Sanders (1985), however, reported a clearance rate half-time for beryllium oxide particles in rats of 833 days. The slow clearance rate suggests that the majority of the beryllium is solubilized, absorbed, and retained intracellularly in the cells lining the lung, probably by reaction with macromolecules. Reeves and Vorwald (1967) found that following cessation of exposure to beryllium sulfate about one-half the pulmonary load was cleared within a few weeks, but the remainder tended to remain for much longer periods. They also theorized that the beryllium probably became incorporated into the nucleus of certain pulmonary cells. Since clearance is apparently quite slow in the rat, it is doubtful that clearance rate differences between humans and laboratory animals will result in important differences in the percentage of deposited dose absorbed.

Finally, consideration should be given to the appropriateness of a surface area versus a body weight correction of inhaled dose. Dose corrections compensating for metabolic rate differences are largely based on the belief that a smaller animal, with a correspondingly more rapid metabolic rate, will inactivate or eliminate potentially harmful xenobiotics more rapidly. On the other hand, if the chemical requires activation, and the rate limiting step is along the activation pathway, then it may not be correct to adjust dose based on surface area. If activation is required, the relationship between exposure levels and the area under the time-concentration curve of the active metabolite should be determined. There is no evidence to date, however, that beryllium requires activation.

Some evidence indicates that beryllium may be sequestered in the cells lining the alveoli and bronchioles and is inactivated, or eliminated slowly. According to Vorwald et al. (1966), inhaled beryllium aerosols are precipitated

by lung fluids, but then hydrolysis results in a supply of beryllium ions that enter the cell and react with macromolecules, possibly DNA and RNA. Vorwald and Reeves (1959) found that 85 percent of subcellular beryllium sedimented in the nuclear fraction. Any conclusions were limited since the actual localization of beryllium could not be shown by biochemical means. Firket (1953), however, was able to identify beryllium histochemically in the nucleolus, an organelle made up of macromolecules including RNA. If beryllium reacts with macromolecules and no mechanism is available for elimination or deactivation, then toxic dose levels are not likely to correlate well with metabolic rate. Although the data suggest that beryllium may be bound intracellularly and is eliminated very slowly, the evidence is not sufficiently conclusive to show that a dose adjustment based on metabolic rate is not correct.

The direct experimental evidence available to determine if the rat is uniquely susceptible to the carcinogenic effects of beryllium, is quite limited. While no definitive positive results are available for hamsters, Wagner et al. (1969) reported atypical proliferations in animals of this species exposed to beryl ore at beryllium levels of 620 $\mu g/m^3$, a dose producing tumors in 18 of 19 rats. The authors would have considered these proliferations to be bronchoalveolar tumors except for their small size. It is quite possible that these proliferations would have progressed to tumors if the hamster had a longer life span.

Although statistically significant positive responses were not seen in guinea pigs, Schepers (1971) reported the occurrence of lung tumors in 2 of 20 animals exposed to beryllium sulfate and in 1 of 30 males and 1 of 20 females exposed to beryllium oxide. Since lung tumors are extremely rare in guinea pigs, the data are indicative of a possibly positive response even if exposure conditions were not well described and control values were not reported.

The only other species other than rats in which a clear-cut response occurred was the rhesus monkey (Vorwald et al., 1966; Vorwald, 1968). No tumors were detected in five monkeys dying of pulmonary disease the first two years of exposure. Eight of 11 monkeys, however, surviving exposure to 39 $\mu g/m^3$ beryllium, an average of 15 hours per week, for greater than two years up to 10 years, developed lung cancer. Based on this one study, monkeys appear to be as sensitive to cancer induction by beryllium as rats.

The data for hamsters and guinea pigs is only suggestive, while the data on monkeys is based upon one study which lacked controls. Taken collectively,

however, the evidence suggests that the rat is not uniquely susceptible to lung cancer induction by beryllium. Moreover, the positive results in monkeys, a species much closer phylogenetically to humans than rats, increases the likelihood that humans may also be susceptible.

7.3.2.1 Calculation of the Carcinogenic Potency of Beryllium on the Basis of Animal Data. Of the studies available for estimating the carcinogenic risk of exposure to beryllium, the majority used beryllium salts. Potency values were derived from seven inhalation studies with beryllium sulfate, and one each using beryllium phosphate and beryllium fluoride. This information is presented in Table 7-15. In order to provide some comparison among species, values for guinea pigs and rhesus monkeys were determined, even though the guinea pig study was poorly documented with only suggestive effects, while the monkey study lacked controls. Except for the Reeves and Deitch (1969) study, the investigations were conducted at single dose levels. In these cases, the one-hit model, as described in Section 7.3.1.1 is used as the low-dose extrapolation model. For the data of Reeves and Deitch, the multistage model with time-dependent dose patterns is used as the low dose extrapolation model. The data and calculations for this study are presented in the appendix.

In all of these calculations, the equivalent concentrations are derived by the following procedure, using ventilatory values arrived at as described in Section 7.3.1.3.1. For an experimental exposure concentration of 1 $\mu g/m^3$, where 0.224 m^3/day is assumed to be the volumetric breathing rate for a rat weighing 0.35 kg, and 20 m^3/day is assumed for a 70-kg man, the human equivalent concentration ($\mu g/m^3$) satisfies the equation

$$C = (0.224/20)\ m^3/day \times (70/0.35)^{2/3}\ kg$$

or C = 0.38 $\mu g/m^3$. Therefore, the human equivalent concentration in $\mu g/m^3$ is obtained by multiplying the experimental concentration by 0.38. For a 466-gm guinea pig with a reported daily breathing volume of 0.23 m^3 (Spector, 1971), the human equivalent concentration will equal 0.32 $\mu g/m^3$. For a 2.68-kg rhesus monkey with a reported daily breathing volume of 1.24 m^3/day (Spector, 1971), the human equivalent concentration will equal 0.55 $\mu g/m^3$.

The last column of Table 7-15 represents the carcinogenic potency of beryllium as calculated from each of these studies. Based on the equivalent

TABLE 7-15. DOSE-RESPONSE FROM INHALATION STUDIES WITH BERYLLIUM SALTS ON ANIMALS AND THE CORRESPONDING POTENCY (SLOPE) ESTIMATIONS

Investigator	Beryllium compound	Mean beryllium concentration exposure pattern	Standardized experimental concentration[a] ($\mu g/m^3$)	Pulmonary tumor incidence rate	Human equivalent concentration ($\mu g\ Be/m^3$)	Maximum likelihood estimate slope[b] $(\mu g/m^3)^{-1}$
			RATS			
Vorwald et al. (1966)	$BeSO_4$	2.8 $\mu g\ Be/m^3$ 35 hr/wk for 18 months	0.58	13/21	0.22	4.3×10^{0}
Reeves and Deitch (1969)	$BeSO_4$	35.7 $\mu g\ Be/m^3$ 35 hr/wk for varying durations[c]				8.1×10^{-1}
Reeves and Deitch (1969)	$BeSO_4$	35.7 $\mu g\ Be/m^3$ 35 hr/wk for 18 months	7.4	13/15	2.8	7.1×10^{-1}
Schepers et al. (1957)	$BeSO_4$	33.5 $\mu g\ Be/m^3$ 35 hr/wk for 7.5 months	2.9	58/136	1.1	5.0×10^{-1}
Vorwald (1953)	$BeSO_4$	33 $\mu g\ Be/m^3$ 35 hr/wk for 13 months	5.0	4/8	1.9	3.7×10^{-1}
Schepers (1961)	BeF_2	9 $\mu g\ Be/m^3$ 35 hr/wk for 10.5 months	1.1	11/200	0.42	1.4×10^{-1}
Schepers (1961)	$BeHPO_4$	227 $\mu g\ Be/m^3$ 35 hr/wk for 6.5 months	17.1	7/40	6.5	3.0×10^{-2}

(continued on the following page)

TABLE 7-15. (continued)

Investigator	Beryllium compound	Mean beryllium concentration exposure pattern	Standardized experimental concentration[a] ($\mu g/m^3$)	Pulmonary tumor incidence rate	Human equivalent concentration ($\mu g\ Be/m^3$)	Maximum likelihood estimate slope[b] $(\mu g/m^3)^{-1}$
			GUINEA PIGS			
Schepers (1971)	$BeSO_4$	36 $\mu g\ Be/m^3$ 35 hr/wk for 12 months	5.1	2/20	1.7	6.5×10^{-2}
			RHESUS MONKEYS			
Vorwald (1968)	$BeSO_4$[d]	38.8 $\mu g\ Be/m^3$ 15 hr/wk for 3 years	0.69	8/11[e]	0.36	3.6×10^{0}

[a]Standardized experimental concentration is calculated by c x (h/168) x (L/18) where c is the mean experimental concentration, h is the number of hours exposed per week (168 hours), and L is the number of months exposed.

[b]Estimated by assuming that the control response is zero.

[c]See appendix for details.

[d]A life span of 15 years is assumed.

[e]Response is among animals surviving more than one year.

human concentration, using a surface area correction, the maximum likelihood estimate of slope (MLE) varied from 4.3 to 3.7 x 10^{-1} for rats exposed to beryllium sulfate. The most reliable estimate is 8.1 x 10^{-1} derived from the Reeves and Deitch (1969) study. Beryllium fluoride and beryllium phosphate are somewhat less potent with MLEs of 1.4 x 10^{-1} and 3.0 x 10^{-2}, respectively. In comparing species, rhesus monkeys were at least as sensitive to beryllium sulfate as rats, while guinea pigs were about an order of magnitude less.

Because over 99 percent of beryllium emitted into the atmosphere is the result of oil or coal combustion for electric power generation, the chemical form present in the ambient environment is likely to be beryllium oxide rather than a beryllium salt (see Section 3.4). Based upon the likelihood that beryllium oxide is the primary form of human exposure, an attempt was made to derive a quantitative estimate of risk for this compound. Unfortunately, the available studies utilizing beryllium oxide have even greater limitations than those employing beryllium salts. These studies are listed in Table 7-16 in order of decreasing potency. The first study listed (Wagner et al., 1969) was well designed and conducted. The animals, however, were exposed to beryllium ore. While the beryllium is generally present as an oxide, it is conjugated with fluorides and silicates; thus, altering its physical characteristics and possibly its potency. In the next study carried out by Sanders et al. (1978), the animals were given a single inhalation exposure. Only the deposited amount, but not the concentration or exposure duration, was reported. Vorwald (1962) exposed several groups of rats for periods of three to twelve months, but only reported the total tumor incidence for all groups. The remaining five studies utilized intratracheal instillation, which results in uneven distribution in the lungs and makes dosimetry estimates somewhat uncertain.

Among the inhalation exposures, the MLE varied from 7.4 x 10^{-2} for the beryl ore study to 3.2 x 10^{-3} for the Vorwald (1962) study. The MLEs for the intratracheal instillation studies varied from 1.7 x 10^{-3} to 2.1 x 10^{-4}. In this series, the MLE decreased with increasing firing temperature. Since the solubility of beryllium oxide decreases with increasing firing temperature, these studies point out a relationship between solubility and carcinogenic potency for this compound. The geometric mean of the MLEs from all eight studies was 2.1 x 10^{-3}. This value is in good agreement with the MLE of 2.4 x 10^{-3} derived from human epidemiological data. It is also in good agreement with the MLE of 3.2 x 10^{-3} derived from the 1962 Vorwald study, the only subchronic or longer inhalation study utilizing beryllium oxide.

TABLE 7-16. BERYLLIUM OXIDE DOSE-RESPONSE FROM THREE INHALATION AND FIVE INTRATRACHEAL INSTILLATION STUDIES ON ANIMALS AND THE CORRESPONDING POTENCY (SLOPE) ESTIMATES

Investigator	Beryllium compound	Mean beryllium concentration exposure pattern	Standardized experimental concentration ($\mu g/m^3$)	Pulmonary tumor incidence rate	Human equivalent concentration ($\mu g\ Be/m^3$)	Maximum likelihood estimate slope $(\mu g/m^3)^{-1}$
			INHALATION STUDIES			
Wagner et al. (1969)	Beryl ore	620 $\mu g\ Be/m^3$ 30 hr/wk for 17 months	105	18/19	40	7.4×10^{-2}
Sanders et al. (1978)	Beryllium oxide 1000°C	Single inhalation Alveolar deposition equals 57 µg	4.7	1/29	1.8	1.9×10^{-2}
Vorwald (1962)	Beryllium oxide	9 mg Be/m^3 35-38 hr/wk ~7.5 months	781	22/36	298	3.2×10^{-3}
			INTRATRACHEAL INSTILLATION STUDIES			
Spencer et al. (1972)	Beryllium oxide 500°C	50 mg Be/kg single dose	1430[a]	24/40	544	1.7×10^{-3}
Spencer et al. (1968)	Beryllium oxide 500°C	50 mg Be/kg single dose	1430	23/45	544	1.3×10^{-3}
Ishinishi et al. (1980)	Beryllium oxide 900°C	1 mg Be/dose[b] 15 weekly doses	1230	6/29	468	5.0×10^{-4}
Spencer et al. (1968)	Beryllium oxide 1100°C	50 mg Be/kg single dose	1430	3/19	544	3.2×10^{-4}
Spencer et al. (1968)	Beryllium oxide 1600°C	50 mg Be/kg single dose	1430	3/28	544	2.1×10^{-4}

[a]Based on the assumption that deposition is 100 percent via intratracheal instillation versus 10 percent via inhalation.

[b]A body weight of 350 grams is assumed.

Although each of the studies has important limitations, taken collectively they provide reasonable evidence that the true MLE is likely to be at least in the range of the MLEs derived. Moreover, since the geometric mean of the MLEs for the eight studies do agree quite well with the MLE derived from human data, these estimates do provide support to the quantitation of risk from the human epidemiology studies.

In addition to the previously described methods for deriving an equivalent human concentration, an alternate method has been proposed by Oberdoerster of the University of Rochester (personal communication). In this method, an adjusted human equivalent concentration, which takes into account differences in both deposition efficiency and lung surface area is derived. As a further refinement, concentration per unit of surface area is estimated separately for alveolar and tracheobronchial regions.

The study by Reeves and Deitch (1969), in which rats were exposed to beryllium sulfate at a beryllium concentration of 35 $\mu g/m^3$, was used to demonstrate this method. For a mean particle diameter of 0.35 μm, tracheobronchial deposition was estimated to equal one percent in rats versus two percent in humans. Alveolar deposition was estimated to equal ten percent in rats versus twenty percent in humans. The daily volume of air breathed per day was assumed to equal 0.20 m^3/day for 300 gm rats and 20 m^3/day for a 70 kg man. The dose to the tracheobronchial (tb) region in rats then can be calculated to equal

$$.20\ m^3/day \times .01 \times 35\ \mu g/m^3 = 0.07\ \mu g/day$$

The dose to the alveolar (alv) region equals

$$.20\ m^3/day \times .10 \times 35\ \mu g/m^3 = 0.70\ \mu g/day$$

The human equivalent tb concentration equals

$$(70/.30)^{2/3} \times \frac{.015\ \mu g/day}{20\ m^3/day \times .02} = 1.13\ \mu g/m^3$$

The human equivalent alv concentration equals

$$(70/.30)^{2/3} \times \frac{0.15\ \mu g/day}{20\ m^3/day \times .20} = 1.13\ \mu g/m^3$$

The alveolar surface area for a 300 gm rat was estimated to equal 4453 cm^2 compared with 548,789 cm^2 for humans. Tracheobronchial surface area was estimated to equal 45.7 cm^2 in rats compared with 4060 cm^2 in humans. The alv surface area to body weight ratio is equal to 4453 cm^2/0.3 kg or 14,843 cm^2/kg in the rat and 548,789 cm^2/70 kg or 7040 cm^2/kg in humans. The alveolar surface area per unit body weight is thus 14,843/7040 or 1.89 times greater in the rat while the tracheobronchial surface is 2.62 times greater in the rat using the same method. Adjusting for alv surface area, the human equivalent concentration equals 1.13/1.89 or 0.60 $\mu g/m^3$. Adjusting for relative tb surface area, the human equivalent concentration equals 1.13/2.62 or 0.43 $\mu g/m^3$.

As can be seen, the adjusted human concentration based upon estimated differences in deposition efficiency is about half that using standard methodology. As a result, an MLE calculated on this basis would be about doubled. Making a further adjustment to account for differences in relative lung surface will result in even smaller human equivalent concentrations and thereby greater MLEs.

The application of methodology such as that illustrated above has the potential for greatly refining the quantitative assessment of risk. This method was not used for the development of quantitative risk estimates for beryllium because there is still some uncertainty regarding relative deposition efficiency in laboratory animals and humans. Deposition can vary considerably with breathing patterns and with particle size, shape, and density. It is also uncertain if a higher concentration over a small lung surface area will result in a greater degree of tumor induction than the same total dose deposited over a larger surface. As more data become available reducing uncertainty regarding deposition efficiency, methodology such as this should be incorporated into the quantitative assessment of risk.

7.3.2.2 Calculation of the Carcinogenic Potency of Beryllium on the Basis of Human Data. Given the need to estimate the cancer risk of beryllium and the uncertainty inherent in the use of animal data, it is desirable to use the available human data in some way to estimate the carcinogenic potency of beryllium. Data from Wagoner et al. (1980) are considered appropriate for this purpose. This study is selected because the cohort consisted of beryllium workers employed prior to 1949, when controls on beryllium in the workplace began. The workers' exposures to beryllium before 1949 were very high. A 1947 study reviewed by NIOSH (1972) reported beryllium concentrations in a beryllium extraction plant in Pennsylvania of up to 8840 $\mu g/m^3$. In more than 50 percent

of the determinations reviewed, beryllium concentrations were in excess of 100 $\mu g/m^3$. According to NIOSH (1972), the levels of environmental exposure to beryllium in the workplace were markedly reduced after control measures were instituted in 1949. In one Ohio extraction plant, the beryllium exposure levels were recorded at 2 $\mu g/m^3$ or less during almost all of a seven-year period. The information available about beryllium exposure levels in the workplace and the excess cancer risk observed among workers employed in beryllium production plants is summarized below.

7.3.2.2.1 Information on exposure levels. The beryllium plant studied by Wagoner et al. (1980) was a major beryllium extraction, processing, and fabrication facility located in Pennsylvania. The workplace concentrations of beryllium in various beryllium production plants in Pennsylvania and Ohio were found to be comparable (Eisenbud and Lisson, 1983). Based on the NIOSH (1972) report described previously, the lower-bound estimate of the median exposure concentration exceeded 100 $\mu g/m^3$, since more than 50 percent of the determinations exceeded that level. According to Eisenbud and Lisson (1983), it is likely that this value (100 $\mu g/m^3$) is an underestimation of the actual median exposure level in the workplace, and thus should be considered to be a lower-bound estimate of median level. Eisenbud and Lisson (1983) stated "...published studies of conditions in the Pennsylvania production plant indicate that the levels of exposure prior to installation of dust controls were comparable to conditions in the Ohio plants. Concentrations in excess of 1000 $\mu g/m^3$ were commonly found in all three extraction plants during the late 1940s." On the other hand, it is unlikely that the median level could greatly exceed 1000 $\mu g/m^3$, since at that level almost all of the exposed workers developed acute respiratory diseases (Eisenbud, 1955). Thus, it is reasonable to assume that the median level of beryllium concentration did not exceed 1000 $\mu g/m^3$. In the risk calculation, the median level of beryllium concentration is assumed to range from 100 to 1000 $\mu g/m^3$. This is the narrowest range for median exposure that could be obtained on the basis of available information.

7.3.2.2.2 Information on excess risk. Wagoner et al. (1980) conducted a cohort study of 3055 white males who were initially employed in a plant in Pennsylvania from 1942 to 1967, and who were followed to December 30, 1975. Of particular interest to the present risk assessment is a subcohort of workers who were initially employed prior to 1950, and who were followed for at least 25 years from the date of initial employment. The elevation of lung cancer mortality was originally shown by Wagoner et al. (1980) to be statistically

significant ($p \leq 0.05$). However, the significant elevation of lung cancer mortality disappears after making an adjustment for differences in cigarette smoking between cohort and control populations. For the subcohort of workers who were followed at least 25 years since their initial employment, the smoking-adjusted expected lung cancer deaths are found to range from 13.91 to 14.67, in comparison with the 20 observed lung cancer deaths. The relative risk estimates are 20/13.91 = 1.44 and 20/14.67 = 1.36, which are not statistically significant ($p > 0.05$). Although the epidemiologic study did not show carcinogenic effects, the data can be used to calculate an upper limit of lung cancer risk.

Assuming that the observed cases follow a Poisson distribution and the expected value is constant, the 95 percent confidence limits for the two relative risk estimates, 1.36 and 1.44, are respectively 1.98 and 2.09. The values 1.98 and 2.09 are used to estimate the lifetime lung cancer risk due to 1 $\mu g/m^3$ of beryllium in air.

7.3.2.2.3 Risk calculation on the basis of human data. To calculate the lifetime cancer risk on the basis of information described previously, the median level of beryllium exposure must be converted to the "effective" dose, through multiplying by a factor of (8/24) x (240/365) x (f/L), to reflect that workers were exposed to beryllium 8 hours/day, 240 days/year, for f years out of a period of L years at risk (i.e. from the onset of employment to the termination of follow-up). Two values of f/L are used in the calculation: f/L = 1 and f/L = 0.25. The use of f/L = 1 would avoid overestimating the risk (but could underestimate the risk) if the observation by Reeves and Deitch (1969)--that tumor yield depends not on length of exposure but on age at exposure--is valid. Table 7-17 presents a range of cancer potency estimates calculated under various assumptions about relative risk estimates and level of exposures. The upper-bound estimate of the cancer risk associated with 1 $\mu g/m^3$ of beryllium ranges from $1.6 \times 10^{-4}/(\mu g/m^3)$ to $7.2 \times 10^{-3}/(\mu g/m^3)$, with a geometric mean of $2.4 \times 10^{-3}/(\mu g/m^3)$. Because of the range of uncertainty, this number is rounded to $2 \times 10^{-3}/(\mu g/m^3)$.

7.3.2.3 Risk Due to Exposure to 1 $\mu g/m^3$ of Beryllium in Air. Both animal and human studies have been used to qualitatively evaluate the potential for human carcinogenicity. For quantitative risk assessment purposes, the available data presents some difficult analytical problems. In the case of animal studies, although several forms of beryllium were tested, the design and reporting of many of the studies were inferior by current standards, resulting

TABLE 7-17. UPPER-BOUND CANCER POTENCY ESTIMATES CALCULATED UNDER VARIOUS ASSUMPTIONS

Beryllium concentration in workplace ($\mu g/m^3$)	f/L	"Effective" dose[a] ($\mu g/m^3$)	95 percent upper-bound estimate of relative risk	Cancer potency[b] $(\mu g/m^3)^{-1}$
100	1	21.92	1.98	1.61×10^{-3}
			2.09	1.79×10^{-3}
	0.25	5.48	1.98	6.44×10^{-3}
			2.09	7.16×10^{-3}
1000	1	219.18	1.98	1.61×10^{-4}
			2.09	1.79×10^{-4}
	0.25	54.79	1.98	6.44×10^{-4}
			2.09	7.16×10^{-4}

[a]"Effective" dose is calculated by multiplying the beryllium concentration in the workplace by the factor (8/24) x (240/365) x (f/L).

[b]For a given "effective" dose d and a relative risk R, the carcinogenic potency is calculated by the formula B = (R-1) x 0.036/d, where 0.036 is the estimated lung cancer mortality rate in the U.S. population.

in a clear basis for uncertainty about the reasonableness of the upper-limit risk estimates. The epidemiologic data, while being useful for analysis of cancer incidence, nevertheless, has interpretive limitations because of the uncertainties regarding exposure levels.

Despite the uncertainties and weaknesses of the individual studies, the cancer response in beryllium exposed animals is very strong and there seems to be a pattern of response which relates to the beryllium specie tested (i.e. oxide, sulfate, etc.). The unit risks derived from the animal data sets are best viewed as a sensitivity analysis as opposed to a collection of reasonable upper-bound risk values. The sensitivity relates to beryllium specie tested and for beryllium oxide alone, perhaps to solubility and firing temperature. The epidemiology based risk analysis is also a sensitivity analysis which results from the need to make fundamental assumptions about exposure together with the use of nonsignificant incidence data in order to derive an upper-limit risk approximation. Interestingly, the two distinct sensitivity analyses

(animal data, human data) correlate very closely for beryllium oxide, there being no human data to compare to the animal data for beryllium sulfate and other beryllium compounds.

Many of the animal experiments used beryllium salts, a form not likely to be present either in ambient air or in occupational settings. In mining operations, for example, the beryllium present in the ore is in the form of an oxide, but may be bound with other chemicals as well. In the extraction process, the primary product, beryllium oxide, is then reduced to the metallic form. In operations such as melting, pouring, or welding of beryllium, fumes consisting of fine particles of beryllium oxide are produced by condensation from the vapor phase. Other sources of workplace contamination result from metallic dusts generated by a variety of operations such as crushing, grinding, or cutting of beryllium-containing material. For further details regarding industrial processing of beryllium, refer to Tepper et al. (1961). Beryllium is most commonly found in ambient air as a trace metal component of fly ash emitted from coal-burning electric power generating plants. Since fly ash is a combustion product, the beryllium again is primarily present as the oxide.

Although all of the animal studies were deficient in some respect, the ones utilizing beryllium oxide were more deficient, as a group, than those utilizing beryllium salts. Since humans are likely to be exposed to beryllium as an oxide, however, and since the carcinogenic response was shown to vary with the form of beryllium, the use of beryllium oxide data is considered an important focus in estimating the cancer potency. While the available beryllium oxide studies were individually weak, a correlation of estimates from several data sets would be expected to increase confidence in the results. Potency factors were thus calculated using data from eight beryllium oxide animal studies. The results were reasonably consistent and the geometric mean of all eight potency factors was $2.1 \times 10^{-3}/(\mu g/m^3)$, which closely agrees with the potency factor derived from the human epidemiology data. Although the confidence levels are still too low to recommend a potency factor and unit risk based on the animal data, these estimates, nevertheless, do provide support for the potency estimate derived from the human epidemiology data.

A risk assessment based upon human epidemiology data was calculated based on the occupational exposure study of Wagoner et al. (1980). The narrowest range for median exposure that could be obtained on the basis of available information was 100 to 1000 $\mu g/m^3$. The ratio of exposure duration to duration of risk was assumed to range from a minimum of 0.25 to 1.0. The geometric

mean of the range of potency factors derived using the above assumptions is equal to $2.4 \times 10^{-3}/(\mu g/m^3)$. As indicated in the previous section, this number is rounded to $2 \times 10^{-3}/(\mu g/m^3)$.

The CAG feels that a recommendation for a specific upper-bound estimate of risk is warranted, even though it does evolve from less than ideal data, in order to provide a crude measure of the potential for a public health impact if, in fact, beryllium is a human carcinogen. Some of the risk values discussed in the document are derived from animal data which have significant shortcomings, the result being that the estimates taken as a whole demonstrate a sensitivity analysis of reasonableness rather than being a collection of equally reliable upper-bound values. In a similar manner, the risk estimates derived from the human data have inherent uncertainty because of the need to assume exposure levels and, thus, the risk estimate of $2 \times 10^{-3}/(\mu g/m^3)$ is in effect also the result of a sensitivity analysis.

Taken together the notable comparability of the animal and human based estimates for beryllium oxide encourages one to consider these estimates as being of some utility. Given the correlation of the animal and human estimates, a value of $2 \times 10^{-3}/(\mu g/m^3)$ is considered to be a useful approximation of the upper-limit risk for beryllium oxide. This can be converted to a q_1^* value of 7 $(mg/kg/day)^{-1}$ after adjusting for a weight of 70 kg and 20 m^3 of air breathed/day. The uncertainty of the beryllium oxide risk value in relation to the true risk has two aspects, one being the usual uncertainty which is attributable to the linearized multistage procedure in the case of animal data or the upper limit modelling of human data (i.e. the true risk is not likely to be higher and may be lower). A second uncertainty unique to the beryllium data base relates to the need to make dosimetry assumptions as a part of the risk modelling of the animal and human data. The dosimetry influenced uncertainty should be viewed as potentially causing either an overestimation or underestimation of the upper limit. The utility of these risk values in risk management analysis should be judged with these uncertainties in mind. Hence, whereas one might use these estimates to screen for a possible public hazard, one should exercise much greater caution in using these values for an assessment of individual cancer risk.

Since beryllium salts are more potent, the higher unit risk values derived from these studies should be used in cases of potential human exposure to these forms of beryllium. The uncertainties associated with the beryllium salt risk

estimates [especially beryllium sulfate, risk value of $0.8/(\mu g/m^3)$] is the typical concern associated with the upper-limit estimation from animal studies (the true risk is not likely to be higher and may be lower), there being no significant dosimetry problems with these data.

7.3.3 Comparison of Potency With Other Compounds

One of the uses of quantitative potency estimates is to compare the relative potencies of carcinogens. Figure 7-2 is a histogram representing the frequency distribution of potency indices for 59 suspect carcinogens evaluated by the CAG. The actual data summarized by the histogram are presented in Table 7-18. The potency index used herein was derived from the carcinogenic potency of the compound and is expressed in terms of $(mmol/kg/day)^{-1}$. Where no human data were available, animal oral studies were used in preference to animal inhalation studies, since oral studies have constituted the majority of animal studies.

The potency index for beryllium oxide is $2 \times 10^{+2}$, calculated by multiplying the potency estimate, 7.0/(mg/kg/day), and the molecular weight of beryllium oxide (25). This calculation places the relative potency of beryllium oxide in the third quartile of the 59 suspect carcinogens evaluated by the CAG. The potency index for beryllium sulfate is $3 \times 10^{+5}$ (see Table 7-18), placing beryllium sulfate in the first quartile.

The ranking of relative potency indices is subject to the uncertainties involved in comparing a number of potency estimates for different chemicals, based on varying routes of exposure in different species, by means of data from studies whose quality varies widely. All of the indices presented are based on estimates of low-dose risk, using linear extrapolation from the observational range. These indices may not be appropriate for the comparison of potencies if linearity does not exist at the low-dose range, or if comparison is to be made at the high-dose range. If the latter is the case, then an index other than the one calculated above may be more appropriate.

7.3.4 Summary of Quantitative Assessment

Both animal and human data have been used to calculate the carcinogenic potency of beryllium. Many of the animal studies conducted on beryllium are not well documented, were conducted at single dose levels, and in some cases did not utilize control groups. Nevertheless, because positive effects were

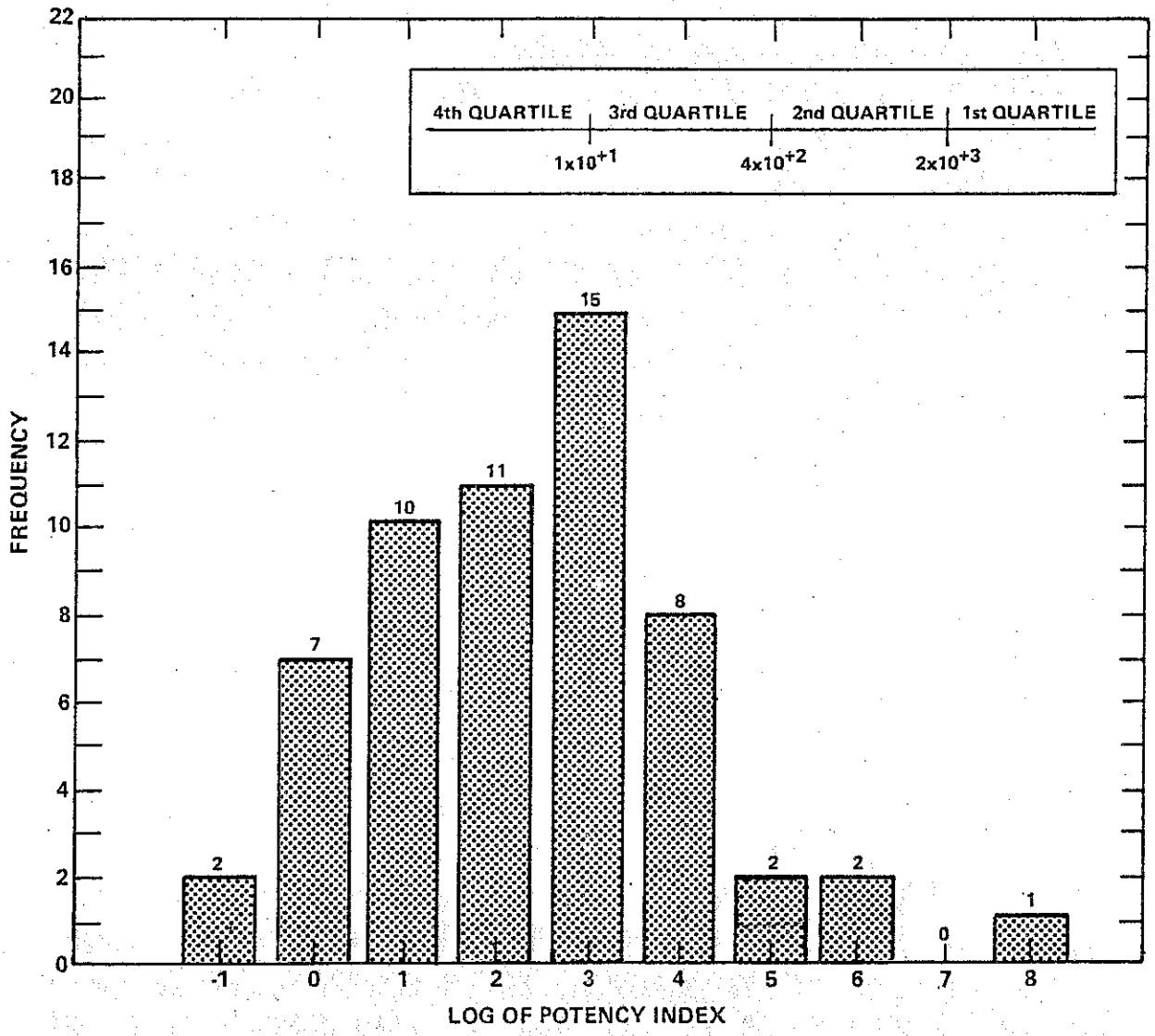

Figure 7-2. Histogram representing the frequency distribution of the potency indices of 59 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 7-18. RELATIVE CARCINOGENIC POTENCIES AMONG 59 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS

Compounds	CAS Number	Level of evidence[a]		Grouping based on EPA criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
		Humans	Animals					
*Acetaldehyde	75-07-0	I	S	B2	7.7×10^{-3}	44	3×10^{-1}	-1
Acrylonitrile	107-13-1	L	S	B1	0.24(W)	53.1	$1 \times 10^{+1}$	+1
*Aldrin	309-00-2	I	S	B2	16	369.4	$6 \times 10^{+3}$	+4
Allyl chloride	107-05-1	I	S	B2	4.7×10^{-4}	76.5	4×10^{-2}	-1
Arsenic	7440-38-2	S	I	A	1.5(H)	149.8	$2 \times 10^{+2}$	+2
B[a]P	50-32-8	I	S	B2	11.5	252.3	$3 \times 10^{+3}$	+3
Benzene	71-43-2	S	S	A	2.9×10^{-2}(W)	78	2×10^{0}	0
Benzidene	92-87-5	S	S	A	234(W)	184.2	$4 \times 10^{+4}$	+5
Beryllium oxide	7440-41-7	I	S	B2	7.0(W)	25	$2 \times 10^{+2}$	+2
Beryllium sulfate	13510-49-1	I	S	B2	$3 \times 10^{+3}$	105	$3 \times 10^{+5}$	+5
1,3-Butadiene	106-99-0	I	S	B2	1.8(I)	54.1	$1 \times 10^{+2}$	+2
Cadmium	7440-43-9	L	S	B1	6.1(W)	112.4	$7 \times 10^{+2}$	+3
Carbon tetrachloride	56-23-5	I	S	B2	1.30×10^{-1}	153.8	$2 \times 10^{+1}$	+1
Chlordane	57-74-9	I	S	B2	1.3	409.8	$5 \times 10^{+2}$	+3
Chlorinated ethanes								
1,2-Dichloroethane (Ethylene dichloride)	107-06-2	I	S	B2	9.1×10^{-2}	98.9	9×10^{0}	+1
Hexachloroethane	67-72-1	I	L	C	1.42×10^{-2}	236.7	3×10^{0}	0
1,1,2,2-Tetrachloroethane	79-34-5	I	L	C	0.20	167.9	$3 \times 10^{+1}$	+1
1,1,2-Trichloroethane	79-00-5	I	L	C	5.73×10^{-2}	133.4	8×10^{0}	+1
Chloroform	67-66-3	I	S	B2	8.1×10^{-2}	119.4	$1 \times 10^{+1}$	+1

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TABLE 7-18. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on EPA criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
Chromium VI	7440-47-3	S	S	A	41(W)	100	$4x10^{+3}$	+4
Coke Oven Emissions		S	S	A	2.16(W)	NA	NA	NA
DDT	50-29-3	I	S	B2	0.34	354.5	$1x10^{+2}$	+2
3,3-Dichlorobenzidine	91-94-1	I	S	B2	1.69	253.1	$4x10^{+2}$	+3
1,1-Dichloroethylene (Vinylidene chloride)	75-35-4	I	L	C	1.16(I)	97	$1x10^{+2}$	+2
Dichloromethane (Methylene chloride)	75-09-2	I	S	B2	$1.4x10^{-2}$(I)	84.9	$1x10^{0}$	0
*Dieldrin	60-57-1	I	S	B2	20	380.9	$8x10^{+3}$	+4
2,4-Dinitrotoluene	121-14-2	I	S	B2	0.31	182	$6x10^{+1}$	+2
Diphenylhydrazine	122-66-7	I	S	B2	0.77	180	$1x10^{+2}$	+2
Epichlorohydrin	106-89-8	I	S	B2	$9.9x10^{-3}$	92.5	$9x10^{-1}$	0
Bis(2-chloroethyl)ether	111-44-4	I	S	B2	1.14	143	$2x10^{+2}$	+2
Bis(chloromethyl)ether	542-88-1	S	S	A	9300(I)	115	$1x10^{+6}$	+6
Ethylene dibromide (EDB)	106-93-4	I	S	B2	41	187.9	$8x10^{+3}$	+4
Ethylene oxide	75-21-8	L	S	B1	$3.5x10^{-1}$(I)	44.1	$2x10^{+1}$	+1
Heptachlor	76-44-8	I	S	B2	4.5	373.3	$2x10^{+3}$	+3
Heptachlor epoxide	1024-57-3	I	S	B2	9.1	389.32	$4x10^{+3}$	+4
Hexachlorobenzene	118-74-1	I	S	B2	1.67	284.4	$5x10^{+2}$	+3
Hexachlorobutadiene	87-68-3	I	L	C	$7.75x10^{-2}$	261	$2x10^{+1}$	+1

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TABLE 7-18. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Animals	Grouping based on EPA criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
Hexachlorocyclohexane								
technical grade					2.0	290.9	$6x10^{+2}$	+3
alpha isomer	319-84-6	I	S	B2	2.7	290.9	$8x10^{+2}$	+3
beta isomer	319-85-7	I	L	C	1.5	290.9	$4x10^{+2}$	+3
gamma isomer	58-89-9	I	S-L	B2-C	1.1	290.9	$3x10^{+2}$	+3
Hexachlorodibenzodioxin	34465-46-8	I	S	B2	$6.2x10^{+3}$	391	$2x10^{+6}$	+6
Nickel refinery dust		S	S	A	0.84(W)	240.2	$2x10^{+2}$	+2
Nickel subsulfide	0120-35-722	S	S	A	1.7(W)	240.2	$4x10^{+2}$	+3
Nitrosamines								
Dimethylnitrosamine	62-75-9	I	S	B2	25.9(not by q_1^*)	74.1	$2x10^{+3}$	+3
Diethylnitrosamine	55-18-5	I	S	B2	43.5(not by q_1^*)	102.1	$4x10^{+3}$	+4
Dibutylnitrosamine	924-16-3	I	S	B2	5.43	158.2	$9x10^{+2}$	+3
N-nitrosopyrrolidine	930-55-2	I	S	B2	2.13	100.2	$2x10^{+2}$	+2
N-nitroso-N-ethylurea	759-73-9	I	S	B2	32.9	117.1	$4x10^{+3}$	+4
N-nitroso-N-methylurea	684-93-5	I	S	B2	302.6	103.1	$3x10^{+4}$	+4
N-nitroso-diphenylamine	86-30-6	I	S	B2	$4.92x10^{-3}$	198	$1x10^{0}$	0
*PCBs	1336-36-3	I	S	B2	7.7	324	$2x10^{+3}$	+3
Tetrachlorodibenzo-p-dioxin (TCDD)	1746-01-6	I	S	B2	$1.56x10^{+5}$	322	$5x10^{+7}$	+8
*Tetrachloroethylene (Perchloroethylene)	127-18-4	I	S	B2	$5.1x10^{-2}$	165.8	$8x10^{0}$	+1
Toxaphene	8001-35-2	I	S	B2	1.13	414	$5x10^{+2}$	+3
Trichloroethylene	79-01-6	I	S	B2	$1.1x10^{-2}$	131.4	$1x10^{0}$	0
2,4,6-Trichlorophenol	88-06-2	I	S	B2	$1.99x10^{-2}$	197.4	$4x10^{0}$	+1

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TABLE 7-18. (continued)

Compounds	CAS Number	Level of evidence[a] Humans	Level of evidence[a] Animals	Grouping based on EPA criteria	Slope[b] $(mg/kg/day)^{-1}$	Molecular weight	Potency index[c]	Order of magnitude (log_{10} index)
Unleaded gasoline vapor		I	S	B2	3.5×10^{-3}	110[d]	4×10^{-1}	0
Vinyl chloride	75-01-4	S	S	A	2.3	62.5	$1 \times 10^{+2}$	+2

[a]S = Sufficient evidence; L = Limited evidence; I = Inadequate evidence.

[b]Animal slopes are 95% upper-bound slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear nonthreshold model. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available. The slope value is an upper bound in the sense that the true value (which is unknown) is not likely to exceed the upper bound and may be much lower, with a lower bound approaching zero. Thus, the use of the slope estimate in risk evaluations requires an appreciation for the implication of the upper-bound concept as well as the "weight of evidence" for the likelihood that the substance is a human carcinogen.

[c]The potency index is a rounded-off slope in $(mmol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by the molecular weight of the compound.

[d]The molecular weight is based on the weighted average of the compounds present in gasoline. Some variation may be expected among samples.

NA = not applicable.

* = currently under review.

seen in multiple species, at multiple sites, and often at very low doses, these studies collectively provide sufficient animal evidence for carcinogenicity. In the present report, data from animal inhalation and intratracheal studies (using rats, guinea pigs, or rhesus monkeys exposed to a variety of beryllium compounds) have been used to calculate the upper bounds for the potency of beryllium. The maximum likelihood slope estimates, calculated on the basis of animal data, vary from 2.1×10^{-4} to $4.3/(\mu g/m^3)$, a range of four orders of magnitude.

The magnitude of the potency appears to depend primarily on the beryllium compound used in the experiment, although some variability in sensitivity among species was also seen with guinea pigs responding to a lesser degree than rats or monkeys. Among the beryllium compounds examined in the animal studies, beryllium oxide is the least carcinogenically potent, while beryllium sulfate ($BeSO_4$) is the most potent. Solubility appears to be one factor affecting potency. In the intratracheal instillation studies of Spencer et al. (1968, 1972), beryllium oxide calcined at 1100°C and 1600°C was much less potent than the more soluble form of beryllium oxide which was calcined at 500°C. If one adopts the most conservative approach, the maximum potency estimate, $4.3/(\mu g/m^3)$, would be used to represent the carcinogenic potential of beryllium sulfate. This potency is estimated on the basis of animal data (Vorwald et al., 1966) obtained in an experiment in which the level of exposure to beryllium sulfate was very similar to occupational exposure conditions. Thus, the high potency estimate is not due to the use of a particular low-dose extrapolation model. Since most beryllium compounds present in ambient air or the workplace environment are not in the form of beryllium salts, but are more likely to be the less potent beryllium oxide, use of the sulfate potency estimate would clearly overestimate the human risk. The geometric mean of $2.1 \times 10^{-3}/(\mu g/m^3)$, obtained from eight animal studies utilizing beryllium oxide or beryllium ore is considered to more accurately represent human risk to beryllium compounds present in ambient air.

Data from the epidemiological study by Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been used to develop a cancer risk estimate associated with exposure to air contaminated with beryllium. Two upper-bound relative risk estimates, 1.98 and 2.09 from the human data, have been used in the calculations. In recognition of the greater uncertainty associated with the exposure estimation, four

different "effective" levels of exposure that reflect various uncertainties, along with two relative risk estimates, have been used in the present calculations. As a result, eight potency estimates have been calculated, ranging from $1.6 \times 10^{-4}/(\mu g/m^3)$ to $7.2 \times 10^{-3}/(\mu g/m^3)$, with the geometric mean of the eight estimates being $2.4 \times 10^{-3}/(\mu g/m^3)$. Rounding off this number because of the level of uncertainty, the incremental life time cancer risk (based upon epidemiologic data) associated with 1 $\mu g/m^3$ of beryllium in the air is thus calculated to be 2×10^{-3}. This estimate could be considered an upper-bound estimate of the cancer risk because low-dose linearity is assumed in the extrapolation and the 95 percent upper-confidence limits of the relative risks are used in the calculations. With these quantitative approaches, the CAG has calculated two risk estimates, one from epidemiologic data and one from animal data, for exposures to mainly oxides of beryllium. These rounded estimates, $2 \times 10^{-3}/(\mu g/m^3)$ each, are in complete agreement. The risk estimates for the salts of beryllium (i.e., sulfate) are much higher and are derived from animal data only.

7.4 SUMMARY

7.4.1 Qualitative Summary

Experimental beryllium carcinogenesis has been induced by intravenous or intramedullary injection of rabbits, and by inhalation exposure or intratracheal instillation of rats and monkeys.

Osteosarcomas were induced in rabbits by intravenous injection of zinc beryllium silicate (9 studies), beryllium oxide (2 studies), metallic beryllium (1 study) and by intramedullary injection of zinc beryllium silicate and beryllium oxide (1 study each). Lung tumors were induced in rats by intratracheal instillation of beryllium oxide (4 studies), beryllium hydroxide (2 studies), metallic beryllium (2 studies), beryl ore (1 study) and in monkeys by beryllium oxide (1 study). Lung tumors were also induced in rats by inhalation of beryllium sulfate (5 studies), beryllium phosphate, beryllium fluoride, and beryl ore (1 study each), and in monkeys by beryllium sulfate (1 study). No significant neoplastic responses were observed via the intracutaneous or percutaneous routes, while the responses via the dietary routes were either negative or equivocal. This was considered to be due to low absorption efficiency resulting from precipitation of beryllium compounds in the small intestine.

The beryllium-induced osteosarcomas in rabbits were shown to be highly invasive and to readily metastasize. They were judged to be histologically indistinguishable from non-beryllium-induced human osteosarcomas, although the sites may be different.

As noted above, positive carcinogenic responses in animals were obtained in multiple species and through various routes of exposure. In studies using either inhalation or the intravenous injection route, positive results were obtained in multiple experiments. For several of the beryllium compounds tested, such as beryllium sulfate, significant responses were obtained at low dose levels. Based on the above findings, the overall evidence for carcinogenicity of beryllium in animals is convincing despite the limitations of many of the studies. According to EPA's criteria for evaluating the weight of evidence for carcinogenicity (U.S. EPA, 1986), the evidence for carcinogenicity of beryllium in animals is considered to be "sufficient".

Although several studies (Wagoner et. al., 1980; Mancuso, 1979; Manusco, 1980) claim a statistically significant excess risk of lung cancer in individuals exposed to beryllium, all of the studies cited have deficiencies that limit definitive conclusions regarding a true carcinogenic association. Support for finding an excess risk of lung cancer in beryllium-exposed persons consists of evidence from cohort mortality studies of two beryllium production facilities. None of these studies are independent as they are all based on the same groups of workers. Extensive collaboration existed between the authors of these studies. The expected lung cancer deaths used in all of these studies were based on a NIOSH computer-based life-table program known to produce an 11-percent underestimation of expected lung cancer deaths. Furthermore, the studies did not adequately address the confounding effects of smoking or of exposures received during prior or subsequent employment in other non-beryllium industries in the area. Many of these industries were known to produce other potential carcinogens. Problems in the design and conduct of the studies further weaken the strength of the findings. After correcting the life-table error and adjusting for some of the problems described above, the finding of a significant excess risk is no longer apparent. While the possibility remains that the portion of the reported excess lung cancer risk remaining in these studies may, in fact, be due to beryllium exposure, the epidemiologic evidence is, nevertheless, considered to be "inadequate" according to EPA's criteria for evaluating the weight of evidence provided by epidemiologic data.

Limited testing has shown beryllium sulfate and beryllium chloride to be nonmutagenic in bacterial and yeast gene mutation assays. In contrast, gene mutation studies in cultured mammalian cells, Chinese hamster V79 cells, and Chinese hamster ovary (CHO) cells have yielded positive mutagenic responses for beryllium. Beryllium increased the infidelity of DNA and RNA polymerase in prokaryotes. Chromosomal aberration and sister chromatid exchange studies in cultured human lymphocytes and Syrian hamster embryo cells have also resulted in positive mutagenic responses for beryllium. In DNA damage and repair assays, beryllium is negative in the pol, rat hepatocyte, and mitotic recombination assays but is weakly positive in the rec assay. Based on the information available, beryllium appears to have the potential to cause mutations.

Using the EPA criteria for evaluating the overall weight of evidence for carcinogenicity in humans, beryllium is most appropriately classified as group B2, a probable human carcinogen. This category is reserved for those chemicals having sufficient evidence for carcinogenicity in animals but inadequate evidence in humans.

7.4.2 Quantitative Summary

Both animal and human data are used to estimate the carcinogenic potency of beryllium. Among the animal studies, only data from inhalation exposures or intratracheal instillation are used because the intravenous or intramedullary exposure routes are not considered to be directly relatable to human exposures, and all dietary ingestion studies yielded negative results. Many of the animal inhalation studies for beryllium are not well documented, were conducted at single-dose levels, and, in some cases, did not utilize control groups. Collectively, however, the studies provide a reasonable basis for estimating potency (at least for beryllium sulfate and beryllium oxide), as exemplified by the consistency of response in rats. Data from nine studies (7 studies of rats, 1 study of guinea pigs, and 1 study of monkeys) using beryllium sulfate, phosphate, and fluoride have been used to calculate the upper bounds for the carcinogenic potency of beryllium salts. Data from eight studies with rats have been used to calculate the upper bounds for the carcinogenic potency of beryllium oxide. The upper-bound potency estimates from the data based on exposure to beryllium sulfate equal $3.6/(\mu g/m^3)$ in monkeys, $6.5 \times 10^{-2}/(\mu g/m^3)$ in guinea pigs and range from $4.3/(\mu g/m^3)$ to $3.7 \times 10^{-1}/(\mu g/m^3)$ in rats. Estimates derived from responses in rats exposed to beryllium fluoride and beryllium

phosphate equal $1.4 \times 10^{-1}/(\mu g/m^3)$ and $3.0 \times 10^{-2}/(\mu g/m^3)$, respectively. Potency estimates derived from responses of rats exposed to beryllium oxides ranged from $7.4 \times 10^{-2}/(\mu g/m^3)$ to $2.1 \times 10^{-4}/(\mu g/m^3)$.

The magnitude of the potency estimates from animal data depends to a large extent on the beryllium compound used in the experiment, although some variability in sensitivity among species is also seen, with guinea pigs responding to a lesser degree than rats or monkeys. Among the beryllium compounds examined in the animal studies, beryllium sulfate ($BeSO_4$) is the most potent, with beryllium fluoride and beryllium phosphate somewhat less so and beryllium oxide the least potent. There is some indication that the carcinogenic potency of beryllium oxide varies with the firing temperature. The low-temperature fired, more soluble oxides appear somewhat more potent than those fired at higher temperatures. If one adopts an approach which selects data from the most sensitive experimental animal species and the most potent compound as being representative of risk to humans, the maximum potency estimate, $4.3/(\mu g/m^3)$, would be used to represent the carcinogenic potential of beryllium. This potency is estimated on the basis of data from rats exposed by inhalation (Vorwald et al., 1966). Since beryllium is most commonly present in the ambient air as the oxide, a potency estimate based upon the beryllium oxide studies is considered to be most representative of human risk. Due to the individual weaknesses of each of the eight beryllium oxide studies, a potency estimate of $2.1 \times 10^{-3}/(\mu g/m^3)$ was derived by calculating the geometric mean of the individual potency estimates from each of the studies.

Information from the epidemiologic studies by Wagoner et al. (1980) and the industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983) have been used to estimate the cancer risks associated with exposure to workplace air contaminated with beryllium. Even though the epidemiologic evidence does not demonstrate a statistically significant causal association between beryllium and cancer, that does not mean that no risk exists. The size of the study population, the background risk, and a variety of other factors limit the ability of a study to detect small risks. Each study has a level of sensitivity, and the study population may be too small to show a statistically significant association if the true risk is below this level. An upper-bound risk estimate can be calculated from a non-positive, or even negative, study to describe the study's level of sensitivity. Risk levels below that upper bound are completely compatible with the study data. The upper bound may be thought

of as indicating the largest plausible risk that is consistent with the available data. Thus, the epidemiologic studies can be used to estimate a plausible upper bound for the increased cancer risk from human exposure to beryllium.

In the Wagoner et al. (1980) study, 20 lung cancer deaths were observed in a cohort of workers followed for at least 25 years compared with 13.91 to 14.67 expected ($p < 0.10$). Using the revised estimates of relative risk from this study, two upper-bound relative risk estimates, 1.98 and 2.09, have been used by the CAG to calculate the carcinogenic potency of beryllium. In recognition of the greater uncertainty associated with the exposure estimation, four different "effective" levels of exposure that reflect various uncertainties, along with the two relative risk estimates, have been used in the present calculations. As a result, eight unit risk estimates have been calculated, ranging from $1.6 \times 10^{-4}/(\mu g/m^3)$ to $7.2 \times 10^{-3}/(\mu g/m^3)$, with the geometric mean of the eight estimates being $2.4 \times 10^{-3}/(\mu g/m^3)$. After rounding to one significant figure, the incremental lifetime cancer risk associated with 1 $\mu g/m^3$ of beryllium oxide in the air is thus estimated to be 2×10^{-3}. This estimate could be considered an upper-bound estimate of cancer risk because low-dose linearity is assumed in the extrapolation and the 95 percent upper-confidence limits of the relative risk are used in the calculations. The estimate $2 \times 10^{-3}/(\mu g/m^3)$ is about three times greater than the previous unit risk estimate reported in the review draft of the Health Assessment Document for Beryllium (U.S. EPA, 1984).

The reasons that the updated unit risk estimates are higher are as follows:

1. A statistical upper-confidence limit for the relative risk, rather than a point estimate, has been used in the calculation.

2. The median concentration in the workplace is estimated to range from 100 to 1000 ppm, rather than from 160 to 1000 ppm (as was previously used). In a 1947 study reported by NIOSH (1972), more than 50 percent of air concentrations in the workplace exceeded 100 ppm. If it is assumed, as was in the earlier risk estimate, that the concentration measurements followed a log-normal distribution, then a median value of 160 ppm could be calculated. Since there are no data to substantiate (or to deny) a log-normal assumption, 100 ppm is used as the low median concentration in the workplace.

The greater potency values estimated from some of the animal data are probably due to the different forms of beryllium. In the occupational environment upon which human potency estimates are based, beryllium oxide and beryllium

metal are most commonly present. When animals are exposed to beryllium oxide or oxide-containing beryllium ore, the potency estimates agree with those derived from human exposures.

A major uncertainty of the risk estimate based on human data comes from the derivation of exposure levels in the workplace and the temporal effect of the patterns of exposure. To account for these uncertainties, the "effective" exposure level of beryllium is derived in several ways, and the geometric mean of different potency estimates thus calculated is used to represent the carcinogenic potency of beryllium.

Another uncertainty concerns the use of potency values derived from exposures in the workplace environment to estimate potency from exposure in ambient air. The types of sources which emit beryllium to the ambient air are limited. There is little evidence that ore production is a significant source of beryllium emissions. Metallurgical processing is likewise considered an insignificant source. As much as 95 percent of atmospheric beryllium emissions are estimated to come from coal-fired electric power plants, with most of the remainder resulting from fuel oil combustion (see Chapter 3). During coal combustion beryllium is likely emitted as a relatively insoluble oxide, generally as a trace contaminant of fly ash particles which are even more insoluble. On this basis, the potency of beryllium from this source would be expected to be quite low. Beryllium emissions from fuel oil combustion are similarly likely to occur primarily in the oxide form. Experimental evidence also indicates that beryllium in fly ash has a low degree of potency, since even very high concentrations of fly ash containing other known carcinogens have failed to induce cancer in laboratory animals. On this basis, it is unlikely that values derived from exposure in the workplace will significantly underestimate the potency of beryllium in ambient air, unless soluble beryllium compounds such as fluoride, phosphate, or sulfate are known to be present.

Because of the weaknesses of the animal studies upon which some of the carcinogenic potency estimates were derived, these estimates are judged to be less reliable than those derived from human occupational exposures. They do, however, provide support for the occupationally-derived estimates. Despite some uncertainties concerning exposure levels in the workplace and possible differences in the forms of beryllium found in ambient air compared with the workplace environment, the CAG-revised relative risks from the Wagoner et al. (1980) epidemiologic study were considered to be the best choice for estimating

the upper-bound incremental cancer risk for inhalation exposure to mixtures of beryllium compounds (mostly beryllium oxide) likely to be present in ambient air.

The upper-bound incremental unit risk of $2 \times 10^{-3}/(\mu g/m^3)$ results in a potency index of $2 \times 10^{+2}$, which places beryllium oxide in the third quartile of the 59 suspect carcinogens evaluated by the CAG.

7.5 CONCLUSIONS

Using EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) to classify the weight of evidence for carcinogenicity in experimental animals, there is sufficient evidence to conclude that beryllium and beryllium compounds are carcinogenic in animals. This evidence is based upon the induction of osteosarcomas and chondrosarcomas by intravenous and intramedullary injection in rabbits and upon the induction of lung tumors in rats and monkeys by inhalation and intratracheal instillation. Although results were equivocal or negative for ingestion, it is believed that if an agent is carcinogenic by one route it is potentially carcinogenic by any route. The lack of a definitive response via the ingestion route is considered most likely due to low absorption efficiency. Due to limitations in methodology, the epidemiological evidence is considered to be "inadequate", even though significant increases in lung cancer were seen in some epidemiology studies of occupationally exposed persons.

A potency of $2.4 \times 10^{-3}/(\mu g/m^3)$ was derived from the occupational studies involving human exposure to beryllium compounds (thought to be mostly beryllium oxide) commonly present in the workplace.

The carcinogenic potency of inhaled beryllium derived from animal studies varies with the form of beryllium. Potency values for beryllium sulfate ranged from 4.3 to $3.7 \times 10^{-1}/(\mu g/m^3)$ with the most reliable estimate being 8.1×10^{-1}, while those derived from studies using beryllium fluoride or phosphate equalled 1.4×10^{-1} and $3.0 \times 10^{-2}/(\mu g/m^3)$, respectively. The geometric mean of potency values derived from eight studies utilizing beryllium oxide was $2.1 \times 10^{-3}/(\mu g/m^3)$. Since beryllium oxide is considered to be the major form of human exposure, this latter value provides support for the occupationally derived potency of similar magnitude, even though individual weaknesses in each of the animal studies argue against the recommendation of an animal-only based carcinogenic potency.

Recognizing that the carcinogenic potency of inhaled beryllium varies according to the form of beryllium present, an upper-bound incremental lifetime cancer risk for continuous inhalation exposure at 1 μg Be/m^3, rounded to one significant figure, is estimated to be 2×10^{-3} for general ambient conditions. This presumes that beryllium is present in ambient air primarily in the oxide form. The upper bound means that the actual unit risk is not likely to be higher, but could be lower than 2×10^{-3}. In addition, there is an added uncertainty regarding this value in the sense that it may over- or underestimate an upper bound due to assumptions made about dosimetry in the animal and human risk modelling. This value places beryllium oxide in the the third quartile of 59 suspect carcinogens evaluated by the CAG. It should be cautioned, however, that if compounds such as beryllium fluoride, phosphate, and sulfate are known to be present in other than a small percentage of total beryllium in the ambient air, this potency estimate (2×10^{-3}) will likely underestimate the potential carcinogenic risk. Conversely, since beryllium has not been shown definitively to induce neoplasms via oral ingestion in any studies to date, this potency estimate is likely to overestimate risk by this route.

The question of beryllium potency by ingestion is highly uncertain and debatable due to the equivocal or negative results from ingestion studies. From a weight-of-evidence point of view, however, the potential for human carcinogenicity by this route cannot be dismissed. The Ambient Water Quality Criteria Document for Beryllium (U.S. EPA, 1980) provided an upper-limit potency estimate based upon the negative oral study of Schroeder and Mitchener (1975a). This 1980 estimate was even higher than the inhalation potency estimate presented in this assessment, thus, casting much doubt on its reasonableness. The lack of clear-cut tumor induction, coupled with the demonstrated very low beryllium absorption in the intestinal tract, suggests that the oral potency could not be higher than the inhalation estimate and is just as likely to be insignificant (i.e., close to zero).

8. REFERENCES

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APPENDIX

ANALYSIS OF INCIDENCE DATA WITH TIME-DEPENDENT DOSE PATTERN

Table A-1 presents time-to-death data with or without lung tumors. These data are reconstructed from Figure 1 in Reeves and Deitch (1969), in which study animals were exposed to beryllium by inhalation at a concentration of 35 $\mu g/m^3$, 35 hours/week, for specific durations during the 24-month observation period.

The computer program ADOLL1-83, developed by Crump and Howe (1984), has been used to fit these data. Models with one to seven stages, and with one of the stages affected by the dose, have been calculated. The model with the maximum likelihood has been selected as the best-fitting model. The identified best-fitting model has six stages, with the fifth stage dose-affected. Using this model, the maximum likelihood estimate of the slope (linear component), under the assumption of constant exposure, is $0.81/\mu g/m^3$. The 95 percent upper-confidence limit for the slope is $1.05/\mu g/m^3$.

TABLE A-1. TIME-TO-DEATH-DATA[a]

Exposure period[b]	Time-to-death
1. Control	19^-, $20^-(2)$, $21^-(6)$, $22^-(8)$, $24^-(8)$
2. 14th - 19th month	$14^-_+(2)$, 15^-, $20^-(4)$, 20^+, $21^-(5)$, 21^+, $22^-(5)$, $24^-(3)$, 24^+
3. 11th - 16th month	$20^-(2)$, $21^-(5)$, 21^+, 22^-, $22^+(3)$, $24^+(9)$
4. 8th - 13th month	13^-_+, 14^-, $20^+(2)$, $21^-(5)$, 21^+, $22^+(6)$, $23^-(2)$, $24^-(4)$, $24^+(3)$
5. 5th -10th month	13^-, $19^-(3)$, $20^+(3)$, $21^-(2)$, $21^+(4)$, $22^-(4)$, 23^-, $24^+(3)$
6. 2nd - 8th month	16^-_+, 17^-, 18^-, $19^-(4)$, $20^-(2)$, 20^+, $21^-(3)$, $21^+(3)$, 22^-, $22^+(6)$, 24
7. 8th - 19th month	$15^-_-(2)$, 17^-_+, 19^-, $20^-(3)$, $21^-(3)$, $21^-(5)$, $21^-(3)$, $22^+(2)$, $24^-(2)$, $24^+(4)$
8. 2nd - 13th month	14^-, 18^-, $19^-(4)$, $20^+(3)$, $21^-(6)$, $22^+(4)$, $24^+(2)$
9. 2nd - 19th	16^-, $18^-(4)$, $19^-(2)$, $20^-(5)$, $20^+(3)$, $21^+(3)$, 21^-, 22^+

[a] $t^+(n)$ and $t^-(n)$ indicate, respectively, the time-to-death with and without lung tumor; n is the number of replications.

[b] All animals were exposed to beryllium at a concentration of 35 $\mu g/m^3$, 35 hours/week.

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