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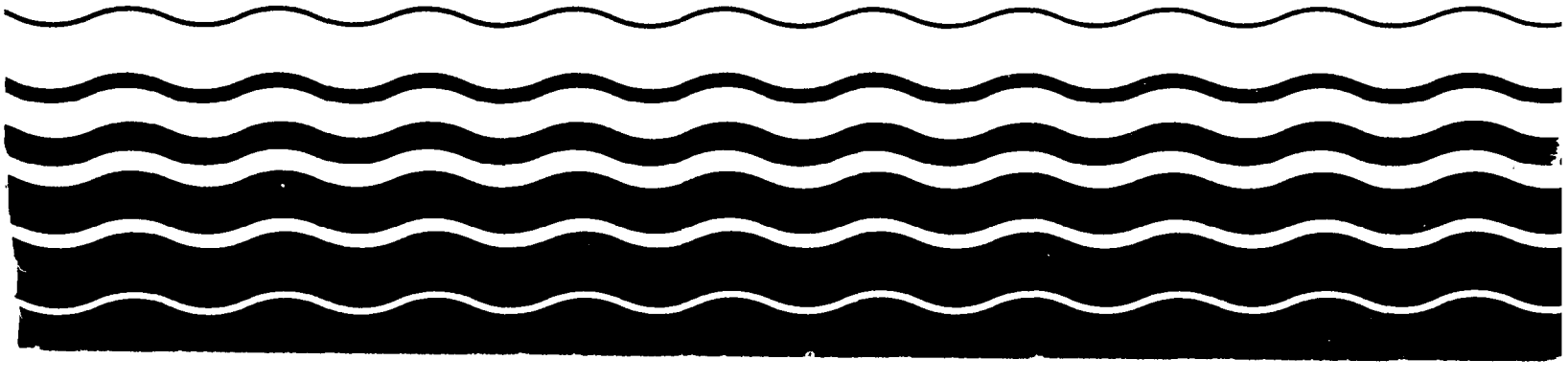
Ambient Water Quality Criteria for Beryllium



AMBIENT WATER QUALITY CRITERIA FOR

BERYLLIUM

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
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BERYLLIUM

CRITERIA

Aquatic Life

The available data for beryllium indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 130 and 5.3 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested. Hardness has a substantial effect on acute toxicity.

The limited saltwater data base available for beryllium does not permit any statement concerning acute or chronic toxicity.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of beryllium through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 37 ng/l, 3.7 ng/l, and 0.37 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 641 ng/l, 64.1 ng/l, and 6.41 ng/l, respectively.

INTRODUCTION

Beryllium, atomic weight 9.01, is a dark gray metal of the alkaline earth family. It is less dense than aluminum and is used in the production of light alloys, copper, and brass (Lange, 1956). Its physical properties include a melting point of 1,287°C and a boiling point of 2,500°C (Windholz, 1976). World production was reported as approximately 250 tons annually, but much more reaches the environment as emissions from coal burning operations (Tepper, 1972). Most common beryllium compounds are readily soluble in water. The hydroxide is soluble only to the extent of 2 mg/l (Lange, 1956). Beryllium forms chemical compounds in which its valence is +2. At acidic pH it behaves as a cation but forms anionic complexes at pH greater than 8 (Krejci and Scheel, 1966). The major source of beryllium in the environment is the combustion of fossil fuels (Tepper, 1972). Beryllium enters the waterways through weathering of rocks and soils, through atmospheric fallout and through discharges from industrial and municipal operations.

Analyses of surface, ground, and rain waters have shown that, in general, beryllium concentrations are well below 1 µg/l. Meehan and Smythe (1967) reported that the maximum beryllium concentration in 20 rain water samples and 56 river water samples (from 5 different Australian rivers) was 0.18 µg/l. In a study of beryllium in ground water, drinking water, and surface water, Reichert (1973) found that even in the heavily polluted Rhine and Main Rivers (Germany), the concentration was below 0.02 µg/l. Hem (1970) estimates that the average concentration of beryllium in fresh surface waters is less than 1 µg/l.

Beryllium is concentrated in silicate minerals relative to sulfides. In common crystalline rocks, the element is enriched in the feldspar minerals relative to ferromagnesium minerals and apparently replaces the silicon ion;

85-98 percent of the total crustal beryllium may be bound in the feldspar structures (Beus, 1966). Beryllium is thought to become concentrated in the later stages of magmatic differentiation. The greatest known concentrations of beryllium are found in certain pegmatite bodies, where crystals of beryl account for a few percent of the total pegmatite volume, and may be found in several of the strata of zoned-dykes. The element is sometimes concentrated in hydrothermal veins, and some granitic rocks contain sufficient amounts to permit the crystallization of small amounts of beryl. During the weathering of crystalline rocks and during sedimentation processes, beryllium appears to follow the course of alumium, and it becomes enriched in some bauxite deposits, clays, and deep-sea sediments.

Beryllium has a complicated coordination chemistry and can form complexes, oxycarboxylates, and chelates with a variety of materials (Bertin and Thomas, 1971). In aqueous solution, beryllium does not exist as actual Be^{+2} ions, but as hydrated complexes (Cotton and Wilkinson, 1972). Complexing of beryllium may result in soluble beryllium concentrations in excess of those predicted on the basis of conventional thermodynamic considerations.

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Aquatic Life Toxicology*

INTRODUCTION

The available data base for the effects of beryllium on freshwater organisms is limited to seven species of fishes, two species of salamanders, one invertebrate species, and one green alga. Chronic test data are not available for any species of fish. A chronic test has been conducted with the invertebrate Daphnia magna. The data on a green alga indicate that it is a resistant species. Beryllium does not appear to bioconcentrate in fish to a great extent and has a short half-life in fish tissue.

Hardness and associated alkalinity have been shown to influence the toxicity of metals to freshwater organisms. The data indicate that the acute toxicity of beryllium to freshwater fishes is related to hardness, with beryllium being more toxic in soft water.

All test results are expressed in terms of the metal.

EFFECTS

Acute Toxicity

Acute toxicity data for one freshwater invertebrate species, Daphnia magna, are available (Table 1). The 48-hour values are 2,500 and 7,900 µg/l. Since these tests were conducted at only slightly different hardnesses, no relationship of toxicity and hardness could be determined. Compared to toxicity data for fish

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

species, at approximately the same hardness, Daphnia magna appears to be comparably sensitive to these fish.

Tarzwell and Henderson (1960) exposed fathead minnows and bluegills to beryllium in static toxicity tests using both soft and hard dilution waters (Table 1). They found that beryllium was more toxic in soft water than in hard water. The 96-hour LC_{50} values for the fathead minnow ranged from 150 µg/l in soft water to 20,000 µg/l in hard water. For the bluegill the 96-hour LC_{50} values were 1,300 µg/l in soft water and 12,000 µg/l in hard water. The 96-hour LC_{50} values for the fathead minnow and bluegill tested in soft water represent an order of magnitude difference in the sensitivity of these two species.

Slonim and Slonim (1973) also reported on the effect of water hardness on the toxicity of beryllium to fish (Table 1). They exposed guppies in static tests to four dilution waters with different hardnesses and developed an exponential equation to describe the relationship of toxicity to hardness. Toxicity increased with decreasing hardness.

Cardwell, et al. (1976) reported 96-hour LC_{50} values for beryllium for three species of fish using flow-through procedures and measured concentrations (Table 1). In a dilution water with a hardness of about 140 mg/l as $CaCO_3$, the 96-hour LC_{50} values ranged from 3,250 µg/l for juvenile fathead minnows to 4,800 µg/l for juvenile goldfish. Three tests with flagfish fry gave 96-hour LC_{50} values that ranged from 3,530 to 4,440 µg/l.

The fathead minnow was the only species tested using both static and flow-through conditions. However, the dilution waters

were not similar; thus it is not possible to evaluate the effect of test method on these results.

Chronic Toxicity

No chronic tests have been conducted with freshwater fishes. However, the chronic effects of beryllium on Daphnia magna have been studied (Tables 2 and 5). In the only typical chronic test available, effects on reproduction were observed at 7.3 µg/l and no effects were observed at 3.8 µg/l. The 48-hour EC_{50} determined with the same species and same water is 2,500 µg/l (Kimball, manuscript) which indicates a large difference between acute and chronic toxicity.

A multi-generation test by Lebedeva (1960) with Daphnia magna resulted in shortened lifespan and reduced reproduction (in the second generation) at an unmeasured beryllium concentration of 50 µg/l (Table 5). The result is not used in the derivation of the chronic value for that species since, according to the Guidelines, chronic test results must be based on measured concentrations.

Plant Effects

There was one study describing the effects of beryllium on freshwater plants (Karlander and Krauss, 1972). Growth of the green alga, Chlorella vannieli, was inhibited at a concentration of 100,000 µg/l (Table 3).

Residues

A study of bioconcentration of beryllium by the bluegill exposed for 28 days resulted in a bioconcentration factor of 19 (Table 4) with a half-life of one day in the whole body (U.S. EPA, 1978). No maximum permissible tissue concentration is available;

therefore, a Residue Limited Toxicant Concentration cannot be calculated.

Miscellaneous

Cardwell, et al. (1976) extended the exposure time past 96 hours for the acute tests with fathead minnows and goldfish (Table 5). For both species there was continued mortality after 96 hours of exposure in the flow-through test. For the fathead minnow, the LC_{50} value of 3,250 µg/l at 96 hours decreased to 2,200 µg/l at 336 hours. For the goldfish the LC_{50} value of 4,800 µg/l at 96 hours decreased to 3,300 µg/l at 240 hours. The 96-hour LC_{50} values for the brook trout and channel catfish were greater than 5,090 µg/l.

Slonim and Ray (1975) conducted acute tests using two species of salamanders. The two species were similar in sensitivity to the lethal effects of beryllium, and beryllium was more toxic in soft water. Sensitivity of the salamanders was similar to that for the guppy in hard water, but salamanders were less sensitive in soft water than was the guppy.

Jackim, et al. (1970) observed reduced alkaline phosphatase activity in the saltwater mummichog at concentrations of beryllium as low as 9 µg/l. Gross embryonic deleterious effects were observed in the sea urchin at a concentration of 9,010 µg/l (Evola-Maltese, 1957). No other data on the effects of beryllium on saltwater species are available.

Summary

Acute toxicity data are available for beryllium and the fathead minnow, guppy, and bluegill at different levels of hardness

(about 20 and 400 mg/l) that indicate that over this range of hardness acute toxicity decreases about two orders of magnitude with increasing hardness. No relationship is available for hardness and invertebrate species. Of the various fish species tested at similar levels of hardness, there does not appear to be much difference in sensitivity. There is only one chronic test with a freshwater organism and nothing can be said concerning the relationship of hardness and chronic toxicity. The 48-hour EC_{50} and chronic values for Daphnia magna in the same test water were 2,500 and 5.3 µg/l which indicates a very large difference between acute and chronic toxicity. The bioconcentration factor for the bluegill was 19 and the half-life in tissues was short.

The only data available for beryllium and saltwater species result from physiological studies with the mummichog and embryonic development of the sea urchin.

CRITERIA

The available data for beryllium indicate that acute and chronic toxicity to freshwater aquatic life occur at concentrations as low as 130 and 5.3 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested. Hardness has a substantial effect on acute toxicity.

The limited saltwater data base available for beryllium does not permit any statement concerning acute or chronic toxicity.

Table 1. Acute values for beryllium

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50 (µg/l)**	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	S, U	Beryllium chloride	180	7,900	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S, M	Beryllium sulfate	220	2,500	Kimball, Manuscript
Goldfish, *Carassius auratus*	FT, M	Beryllium sulfate	147	4,800	Cardwell, *et al.* 1976
Fathead minnow, *Pimephales promelas*	FT, M	Beryllium sulfate	140	3,250	Cardwell, et al. 1976
Fathead minnow, *Pimephales promelas*	S, U	Beryllium sulfate	20	200	Tarzwell & Henderson, 1960
Fathead minnow, *Pimephales promelas*	S, U	Beryllium sulfate	20	150	Tarzwell & Henderson, 1960
Fathead minnow, *Pimephales promelas*	S, U	Beryllium sulfate	20	150	Tarzwell & Henderson, 1960
Fathead minnow, *Pimephales promelas*	S, U	Beryllium sulfate	400	11,000	Tarzwell & Henderson, 1960
Fathead minnow, *Pimephales promelas*	S, U	Beryllium sulfate	400	20,000	Tarzwell & Henderson, 1960
Fathead minnow, *Pimephales promelas*	S, U	Beryllium sulfate	400	15,000	Tarzwell & Henderson, 1960
Fathead minnow, *Pimephales promelas*	S, M	Beryllium sulfate	220	18,000	Kimball, Manuscript
Flagfish, *Jordanella floridae*	FT, M	Beryllium sulfate	140	4,440	Cardwell, et al. 1976
Flagfish, *Jordanella floridae*	FT, M	Beryllium sulfate	140	3,530	Cardwell, et al. 1976
Flagfish, *Jordanella floridae*	FT, M	Beryllium sulfate	140	3,530	Cardwell, et al. 1976

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50 (µg/l)**	Reference
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	450	32,000	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	450	28,000	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	450	32,000	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	450	24,000	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	22	160	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	450	19,000	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	23	450	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	23	130	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	23	200	Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	400	20,000	Slonim & Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	275	13,700	Slonim & Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	150	6,100	Slonim & Slonim, 1973
Guppy, *Poecilia reticulata*	S, U	Beryllium sulfate	22	160	Slonim & Slonim, 1973
Bluegill, *Lepomis macrochirus*	S, U	Beryllium sulfate	400	12,000	Tarzwell & Henderson, 1960

Table 1. (Continued)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	LC50/EC50 (µg/l)**	Reference
Bluegill, *Lepomis macrochirus*	S, U	Beryllium sulfate	20	1,300	Tarzwell & Henderson, 1960

* S = static, FT = flow-through, U = unmeasured, M = measured

**Results are expressed as beryllium, not in terms of the compound.

No Final Acute Equation is calculable since the minimum data base requirements are not met.

Table 2. Chronic values for beryllium (Kimball, Manuscript)

Species	Method*	Chemical	Hardness (mg/l as $CaCO_3$)	Limits (µg/l)**	Chronic Value (µg/l)**
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	LC	Beryllium sulfate	220	3.8-7.3	5.3

* LC = life cycle or partial life cycle

**Results are expressed as beryllium, not in terms of the compound.

Table 3. Plant values for beryllium (Kariander & Krauss, 1972)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Effect	Result (ug/l)*
	FRESHWATER SPECIES			
Green alga, *Chlorella vannieli*	Beryllium chloride	-	Growth inhibited at suboptimum conditions	100,000

* Result is expressed as beryllium, not in terms of the compound.

Table 4. Residues for beryllium (U.S. EPA, 1978)

Species	Tissue	Chemical	Hardness (mg/l as $CaCO_3$)	Bioconcentration factor	Duration (days)
		FRESHWATER SPECIES			
Bluegill, *Lepomis macrochirus*	whole body	Beryllium chloride	180	19	28

Table 5. Other data for beryllium

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result (µg/l)*	Reference
			FRESHWATER SPECIES			
Cladoceran, Daphnia magna	Beryllium chloride	-	119 days	Reproduction and longevity	50	Lebedeva, 1960
Cladoceran, Daphnia magna	Beryllium nitrate	300	24 hrs	LC50	18,000	Bringman & Kuhn, 1977
Cladoceran, Daphnia magna	Beryllium chloride	175	21 days	Survival	<620	U.S. EPA, 1978
Brook trout, Salvelinus fontinalis	Beryllium sulfate	140	96 hrs	LC50	>5,090	Cardwell, et al. 1976
Goldfish, Carassius auratus	Beryllium sulfate	147	240 hrs	LC50	3,300	Cardwell, et al. 1976
Goldfish, Carassius auratus	Beryllium nitrate	50	3 days	No hatching of eggs	>200	Hildebrand & Cushman, 1978
Fathead minnow, Pimephales promelas	Beryllium sulfate	140	336 hrs	LC50	2,200	Cardwell, et al. 1976
Channel catfish, Ictalurus punctatus	Beryllium sulfate	140	96 hrs	LC50	>5,090	Cardwell, et al. 1976
Salamander, Ambystoma maculatum	Beryllium sulfate	22	96 hrs	LC50	3,150	Slonim & Ray, 1975
Salamander, Ambystoma maculatum	Beryllium sulfate	22	96 hrs	LC50	8,020	Slonim & Ray, 1975
Salamander, Ambystoma maculatum	Beryllium sulfate	22	96 hrs	LC50	8,320	Slonim & Ray, 1975
Salamander, Ambystoma maculatum	Beryllium sulfate	400	96 hrs	LC50	31,500	Slonim & Ray, 1975
Salamander, Ambystoma maculatum	Beryllium sulfate	400	96 hrs	LC50	18,200	Slonim & Ray, 1975
Salamander, Ambystoma maculatum	Beryllium sulfate	400	96 hrs	LC50	18,200	Slonim & Ray, 1975

Table 5. (Continued)

Species	Chemical	Hardness (mg/l as $CaCO_3$)	Duration	Effect	Result (µg/l)*	Reference
Salamander, *Ambystoma opacum*	Beryllium sulfate	22	96 hrs	LC50	3,150	Slonim & Ray, 1975
Salamander, *Ambystoma opacum*	Beryllium sulfate	400	96 hrs	LC50	31,500	Slonim & Ray, 1975
		SALTWATER SPECIES				
Sea urchin, *Paracentrotus lividus*	-	-	1 hr	Abnormal embryonic development including delay, dwarfism, no ciliary development, incomplete gastrulation	9,010	Evola-Maltese, 1957
Mummichog, *Fundulus heteroclitus*	-	-	96 hrs	Alkaline phosphatase activity inhibition: 36%	9	Jacklm, et al. 1970
Mummichog, *Fundulus heteroclitus*	-	-	96 hrs	Alkaline phosphatase activity inhibition: 62%	90	Jacklm, et al. 1970
Mummichog, *Fundulus heteroclitus*	-	-	96 hrs	Alkaline phosphatase activity inhibition: 70%	900	Jacklm, et al. 1970

* Results are expressed as beryllium, not as the compound.

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

Kopp and Kroner (1967) reported the results of trace metal analyses of 1,577 drinking water samples obtained throughout the United States. Beryllium was detected in 5.4 percent of the samples. Concentrations ranged from 0.01 to 1.22 µg/l, with a mean value of 0.19 µg/l.

Ingestion from Food

Petzow and Zorn (1974) found beryllium concentrations (dry weight) of 0.08 mg/kg in polished rice, 0.12 mg/kg in toasted bread, 0.17 mg/kg in potatoes, 0.24 mg/kg in tomatoes, and 0.33 mg/kg in head lettuce.

Meehan and Smythe (1967) determined beryllium levels in a variety of foodstuffs. Beryllium levels (ppm in ash) for different foodstuffs were: beans, 0.01; cabbage, 0.03; hen eggs, 0.01 (yolk); milk, 0.02; mushrooms 0.12; nuts, 0.01-0.47; tomatoes, 0.02; and baker's yeast, 0.02.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of beryllium which might be ingested from the consumption of fish and shellfish. An analysis (U.S. EPA, 1980) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980).

A measured BCF of 19 was obtained for beryllium using bluegills (U.S. EPA, 1978). For lack of other information, a value of 19 can be used as the weighted average bioconcentration factor for beryllium and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans.

Inhalation

The detection of beryllium in air is infrequent and usually in trace amounts. According to Tabor and Warren (1958) and the National Air Sampling Network (1968), beryllium was present in 12 percent of 440 samples analyzed from 16 cities. Concentrations ranged from 0.001 to 0.002 $\mu g/m^3$ in urban areas and considerably lower (0.00013 $\mu g/m^3$) in more rural areas. The U.S. EPA (1971) found that samples collected at 100 stations during 1964 to 1965 had a 24-hour average beryllium concentration of less than 0.0005 $\mu g/m^3$. The maximum beryllium value was 0.008 $\mu g/m^3$. At a beryllium extraction plant in Ohio, beryllium concentrations were generally around 2 $\mu g/m^3$ over a 7-year period (Breslin and Harris, 1959).

The burning of coal for space heating and electric power generation appears to constitute the greatest threat to the environment from beryllium. Tepper (1972a) calculated that if 500 million tons of Illinois and Appalachian coal with a beryllium content of 2.5 ppm were burned annually, the potential release of beryllium from coal in this country would approximate 1,260 tons or five times the world production. This could result in considerable contamination of soil, water, and plants as well as air.

Dermal

Exposure to soluble beryllium compounds can cause contact dermatitis. It is not readily absorbed, however, since ionic beryllium becomes bound to epidermal constituents, mainly alkaline phosphatase and nucleic acids (Belman, 1969). In general, the incidence of beryllium dermatitis is primarily confined to occupational exposure.

PHARMACOKINETICS

Absorption

Studies by Hyslop, et al. (1943) showed the amount of beryllium retained by animals was small (0.006 percent) compared with that ingested. A reason for the limited absorption was due to precipitation of soluble salts in the alimentary tract while the insoluble compounds were not appreciably dissolved in serum or gastric juice. Low absorption was also described by Reeves (1965) who reported that 60 to 90 percent of the beryllium ingested by rats was recovered in the feces.

Distribution

Although the lungs are the primary point of entry for beryllium, they are not the principal site of deposition for soluble beryllium compounds. Citrated beryllium was almost completely mobilized from the lungs within 4 days following exposure (Van Cleave and Kaylor, 1955). Insoluble beryllium compounds such as beryllium ores, however, tend to remain in the lung indefinitely (Wagner, et al. 1969). Only 12 to 21 percent of high temperature-fired BeO aerosols were cleared from the lungs of rats in 63 days (Sanders, et al. 1974). Increased levels of beryllium have been reported in

the lymph nodes and lungs of humans more than 20 years after termination of occupational exposure (Sprince, et al. 1976).

Van Cleave and Kaylor (1955) studied the distribution of beryllium in rats. Following intravenous administration, beryllium was carried to all tissues and could be detected in most organs. During the first several weeks after injection, smaller doses (50 µg Be/kg) tended to accumulate in the skeleton and larger doses (500 µg Be/kg) in the liver. After about 100 days beryllium was gradually mobilized from the liver of rats and transferred to the skeleton.

Studies with intravenously or intramuscularly injected ^{7}Be, a strong gamma emitter, indicated that both ionic and citrate-complexed beryllium were definitely bone seekers (Crowley, et al. 1949; Klemperer, et al. 1952). Bone radiographs of the distal end of the femur revealed deposits of beryllium in osteoid tissue adjacent to the epiphyseal plate (Kaylor and Van Cleave, 1953). Studies with BeO, injected intratracheally in rats, indicated that the greatest concentrations were deposited in the bone with the next most common sites being spleen, liver, kidney, and muscle (Spencer, et al. 1972).

Beryllium was shown to have a special affinity for nuclei and nucleoli in lung and liver cells (Witschi and Aldridge, 1968; Robinson, et al. 1968). According to Reeves (1977) the concensus of studies indicated that the bulk of circulating beryllium is in the form of a colloidal phosphate, probably adsorbed on plasma α-globulin, with minor portions carried as citrate or hydroxide.

Metabolism

Early work concerning the metabolism of beryllium centered on its effects in producing rickets in animals. Several enzyme systems such as alkaline phosphatase (Klemperer, et al. 1949; Grier, et al. 1949), phosphoglucomutase (Hashimoto, et al. 1967), and sodium and potassium activated ATPase (Toda, 1968) have been shown to be inhibited by micromolar beryllium concentrations. The rickets-producing effects of beryllium were thought to be due partly to the alkaline phosphatase inactivating action of beryllium, causing, in particular, an inhibition of endochondreal calcification of cartilage (Vorwald, et al. 1966).

Earlier studies suggesting that immunologic mechanisms are implicated in the toxicology of beryllium in chronic beryllium disease (Sterner and Eisenbud, 1951) are supported by more recent evidence. For example, Alekseeva (1965) produced hypersensitivity in guinea pigs by intradermal beryllium injections. Belman (1969) developed hypersensitivity in guinea pigs by the application of beryllium fluoride to the skin. Vasil eva (1969) induced skin hypersensitivity to beryllium chloride in rats.

In humans, Curtis (1951) showed that application of a cutaneous patch test containing nonirritating concentrations of soluble beryllium could elicit a positive reaction on subsequent testing of the same material. Resnick, et al. (1970) measured immunoglobulin fractions and showed increased IgG in most patients who previously had acute beryllium reactions or a history of dermatitis.

Kharlamova and Potapova (1968) have shown that beryllium can be concentrated in the nuclei, while others (Marcotte and Witschi,

1972; Witschi, 1968, 1970) reported that beryllium interferes with DNA metabolism in the liver.

Beryllium has also been reported to induce chromosomal and mitotic abnormalities in cell cultures (Vegni-Talluri and Guiggiani, 1967). Exposure of calf thymus DNA to a 0.056N concentration of beryllium caused molecular aggregation and flocculation, pointing to an irreversible and deleterious effect of beryllium on nucleic acid (Needham, 1974). More recently, it has been shown that the beryllium ion (Be^{+2}) increases the misincorporation of nucleotides during polymerization by DNA polymerase (Luke, et al. 1975; Loeb and Sirover, 1977). A possible mechanism was considered to be associated with an inhibition of 3',5'-exonuclease activity. This exonuclease which is an integral part of the polymerase is thought to perform an editing function to remove noncomplementary (incorrect) nucleotides during polymerization (Brutlag and Kornberg, 1972). Sirover and Loeb (1976) however, using polymerase from avian myeloblastosis virus, showed that Be^{+2} altered the accuracy of DNA synthesis. This polymerase lacks 3' - 5' proof reading exonuclease activity and thus may not excise a mismatched nucleotide. These results show that beryllium can influence the ac curacy of DNA replication in vitro and suggest that it may have the same effect in vivo.

Excretion

Small doses of intravenously administered ^{7}Be in rats tended to be either excreted mostly in the urine or deposited in the kidney or bone (Scott, et al. 1950). Van Cleave and Kaylor (1955) reported that citrated beryllium sulfate given intratracheally was

almost completely mobilized from the lungs after 4 days. Seventy-nine percent was eliminated, primarily in the urine, with the remainder deposited in the bones. At tracer levels, the non-citrated beryllium sulfate remained in the lungs somewhat longer but was also mobilized at a rapid rate after 16 days. Ultimately, the amounts deposited in the skeleton and excreted did not differ in comparison with the citrated form. Zorn, et al. (1977) reported that the concentration of beryllium from aerosol inhalation was high in the alveoli and nasopharyngeal region, but low in the terminal bronchioles. Evidently ciliary action clears the small airways quite rapidly. In general, a fraction of a dose of beryllium taken in either through the lung or digestive tract is excreted fairly quickly, with most of the remainder ultimately stored in the long bones. Once deposited it is removed very slowly. The half-life for ^{7}Be was reported to equal 1,210, 890, 1,770, and 1,270 days in mice, rats, monkeys, and dogs, respectively (Furchner, et al. 1973).

Underwood (1951) showed tubular excretion mechanism. Attempts to rid the body of deposited beryllium with chelating agents have been successful in animal experiments (Schubert and White, 1950; Schubert and Rosenthal, 1959) but not in clinical experience (Dequinalt and Haguenoer, 1973). In studies conducted with cows an insignificant amount of injected radioactive beryllium was recovered in the milk (Mullen, et al. 1972).

EFFECTS

Acute, Subacute, and Chronic Toxicity

Intravenous beryllium is highly toxic to animals in small doses. The LD_{50} for 200 g male rats injected intravenously with soluble beryllium salts was reported to be 0.44 mg Be/kg (Witschi and Aldridge, 1967), and 0.51 mg Be/kg for female rats injected with $BeSO_4$ (Vacher and Stoner, 1968). Death was attributed to biochemical disturbances caused by progressive destruction of liver tissue (Aldridge, et al. 1949). The toxicity of beryllium was greatly decreased when ingested. The oral LD_{50} of $BeCl_2$ in rats was reported to be 9.7 mg/kg as Be (U.S. EPA, 1977). Rats survived for several weeks when fed diets containing up to 2 percent beryllium carbonate (Guyatt, et al. 1933) and at least 50 days when fed 0.24 gm/day beryllium carbonate (0.03 gm/day Be) (Businco, 1940). There have been no reported cases of oral toxicity in humans.

Inhaled BeO aerosol at a concentration of 194 $\mu g/m^3$ Be was acutely toxic to rats while 42 $\mu g/m^3$ produced pathologic changes within 3 months (Vorwald, et al. 1966). Concentrations acutely toxic in humans are less well defined. For example, concentrations of 30 mg/m^3 beryllium oxide in the air produced no acute cases in one short-term exposure of humans, while in another 4 mg/m^3 produced both a high incidence of acute disease and fatalities (National Academy of Science (NAS, 1958). The differences were probably due to the temperature at which beryllium oxide was produced. If calcined at 500°C a relatively soluble product with large surface area is formed while calcining at 1,600°C results in an insoluble form. Beryllium oxide calcined at 500°C caused pulmonary

damage in rabbits at dose levels of 2 mg/kg body weight when given intratracheally while beryllium oxide calcined at 1,600°C produced no reaction greater than expected for an inert dust (Spencer, et al. 1968).

Acute disease has occured in humans following inhalation of highly soluble beryllium salts at concentrations lower than 100 $\mu g/m^3$ (Hall, et al. 1959). Unfortunately, the time periods for the above exposures were not specified. A report by the National Academy of Sciences (NAS, 1958) indicated that acute beryllium disease did not occur in humans at ambient air concentrations of 25 $\mu g/m^3$ or less. In the same report no lung damage was reported in experimental animals exposed to 40 $\mu g/m^3$. Hardy (1955) reported that acute beryllium poisoning is related to the intensity of exposure with removal leading to a disappearance of symptoms.

Tepper, et al. (1961) arbitrarily defined acute beryllium disease to include those beryllium induced disease patterns with less than 1 year natural duration. Diseases fitting this definition will be included in this category. The symptoms of acute toxicity have been described in detail by Tepper, et al. (1961), De Nardi, et al. (1953) and Hardy and Stoeckle (1959).

Acute skin effects include contact dermatitis characterized by reddened, elevated, or fluid-accumulated lesions on exposed surfaces (Van Ordstrand, et al. 1945). This disease has not been seen in workers handling insoluble forms of beryllium such as beryllium hydroxide, pure beryllium, and vacuum cast beryllium (Comm. Occ. Dis. Chest, 1965), but may occur following contact with soluble beryllium salts (McCord, 1951).

Beryllium ulcers result from implantation of soluble or insoluble beryllium materials in cutaneous areas previously injured as a result of abrasions, cuts, etc. Removal of the foreign material is necessary for healing to take place.

Ocular effects include inflammation of the conjunctiva from splash burns or in association with contact dermatitis (Van Ordstrand, et al. 1945). Corneal burns may occur resembling those produced by acids and alkalis.

Respiratory effects include rhinitis, pharyngitis, tracheobronchitis, and acute pneumonitis. The following response to a relatively soluble compound, beryllium oxide calcined at 500°C, was described by Tepper (1972b) as a widely dispersed focal pneumonitis of granulomatous nature. The lesions had a dense central core of proliferating histiocytes clustered around aggregations of beryllium oxide particles often invested by epitheliod cells and one or two layers of fibroblasts. A few lymphocytes, plasma cells, or occasional multinucleated giant cells participated in the reaction. With time the lesions became less cellular, more collagenous, and finally hyalinized. The degree of effects can vary widely, with recovery times ranging from 1 to 6 weeks for mild cases and up to 6 months after acute pneumonia. Tepper, et al. (1961) reported 18 cases of acute beryllium pneumonitis fatalities following development of pulmonary edema.

Beryllium rhinitis and pharyngitis involve inflammation of the nasal mucosa and pharynx, frequently accompanied by mild nosebleeds. Fluid and blood accumulate in the mucous membranes and

ulcerations occur. This condition is difficult to diagnose since it closely resembles that seen with the common cold.

Acute tracheobronchitis also results in nonspecific symptoms. The effects are characterized by nonproductive spasmodic cough, substernal discomfort, burning, tightness of the chest, and moderate difficulty with breathing upon exertion. Recovery is usually complete within 1 to 4 weeks (De Nardi, et al. 1953).

Most of the acute respiratory symptoms and pathologic changes cannot be differentiated from the inflammatory reaction to other types of irritants. Positive identification may require a knowledge of past exposure and possible tissue analysis. The onset of acute respiratory symptoms can occur within a few hours after brief exposure to a high concentration of beryllium. More commonly, however, the illness is insidious in nature, developing over 1 to 3 weeks (Tepper, et al. 1961).

Acute pneumonitis has been produced by inhalation of virtually all beryllium compounds. These include beryllium metal, oxide, sulfate, fluoride, hydroxide, and chloride (Durocher, 1969). The acute changes result from the inhalation and deposition of beryllium compounds either as mists of the soluble salts or as fumes and dust of the relatively insoluble compounds, primarily the oxides.

Chronic beryllium disease differs from the acute form in several ways: (1) its occurrence is often separated from the time of exposure by periods ranging up to several years; (2) it has a prolonged duration with little evidence of a lasting cure; (3) it is commonly progressive in spite of cessation of exposure; and (4) it is a systemic disease (Tepper, et al. 1961). A study of chronic

beryllium cases by Hardy and Stoeckle (1959) showed the latent period between last exposure and the onset of symptoms to vary, with 41 percent of the symptoms being manifested in the first month and 29 percent in 1 to 5 years. The most common clinical symptoms include granulomatous inflammation of the lungs, with accompanying cough, chest pain, and general weakness (Hardy and Stoeckle, 1959). Systemic effects include right heart enlargement with accompanying cardiac failure, enlargement of the liver and spleen, cyanosis, digital clubbing, and the appearance of kidney stones (Hall, et al. 1959). A systemic effect reported in dogs, rabbits, and rats, but not in man, is the development of a macrocytic anemia (Stokinger, et al. 1951).

One of the earliest observed effects of beryllium toxicity was the development of a rachitic bone change after addition of soluble beryllium salts to the diet of poultry and livestock (Branion, et al. 1931; Guyatt, et al. 1933; Kay and Guyatt, 1933; Kay and Skill, 1934). Osteosclerotic changes were also noted in rabbits when beryllium was given intravenously (Gardner and Heslington, 1946).

Beryllium rickets is a disease that has not been reported in man. While there is no reason to believe it cannot be induced in humans, the concentrations in the food or water required to produce rickets in animals (0.125 percent beryllium carbonate for a mild case) make this an unlikely occurrence (Guyatt, et al. 1933).

The predominant pulmonary pathology consists of an interstitial diffuse inflammatory process which is distinctively chronic in nature and without the edemetous and exudative changes seen in acute disease. The scattered focal lesions are composed mainly of

large monocytes and are irregular in shape due to extensions into contiguous alveolar walls which are variously thickened with inflammatory cells (Vorwald, 1966). Granulomatous lesions are also seen in skin, liver, kidney, lymph nodes, and skeletal muscles (Dudley, 1959).

Chronic beryllium disease can be produced in experimental animals with low concentrations of soluble beryllium compounds. Rats exposed for up to 6 months to an aerosol of 35 $\mu g/m^3$ $BeSO_4$ developed typical chronic pneumonitis along with granulomatous lesions and some neoplasms (Schepers, et al. 1957). Exposure of monkeys to 35 $\mu g/m^3$ $BeSO_4$ or to intratracheal instillations of a 5 percent suspension of beryllium oxide resulted in chronic pneumonitis in all animals (Vorwald, et al. 1966). Exposure of rats for 560 days to aerosols containing 2.8 $\mu g/m^3$ beryllium did not result in significant effects while 21 $\mu g/m^3$ produced changes only in long surviving rats (Vorwald, et al. 1966).

Concentrations of beryllium resulting in chronic disease in humans are more difficult to determine. Chronic and acute beryllium poisoning were common prior to setting of air standards in 1949, but lack of consistent monitoring prior to this time makes it difficult to relate exposure levels to disease. Ambient air concentrations were evidently quite high. For example, a 1946 survey of a beryllium plant by Laskin, et al. (1946) indicated beryllium dust concentrations of 110 to 533 $\mu g/m^3$ during beryllium furnace coke removal operation. Zielinski (1961) reported levels of 11,330 to 43,300 $\mu g/m^3$ in a beryllium alloy plant.

Since the early 1950's, evidence has been presented indicating that the 2 $\mu g/m^3$ standard was generally being met. For example, at one beryllium extraction plant, ambient air concentrations measured over a 7 year period were at or below 2 $\mu g/m^3$ (Breslin and Harris, 1959). Williams (1961) presented results of surveys of beryllium exposures in 15 plants of various types which indicated that exposures were effectively controlled below the current standard in the preponderance of cases. Nevertheless, 76 new cases of beryllium disease have been added to the Beryllium Case Registry (BRC) from 1966 to 1974 of which at least 36 involved exposure since 1949 (Hasan and Kazemi, 1974).

A more recent study indicated that beryllium pollution was not being effectively controlled at all production facilities. Kanarek, et al. (1973) reported that ambient air concentrations at a beryllium extraction and processing plant ranged up to 50 times that of the accepted peak concentration of 25 $\mu g/m^3$. Some of the concentrations are listed here:

Location	Operation	Range of beryllium concentration $\mu g/m^3$
A. Billet Plant	All	0.35-213
	Fluoride area	0.67-213
	Reduction	0.43-22.5
	Hydroxide	2.0-33.2
	Bead handling	1.8-88
B. Fabrication Plant	All	0.31-1,310
	Vacuum drying	1.74-1,310
	Vacuum furnace	3.67-15.31
	Die loading	7.0-24.4
	Power handling	7.85-219
	Material transfer	3.90-1,290
	Machine shop	0.31-6.4

Two hundred fourteen of the 245 full-time employees at this plant were studied in 1971. Thirty-one had chest radiographic abnormalities compatible with interstitial disease and 20 had hypoxemia at rest. A followup was conducted during 1974 (Sprince, et al. 1978). New engineering and safety controls had resulted in a decrease in peak concentrations of beryllium to less than 25 $\mu g/m^3$ in all work areas. In the vacuum drying area the peak concentration had decreased from 1,310 $\mu g/m^3$ to less than 2 $\mu g/m^3$. Improvement was noted in 13 of 20 workers previously identified as hypoxemic. Eighteen of 31 with radiographic abnormalities in 1971 were available for followup. Of these 9 had reverted to normal.

Not all cases of chronic beryllium disease occurred during industrial exposure. Sterner and Eisenbud (1951) reported 13 cases in a population living within 3/4 of a mile from one beryllium plant. Air concentrations of beryllium were reported to range from 0.01 to 0.1 $\mu g/m^3$. By 1960 the Beryllium Case Registry contained 47 well-documented cases of so-called neighborhood disease (Tepper, et al. 1961). Lieben and Williams (1969) reported that all the nonoccupational cases studied by them could be attributed to contact with beryllium through routes other than outdoor air pollution. This included handling of polluted garments or other contact with contaminated objects or people. It is thus uncertain whether concentrations of 0.01 to 0.1 $\mu g/m^3$ beryllium in the air can cause beryllium disease.

Synergism and/or Antagonism

Studies conducted in attempting to discover a therapeutic agent that would neutralize the acute biologic effect of toxic

beryllium compounds were summarized by Vorwald, et al. (1966). The only compound discovered up to this time having a reasonable degree of effectiveness in laboratory animals was aurintricarboxylic acid (ATA). This compound formed a chelate that tended to accumulate in the kidneys and spleen but not in the bones. The use of salicylates in conjunction with ATA was also considered beneficial. ATA was mildly toxic with an intravenous LD_{50} of 440 mg/kg for mice and 450 mg/kg for rats. The use of chelating agents for the alleviation of chronic poisoning, however, was not effective in clinical trials (Reeves, 1977).

Beryllium oxide was reported to potentiate the carcinogenicity of 20-methyl cholanthrene (20-MC) to a much higher degree than did carbon black (Uzawa, 1963). The fluoride ion has a synergistic effect on the acute toxicity of beryllium. Inhaled BeF_2 produced about twice the toxic effect in laboratory animals as $BeSO_4$ at any given concentration (Stokinger, et al. 1950).

Teratogenicity

Information relating to possible teratogenic effects of beryllium is limited. Beryllium is reported to inhibit the embryonic development of the snail, Lymnea stagnalis, resulting in peculiar morphogenic abnormalities (Raven and Spronk, 1953). Thornton (1950) observed inhibition of regeneration of the limbs of the salamander, Amblystoma punctatum, when immersed in 0.05 molar beryllium nitrate solution. A pregnant rat fed 75 mg beryllium carbonate daily delivered three offspring of normal weight and appearance. Treatment, however, was not begun until the 18th day of

pregnancy, well past the critical period for teratogenic effects (Businco, 1940).

Carcinogenicity

Lung cancer and bone cancer, or osteosarcoma, are the two types of malignancies commonly induced in experimental animals by beryllium. Osteosarcoma was first reported by Gardner and Heslington (1946). Their results have since been confirmed numerous times. These studies are listed in Table 1. As can be seen in the table, the great majority of the studies were carried out using rabbits injected intravenously. Dutra, et al. (1951) reported the only case of osteosarcoma from inhalation of a beryllium compound. Most compounds tested appeared to be effective in producing osteosarcoma when injected intravenously, even metallic beryllium.

Studies designed to induce lung cancer are listed in Table 2. As can be seen, inhalation or intratracheal instillation of the beryllium compounds were the primary routes of administration. The lung was not the primary site of cancer induced by intravenous injection but this was due to metastases from the bone. In general, the more soluble compounds are more effective in producing both lung cancer and berylliosis. For example, beryllium oxide produced at a temperature of 500°C was much more effective than that produced at 1,600°C, with the primary difference being solubility (Spencer, et al. 1968).

As reviewed previously, large concentrations of beryllium carbonate were fed to animals in the 1930s to produce a type of osteosclerosis. Although osteosarcoma was not reported, the experiments were generally terminated before the development of cancer would be

TABLE 1

Induction of Osteosarcomas in Experimental Animals by Beryllium

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding*	Time of measurement (mos.)	Reference
Beryllium oxide	6 mg/m^3	Inhalation	5 hrs/day, 5 days/wk.,11 mos.	Rabbit	16	11	Dutra, et al. 1951
	Not reported	Multiple intravenous		Rabbit	25	Not reported	Mash, 1950
	90-660 mg as Be, 13-116 mg/kg body wt. as Be	17-21 intravenous injections		Rabbit	89	9+	Dutra & Largent, 1950
	100-200 mg total injections	1-45 intravenous		Rabbit	0	Not reported	Kawada, 1963
	1,250 mg total	Intravenous injection	25 wkly injections	Rabbit	72	Not reported	Fodor, 1971
	Large animals: 1 gm. total small animals: <1 gm.	Intravenous		Rabbit	6	15	Komitowski, 1969
	100 mg total	Injection into femur	10 wkly injections	Rabbit	60	19	Kawada, 1963
	450 mg total	Injection into femur	45 wkly injections	Rabbit	88	11	Kawada, 1963
	300 mg total	1 injection into femur		Rabbit	70	12	Kawada, 1963

TABLE 1 (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding*	Time of measurement (mos.)	Reference
Beryllium oxide	300 mg total	Injection, femur periosteum		Rabbit	78	14.5	Kawada, 1963
	10 mg	Implanted under right tibia periosteum		Rabbit male and female	33	10-25	Tapp, 1969
	220-400 mg	Injected into femur	Twice wkly for 1-43 weeks	Rabbit	89	85 days-average latency from last injection	Yamaguchi & Katsura, 1963
	420-600 mg	Injected into femur	Twice wkly for 1-43 weeks	Rabbit	100	85 days-average latency from last injection	Yamaguchi & Katsura, 1963
	620-800 mg	Injected into femur	Twice wkly for 1-43 weeks	Rabbit	50	85 days-average latency from last injection	Yamaguchi & Katsura, 1963
	820-860 mg	Injected into femur	Twice wkly for 1-43 weeks	Rabbit	75	85 days-average latency from last injection	Yamaguchi & Katsura, 1963
Zinc beryllium oxide[a]	1 gm total	Intravenous	20 injections over 6 wks	Rabbit	100	7+	Gardner & Healington, 1946
	1 gm	Multiple intravenous injections		Rabbit	25	30+	Barnes, et al. 1950 Sissons, 1950
	1 gm	Intravenous	22 semi-wkly injections	Rabbit	80	12+	Cloudman, et al. 1949

TABLE 1 (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding*	Time of measurement (mos.)	Reference
Zinc beryllium silicate	0.264 mg	Multiple intravenous injections		Mice	Some positive, percent not reported	Not reported	Cloudman, et al. 1949
	1 gm total	Intravenous	10 wkly injections	Rabbit	Some positive, percent not reported	11-24	Hoagland, et al. 1950
	1 gm total	Intravenous	20 twice-wkly injections	Rabbit	50	9-11	James, et al. 1954
	Not reported	Intravenous	10 wkly injections	Rabbit	71	9-14	Kelly, et al. 1961
	1 gm total	Injection	20 wkly injections	Rabbit	30	Not reported	Higgins, et al. 1964
	10 mg	Implanted under right tibia periosteum		Rabbit	16	10-25	Tapp, 1969
	33 mg as Be	Injection intra-osseous		Rabbit	70	4	Mazabraud, 1975
Beryllium silicate	10 mg	Implanted under right tibia periosteum		Rabbit	16	10-25	Tapp, 1969
Metallic beryllium	40 mg	Intravenous		Rabbit	40	Not reported	Barnes, et al. 1950

TABLE 1 (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding*	Time of measurement (mos.)	Reference
Beryllium phosphate	16 mg total	Injection	10 wkly injections	Rabbit	Some positive, percent unknown	11-24	Hoagland, et al. 1950
Beryllium phosphor[b]	90 mg	Intravenous		Rabbit	1/1	12-14	Dutra & Largent, 1950
	80 mg	Intravenous		Rabbit	1/1	12-14	Dutra & Largent, 1950
	64 mg	Intravenous		Rabbit	0/1	12-14	Dutra & Largent, 1950

*Percent exhibiting tumors or cancer

[a]1 gm of zinc beryllium silicate contains 33.6 mg of Be expressed as the oxide

[b]Be oxide, Zn oxide and silica in a molar ratio of 1:1:1

TABLE 2

Induction of pulmonary cancer in experimental animals by beryllium

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos.)	Reference
Beryllium sulfate	.11 mg as Be	Intratracheal		Rat	Some positive, percent not reported	9 or longer	Vorwald & Reeves, 1959
	55 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 5 days/ wk until sacrifice	Rat	Some positive, percent not reported	9 or longer	Vorwald & Reeves, 1959
	6 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 5 days/ wk until sacrifice	Rat	Some positive, percent not reported	9 or longer	Vorwald & Reeves, 1959
	620 $\mu g/m^3$ 35 $\mu g/m^3$ as Be	Inhalation	6 mos	Rat	Some positive percent not reported	18	Schepers, 1961
	2.32 mg/m^3 0.20 mg/m^3 as Be	Inhalation	6 hr/day, 7 days	Monkey Macacus mullata	0, only 1 of 4 survived 180 days	6	Schepers, 1964
	42 $\mu g/m^3$ as Be	Inhalation	7 hrs/day, 5 days/ wk, 18 mos.	Rat	Almost 100	18	Vorwald, et al. 1966
	21 $\mu g/m^3$ as Be	Inhalation	7 hrs/day, 5 days/ wk, 18 mos.	Rat	Almost 100	18	Vorwald, et al. 1966
	2.8 $\mu g/m^3$ as Be	Inhalation	7 hrs/day, 5 days/ wk, 18 mos.	Rat	62	18	Vorwald, et al. 1966
	35 $\mu g/m^3$ as Be	Inhalation	7 hrs/day, 5 days/ wk, 18 mos.	Rhesus monkey	20, 2 of 10 exposed 3,241 & 3,871 hrs	5-6 yrs	Vorwald, et al. 1966
	34 $\mu g/m^3$ as Be	Inhalation	7 hrs/day, 5 days/ wk, until sacrifice	Rat, male & female	100	13	Reeves, et al. 1967

TABLE 2 (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos.)	Reference
Beryllium oxide	4.5 mg as Be	Intratracheal		Rat	Some positive, percent unknown	9 or longer	Vorwald & Reeves, 1959
	250-500 mg	Intratracheal and/or broncho-mural		Rhesus monkey	15	54+	Vorwald, et al. 1966
	25 mg calcined at 500°C	Intratracheal		Rat, males and females	100	15-20	Spencer, et al. 1968
	25 mg/kg calcined at 1,100°C	Intratracheal		Rat, males and females	25	15-17	Spencer, et al. 1968
	25 mg calcined at 1600°C	Intratracheal		Rat, males and females	30	18-24	Spencer, et al. 1968
	50 mg/kg calcined at 500°C	Intratracheal		Rat, female	0	11	Spencer, et al. 1972
	50 mg/kg calcined at 500°C	Intratracheal		Rat, female	40	17	Spencer, et al. 1972
	50 mg/kg calcined at 500°C	Intratracheal		Rat, female	100	23	Spencer, et al. 1972
Beryllium fluoride	48 $\mu g/m^3$	Inhalation	6 mos.	Rat	Some positive, percent unknown	15	Schepers, 1961
	950 $\mu g/m3$ 180 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 7-16 days	Monkey Macacus mullata	0, all died within 28 days of exposure	less than 1	Schepers, 1964

TABLE 2 (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos.)	Reference
Beryllium flouride & chloride	0.2 gr 0.4 mg/m^3	Inhalation	1 hr/day, 5 days/ wk, 4 mos.	Rat	Some positive, percent unknown	22	Litvinov, et al. 1975
Beryllium phosphate	3.5 mg/m^3	Inhalation	6 mos.	Rat	Some positive, percent unknown	12	Schepers, 1961
	2.32 mg/m^3 0.20 mg/m^3 as Be	Inhalation	6 hrs/day, 30 days	Monkey Macacus mullata	0	up to 9 post-exposure	Schepers, 1964
	13.1 mg/m^3 1.11 mg/m^3 as Be	Inhalation	6 hrs/day, 10 days	Monkey Macacus mullata	25 of 4 exposed 1 survived 82 days post exposure and developed cancer	up to 82 days	Schepers, 1964
Zinc beryllium silicate	24 mg/m^3	Inhalation	6 mos.	Rat	Some positive, percent unknown	9	Schepers, 1961
Beryl ore	15 mg/m^3 210 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 5 days/ wk until sacrifice	Squirrel monkey Salmiri sciurea	0	23	Wagner, et al. 1969
	15 mg/m^3 210 $\mu g/m^3$ as Be	Inhalation	6 hrs/day/ wk until sacrifice	Rat	95	17	Wagner, et al. 1969
	15 mg/m^3 210 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 5 days wk until sacrifice	Hamster	0	17	Wagner, et al. 1969

TABLE 2 (continued)

Compound	Dose	Exposure route	Exposure duration	Species	Percent responding	Time of measurement (mos.)	Reference
Bertrandite ore	15 mg/m^3 620 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 5 days/ wk until sacrifice	Squirrel monkey Samiri sciurea	0	23	Wagner, et al. 1969
	15 mg/m^3 620 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 5 days/ wk until sacrifice	Rat	0	17	Wagner, et al. 1969
	15 mg/m^3 620 $\mu g/m^3$ as Be	Inhalation	6 hrs/day, 5 days/ wk until sacrifice	Hamster	0	17	Wagner, et al. 1969
Beryllium hydroxide	40 µg Be	Intratracheal		Rat 12 mos. old	10	6	Groth & MacKay, 1971
	40 µg Be	Intratracheal		Rat 3 mos. old	0	6	Groth & Mackay, 1971
	4 µg Be	Intratracheal		Rat 12 mos. old	0	6	Groth, et al. 1972
	4 µg Be	Intratracheal		Rat 6 mos. old	0	6	Groth, et al. 1972
	0.4 µg Be	Intratracheal		Rat 12 mos. old	0	6	Groth, et al. 1976
	0.4 µg Be	Intratracheal		Rat 3 mos. old	0	6	Groth, et al. 1976

expected. Casarotto (1952) failed to detect tumors in the parathyroid glands or teeth (the only organs studied) of two dogs; one fed 1.3 gm beryllium carbonate per day for 104 days and the other 0.5 to 1.5 gm per day for 109 days. In longer term studies, Barnes (1948) also failed to detect tumors in mice administered 1 percent beryllium sulfate in the drinking water for 1 year.

More recently, beryllium sulfate at a concentration of 5 ppm as Be in the water, over a life time, caused no change in growth rates, longevity, or incidence of tumors in mice or rats (Schroeder and Mitchener, 1975a,b), except for a small excess of leukemias, termed as lymphoma leukemias by the authors, in female mice and in grossly observed tumors of all sites in male rats. Concurrent work by Morgareidge, et al. (1975) however, in which rats were fed beryllium at concentrations of 5, 50 or 500 ppm in the diet for two years showed a significant increase in lung reticulum cell sarcomas in two of three dose groups when compared to controls for males, according to a reanalysis of the data by the EPA Carcinogen Assessment Group. This tumor type was also higher in females in the lowest two dose groups, but not significantly so.

Although significant results were found upon reanalysis of the data from this latter study, these results do not follow a typical dose response pattern: the lowest dose (5 ppm) produced the most significant response; the highest dose (500 ppm) produced no significant response. Morgareidge, et al. (1975) concluded from their results that evidence did not exist for any neoplastic or pre-neoplastic lesions that correlated with beryllium ingestion.

The majority of industrial exposures to high levels of beryllium took place in the 1940's. Due to a lack of appreciation of the harmful effects, insufficient monitoring information, and a lack of a centralized data base prior to 1951; studies attempting to link beryllium to cancer in humans were not carried out until many years later. Stoeckle, et al. (1969) reported no incidence of cancer in 60 selected cases of beryllium disease first diagnosed between 1944 and 1966. Bayliss (1972) studied medical records of 3,921 males employed in two beryllium plants from January 1942 through December 1967. Mortality from respiratory tract cancer revealed no significant departure from expectation in this population. Hardy, et al. (1967) reported 14 cases of cancer among a group of 535 individuals listed in the Beryllium Case Registry in 1966. These included 3 cases of lung cancer, 3 of bone sarcoma, and one each of cancer of the cervix, skin, CNS, cecum, breast, eye, colon, and nasopharynx. According to Hardy (1976), the bone sarcomas were incorrectly listed and were found only in one case. A significant increase in the incidence of bone or lung cancer could not be detected.

Mancuso (1970) reported 9 deaths due to lung cancer in a cohort of 594 beryllium workers above age 25 at one company, 6 of whom were among 142 individuals indentified as having had prior beryllium-related bronchitis and pneumonitis during 1937-1948. The age-adjusted lung cancer mortality rate was calculated to be equal to 284.3 per 100,000 population for the subcohort with prior respiratory illness, compared with 77.7 per 100,000 for the main cohort. Workers who were employed 1 to 5 calendar quarters had a higher lung cancer rate than those employed for 6 quarters or more. It was

concluded that prior respiratory illness of beryllium workers was associated with high lung cancer mortality rate, but the reverse length-of-exposure/rate-of-incidence correlation could not be explained. Hasan and Kazemi (1974) reported 4 cases of lung cancer among 76 cases added to the registry since 1966, making the total incidence of lung cancer in the U.S. Beryllium Case Registry, as of 1974, 7 in 611, or 1.14 percent.

Niemoller (1963) described three cases of lung carcinoma that he felt were related to beryllium exposure. Two were exposed to beryllium industrially and the third was a smoker. Niemoller based his conclusion on the location of tumors, a history of exposure (either industrial or through smoking), and the presence of beryllium in the tissue. Gold (1967) described a peritoneal mesothelioma of the recto-vaginal septum in a 34-year-old woman. The patient had a history of traumatic vaginal lesions repeatedly exposed by douching with hard water containing soluble beryllium at a level of 0.035 µg/l; the patient also had environmental exposure to asbestos. Analysis of tumor tissue showed presence of beryllium at a level of 0.04 µg/g; asbestos was not demonstrated. This author also believed that the tumor was beryllium-related but the identification of the etiologic factor in all these cases was somewhat conjectural.

Berg and Burbank (1972) observed significant positive correlation between beryllium concentration in drinking water and cancer deaths in 15 regions of the country, ranked according to levels of trace metals. The highest mean positive level was 0.3 µg Be/l for Delaware, Maryland, West Virginia, and Kentucky. Cancers of

breast, bone, and uterus appeared to have a probability of positive association ranging from 0.006 to 0.040, but the association was weak in subgroups.

Three very recently completed and thus far unpublished studies have also claimed that beryllium exposure increased the risk of cancer mortality. These are an updating of the former Bayliss study (Wagoner, et al. 1978a), an updating of the former Mancuso study (Mancuso, 1978), and a study by NIOSH based on the case reports in the U.S. Beryllium Case Registry (Infante, et al. 1978). These papers, or their preliminary drafts, were entered in the record of the hearing on the proposed standard for exposure to beryllium (OSHA, 1977) and were the subject of considerable controversy (Shapley, 1977; Wagoner, et al. 1978b). The matter was reviewed by a panel of uninvolved experts convened for this purpose by the Secretary of H.E.W., and resulted in the following statement:

> The epidemiologic evidence is suggestive that beryllium is a carcinogen in man. The evidence is not at this time judged to be more than suggestive because alternative explanations for the positive findings have not been definitely excluded... Specially designed case control studies are needed to evaluate other risk factors in the beryllium-associated lung cancer cases. Confirmatory retrospective cohort studies should also be conducted. Nevertheless, it would be imprudent from a public health perspective to delay our judgment about beryllium exposure of current workers until these studies are completed. In our opinion, beryllium should be considered as a suspect carcinogen for exposed workers. (Discher, 1978).

In contrast, MacMahon (1978) and MacMahon and Roth (1978) reviewed the U.S. Case Registry (BRC) case studies and reported that they found deficiencies. MacMahon (1978) concluded that the BRC data "cannot be regarded...as evidence that beryllium is

carcinogenic in humans," and suggested that the excess lung cancers noted in the BRC case reports may have resulted from chance, selection bias, heavy smoking among members of the examined cohort, or a combination of these factors.

CRITERION FORMULATION

Existing Guidelines and Standards

The present standard for occupational exposure prescribes an 8-hour time weighted average of 2.0 $\mu g/m^3$ with a ceiling concentration of 5.0 $\mu g/m^3$. In addition, the present standard allows a peak concentration above the ceiling concentration of 25 $\mu g/m^3$ for a maximum duration of 30 minutes (40 CFR 202.48823).

The threshold limit value (TLV) for beryllium was set at 2 $\mu g/m^3$ by the American Conference of Governmental Industrial Hygienists (ACGIH, 1977).

National Emission Standards for Hazardous Air Pollutants set their criterion as: not more than 10 g in 24 hours or emissions which result in maximum outplant concentrations of 0.01 $\mu g/m^3$, 30-day average (U.S. EPA, 1977).

The U.S. Environmental Protection Agency (U.S. EPA) proposed a water quality standard of 11 µg/l for the protection of aquatic life in soft fresh water; 1,100 µg/l for the protection of aquatic life in hard fresh water; 100 µg/l for continuous irrigation on all soils except 500 mg/l for irrigation on neutral to alkaline lime-textured soils (U.S. EPA, 1977).

The National Academy of Science/National Academy of Engineering (NAS/NAE, 1973) Water Quality Criteria recommendation for marine aquatic life is: hazard level - 1.5 ug/l; minimal risk of deleterious effects - 0.1 mg/l; application factor - 0.01 (applied to 96-hr LC_{50}). Their recommendation for irrigation water is: 0.10 mg/l for continuous use on all soils.

Current Levels of Exposure

Concentrations of beryllium in the water supplies tend to be quite low. For example, analysis of 1,577 samples from U.S. surface waters and lakes showed beryllium present in 5.4 percent of the samples with concentrations ranging from 0.01 to 1.22 µg/l with a mean of 0.19 µg/l (Kopp and Kroner, 1967). The concentration of beryllium in seawater was reported equal to 6×10^{-4} µg/l (Goldberg, 1965).

Measurements of beryllium in air samples collected from 100 stations of the National Air Sampling Network (U.S. EPA, 1971) indicated that the average 24-hour concentration was less than 0.0005 $\mu g/m^3$. The maximum value recorded at these stations during 1964 - 1965 was 0.0008 $\mu g/m^3$. Thus, the maximum reported value was only 0.04 percent of the threshold limit value set by the American Conference of Governmental Industrial Hygienists (ACGIH, 1977). Sussman, et al. (1959) reported an average concentration of 0.0281 $\mu g/m^3$ within one-half mile of a large beryllium plant near Reading, PA. Concentrations closer to the plant reached 0.0827 $\mu g/m^3$. Three brands of West German cigarettes were reported to contain beryllium levels of 0.47, 0.68, and 0.74 µg per cigarette with 4.5, 1.6, and 10.0 percent of the beryllium content, respectively, inhaled in the smoke (Petzow and Zorn, 1974). These investigators estimated that the total beryllium intake for humans was about 100 µg/day with only a minor fraction by inhalation. Analysis of lung tissue at autopsy, from persons with no known industrial exposure to beryllium, showed maximum concentrations of 1.98 µg/100 gm tissue (Cholak, 1959).

Special Groups at Risk

Studies of Sterner and Eisenbud (1951) have suggested that a small percentage of the population is sensitive to extremely low concentrations of beryllium in the air, probably through the development of an immune reaction. There is no evidence to date for the development of sensitivity to concentrations of beryllium present in food or water or that sensitivity to low levels of beryllium in the air is aggravated by ingestion of beryllium. No other special groups can be identified as special risks.

Basis and Derivation of Criteria

Experiments have shown that cancer can be induced by beryllium in laboratory animals. As seen in Tables 1 and 2, cancer has been induced by beryllium via inhalation, intratracheal instillation, or intravenous injection. In addition, beryllium chloride has been shown to increase the error frequency of nucleotide base incorporation into DNA in an *in vitro* assay designed to detect potential metal mutagens/carcinogens (Sirover and Loeb, 1976). Although epidemiological studies have failed to establish an incontrovertible link between beryllium exposure and human cancer, the evidence is very suggestive.

The only experiments conducted to date in which beryllium was ingested over a long period of time were those of Schroeder and Mitchener (1975a,b) and Morgareidge, et al. (1975). In the first study, 5 ppm beryllium was added to the water of rats for a lifetime exposure. No statistically significant differences in tumor frequencies between control and experimental rats were found, although there was a slight excess of grossly observed tumors in males of

the treated group (Schroeder and Mitchner, 1975a). Mice, similarly exposed as rats, showed a statistically insignificant excess of lymphoma leukemias in females of the treated group (Schroeder and Mitchener, 1975b). In the latter study, Morgareidge, et al. (1975) exposed rats to levels of beryllium in the diet at concentrations of 5, 50, and 500 ppm. The authors concluded that evidence did not exist for any dose- or treatment-related pathological effects, or any neoplastic or preneoplastic lesions that correlated with beryllium ingestion. However, a reanalysis of this data by the EPA Carcinogen Assessment Group found that the incidence of lung reticulum cell sarcomas was significantly higher in the lowest and intermediate dose groups in males. The Fischer Exact p values were 0.0065 and 0.036, respectively. Lung reticulum cell sarcoma incidence was also higher in females in the lowest two dose groups, but not significantly so.

The significant results in males in this latter study do not follow a typical dose-response pattern: the lowest dose (5 ppm) produced the most significant response; the highest dose (500 ppm) produced no significant response. This lack of trend with dose makes these findings uncertain. Furthermore, these results have never been published. Because of these two shortcomings the Morgareidge, et al. study cannot be used to derive a cancer, or toxicity, based criterion, although it supports such derivations.

The high frequency of osteosarcomas induced in rabbits by intravenous Be and of reticulum cell sarcomas in rats fed beryllium, the positive results of mutagenicity studies, and the suggestive human epidemiology indicate that Be-laden water poses a carcinogenic

risk to man. Based on the above findings and the assumption that beryllium is likely to be carcinogenic after oral ingestion because it is carcinogenic via other routes of exposure, the Schroeder and Mitchener experiment (1975a), which showed a slight insignificant effect after oral exposure, is sufficient to calculate a criterion. Note, however: (1) that it is not the study of Schroeder and Mitchener, but the previously mentioned studies that suggest that Be-laden water poses a carcinogenic risk to man, and, (2) that to extrapolate from the Be studies where the route of administration was by injection or inhalation would yield a lower, and, perhaps, less valid criterion.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Beryllium is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of beryllium in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of beryllium corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every

100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every 1,000,000 people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the following table.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria(1)			
	0	10^{-7}	10^{-6}	10^{-5}
	ng/l	ng/l	ng/l	ng/l
2 liters of drinking water and consumption of 6.5 grams fish and shellfish. (2)	0	0.37	3.7	37
Consumption of fish and shellfish only.	0	6.41	64.1	641

(1) Calculated by applying a linearized multistage model, as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document, to the animal bioassay data presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Six percent of the beryllium exposure results from the consumption of aquatic organisms which exhibit an average

bioconcentration potential of 19-fold. The remaining 94 percent of beryllium exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of beryllium, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding beryllium concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding beryllium concentrations. Because data indicating other sources of beryllium exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

The assumption that beryllium is carcinogenic after oral administration can be questioned, however, in light of the fact that the results of oral studies designed to test this assumption are either negative or uncertain. An alternate method to calculate a protective level would be to use toxicity data as suggested in public comments. A review of the Effects section of this document indicates that the Schroeder and Mitchner (1975a) study is the most suitable for this derivation. The ADI for rats in this study can be estimated by:

5 mg/l x 0.035 l/d $\div$ 0.325 kg/rat = 0.538 mg/d/kg/rat,

where 5 mg/l (5 ppm) is the drinking water level showing no significant effect, 0.035 l is the approximate daily water intake for rats, and 0.325 is the approximate average weight of rats of both sexes in this study.

Dividing this ADI for rats by a safety factor of 1,000, as per NAS Guidelines (NAS, 1977) (because there is no long term or acute oral human data for Be exposure and the results in experimental animals are scanty), and then multiplying by 70 kg (the average weight of a man) yields the "safe" ADI for man:

$$(0.538 \text{ mg/d/kg/rat} \div 1{,}000) \times 70 \text{ kg/man} = 0.0377 \text{ mg/d/man}.$$

The ambient water concentration that results in this ADI for man can be calculated by the following equation:

$$C = \frac{\text{ADI mg/d/man}}{2 \text{ l/d/man} + (0.0065 \text{ kg/d man} \times \text{BCF l/kg})},$$

where 2 liters represents the average daily water intake, 0.0065 kg is the average daily fish consumption, and BCF is the bioconcentration factor for beryllium, which is 19. Thus,

$$C = \frac{0.0377 \text{ mg/d/man}}{2 \text{ l/d/man} + (0.0065 \text{ kg/d/man} \times 19 \text{ l/kg})}$$

$$= 0.0178 \text{ mg/l, or } 17.8 \text{ } \mu\text{g/l}.$$

The Agency recommends the cancer-based criterion (37 ng/l) because this criterion is more protctive of human health. The rationale for this decision is discussed in previous pages (pp. C-34, C-35) and in the Appendix. This criterion will be re-evaluated in the future as additional data on the oral carcinogenicity and/or toxicity of beryllium are discovered.

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APPENDIX I

Summary and Conclusion Regarding Carcinogenicity of Beryllium

Epidemiological studies have failed to establish an incontrovertible link between beryllium exposure and human cancer. However reticulum cell sarcomas were produced in one experimental study by ingestion of beryllium (Morgareidge, et al. 1975). Furthermore, beryllium has induced osteosarcomas in rabbits following intravenous administration (Cloudman, 1949). It has also been reported to be mutagenic at the HGPRT locus in CHO cells (personal communication with Alexander R. Malcolm, National Marine Water Quality Lab., U.S. EPA). In addition, $BECl_2$ at a concentration of 10mm increased by a factor of 15 the error frequency of nucleotide base incorporation into DNA in an in vitro DNA polymerase assay designed to detect potential metal mutagen/carcinogens (Sirover and Loeb, 1976).

The high frequency of osteosarcomas in rabbits induced by intravenous Be and of reticulum cell sarcomas in rats fed beryllium, the positive results from mutagenesis assays, and the suggestive human epidemiology indicate that Be-laden water poses a carcinogenic risk to man.

Although the Morgareidge, et al. (1975) dietary study indicates a significant excess of cancer after beryllium ingestion and, at first appearance, would seem to be the best study from which to

derive a criterion, it cannot be used for such a purpose for reasons previously stated (p. C-34). Therefore, the Schroeder and Mitchner dietary study was used to estimate the criterion associated with a lifetime human cancer risk of 10^{-5}. The resulting ambient water criterion is 37 ng/l.

Derivation of Water Quality Criterion for Beryllium

The experiment of Schroeder and Mitchner (1975a) showed a small, statistically insignificant, excess in grossly observed tumors of all sites in male rats continuously exposed to Be at 5 ppm in their drinking water. These results can be used to estimate the maximum risk that beryllium could pose, or equivalently, the lowest concentration which leads to a 10^{-5} human lifetime cancer risk.[1] The parameters of the extrapolation are:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0.0	4/26
0.25	9/33

le = 1126 days

Le = 1126 days

L = 1126 days

W = 0.385 kg

R = 19 l/kg

With these parameters the carcinogenic potency factor for humans, q_1^*, is 8.84 $(mg/kg/day)^{-1}$. The result is that the water concentration should not exceed 37 ng/l in order to keep the lifetime risk below 10^{-5}.

[1]See the discussion in the "Basis and Derivation of Criteria" section for the justification in the use of this study.

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