UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

April 24, 1987

Honorable Lee M. Thomas
Administrator
U. S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

SAB-EHC-87-028

OFFICE OF
THE ADMINISTRATOR

Dear Mr. Thomas:

The Metals Subcommittee of the Science Advisory Board's Environmental Health Committee has completed its scientific review of EPA's most recent draft of a Health Assessment Document for Beryllium. We are pleased to forward the results of the Subcommittee's review to you.

The Subcommittee agrees with the conclusions reached in the draft document concerning the evidence of carcinogenicity using epidemiological and animal data. The Subcommittee was not able to reach consensus on advising the Agency on the use of existing data to estimate an upper bound to human risk. The Subcommittee continues to disagree with the Agency's choice of a model for the pharmacokinetics of inhaled beryllium particulates. These and other issues are presented in the attached letter.

We would appreciate a formal Agency response to the Subcommittee's scientific advice.

Sincerely,

Richard Griesemer

Richard Griesemer
Chairman
Environmental Health Committee
Science Advisory Board

Norton Nelson

Norton Nelson
Chairman
Executive Committee
Science Advisory Board

cc: A. James Barnes
Vaun Newill
Craig Potter
Terry Yosie

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

February 12, 1987

Dr. Richard A. Griesemer
Chair, Environmental Health Committee
Science Advisory Board
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D. C. 20460

OFFICE OF
THE ADMINISTRATOR

Dear Dr. Griesemer:

The Metals Subcommittee of the Environmental Health Committee has completed its review of a revised draft Health Assessment Document for Beryllium (EPA/600/8-84/026B; April, 1986) prepared by the Office of Research and Development (ORD). This document was a revision of a previous draft dated December, 1984. The latest draft responds to our comments on the earlier version. (See the SAB report of September 23, 1985.)

The draft document includes calculations that are essential to an interpretation of human health effects. The Subcommittee firmly agrees with the conclusions of the revised document that the available epidemiological evidence for carcinogenic effects of beryllium in humans is "inadequate," and that the evidence of carcinogenic effects in animals is "adequate," as defined in EPA's new guidelines for carcinogen risk assessment. This information places beryllium into a qualitative weight-of-the-evidence category of B2 ("a probable human carcinogen").

The human data, although not consistent with the induction of cancer, might be used to estimate an upper bound to human risk. However, a Subcommittee consensus does not exist regarding the advisability of the Agency's using such an estimate. Some Subcommittee members suggest that an upper bound estimate based on inadequate human evidence does not differ conceptually or mathematically from EPA's upper bound estimates for other substances. Other members believe that such an estimate would be misleading and scientifically inappropriate because of the lack of information that beryllium is carcinogenic in humans.

When ORD staff attempt to estimate the quantitative risk of carcinogenicity of beryllium from animal studies, a dilemma arises. First, parenteral administration data, such as those indicating the induction of bone tumors in rabbits after beryllium injections, are unsuitable for reaching any conclusions about the results of inhalation exposure. Second, although the data demonstrate that inhaled beryllium can induce lung tumors in rats, the monkey data are less consistent. Earlier reports of lung tumors in exposed monkeys, conducted without control animals, were not confirmed by a later study conducted under the auspices of the Department of Health, Education and Welfare. Given the lack of suitable control data in the earlier reports, and the fact that they were conducted at a time when investigators tended not to be concerned about the quantitative description of their findings, most Metals Subcommittee members regard the available animal data as inappropriate for quantitative risk estimation.

Comparison of the animal and human data reveals a paradox in the interpretation of carcinogenic risk for beryllium. For this reason, the Subcommittee has reached beyond the description of the data in the draft document and has conducted a detailed analysis of the primary publications about animal carcinogenicity of beryllium. The Subcommittee reviewed sixteen papers which are identified in an attachment to this letter.

The culmination of this additional review has not, however, produced a Subcommittee consensus about the suitability of carcinogencity data from animals for quantitative risk estimation. Some members still would support the use of an upper bound based on the inadequate human evidence because (1) extrapolation between species is not required, and (2) the physico-chemical form of beryllium examined in the epidemiological studies resembles more closely the physico-chemical form to which people are exposed in the environment than does the form examined in animal experiments. Some other members think that a better estimate of the upper bound to human risk can be extrapolated from the animal experiments conducted by Reeves, Deitch and Vorwald. Some members recommend that the Agency estimate carcinogen risks from those data for rats only and not extrapolate to humans. Still other members believe that the data do not justify any quantitative estimates of risk and that a quantitative estimate is not required for regulatory purposes.

Subsequent to the meeting, ORD staff have attempted to prepare carcinogenic risk estimates that are factored for the solubility of the beryllium compound or the firing temperature of beryl ores. While the Subcommittee applauds the development of these hypotheses and hopes that each will be illustrated in the final version of the document for discussion purposes, the relevance of these hypotheses to a regulatory risk assessment is viewed with a great deal of skepticism. The solubility of beryllium compounds in water is not similar, even on a relative basis, to the solubility of the same beryllium compounds in lungs. The solubilization process in the lung involves a fluid of different composition and an active cellular process carried out by macrophages and other cells. Similarly, the firing temperature of beryl ores will affect the particulate properties of the materials used in animal experiments, and the properties of particles are critical to the deposition and solubilization in lung tissue and, thus, to the appearance of lung tumors.

The Subcommittee continues to disagree with the Agency's choice of a model for the pharmacokinetics of inhaled beryllium particulates. In both the current and previous draft Health Assessment Documents, EPA has evaluated inhaled beryllium in places as if it were a gas. The Subcommittee urges that staff develop a model that incorporates the features of: (1) particulate inhalation, (2) dose to the pulmonary tree, (3) pulmonary retention and distribution, (4) pulmonary absorption, and (5) dose rate to sensitive cells. The Subcommittee understands that the existing data are not entirely suitable for such a model and that staff will have to use more assumptions. However, the advantages of such a model over the current approach are that (1) its description in Agency assessments will highlight the major sources of uncertainty and the important data gaps, (2) the Agency will not have to overthrow its conceptual approach as new, more

appropriate data become available, and (3) it would incorporate state-of-the-art information on the processes involved, which the current model does not. Moreover, suggestions by Metals Subcommittee members should help with this effort.

The interpretation of a quantitative carcinogenic risk estimate for beryllium pushes scientific uncertainty and extrapolation to the limit because of some significant gaps in scientific information. Under this circumstance, it should not be surprising that the Subcommittee cannot form a consensus. However, the Subcommittee does not believe that filling the data gaps is an important Agency research need because of other significant health research priorities, and because current information does not indicate that beryllium represents a serious public health problem.

Cases of chronic beryllium disease, a pulmonary condition, did occur under the exposure circumstances that existed before EPA's current standard of 0.01 ug/m^3 for ambient air and adoption of the practice of washing workers' clothing in plants. The standard has been effective in that no "neighborhood" cases of chronic beryllium disease have been reported since it took effect. In contrast, the subjects of the epidemiological studies reviewed in EPA's assessment were exposed to high levels of beryllium at a time when no standard was in place. Since the epidemiological studies based on those conditions provide inadequate evidence for human lung cancer, it is implausible to expect detectable lung cancer in humans exposed to beryllium levels in the environment today.

Sincerely,

Bernard Weiss

Bernard Weiss, Ph.D.
Chair, Metals Subcommittee

Ronald Wyzga

Ronald Wyzga, Sc.D.
Vice-chair, Metals Subcommittee

ATTACHMENT

(1) A.L. REEVES, D. DEITCH and A. J. VORWALD, "Beryllium Carcinogenesis: I. Inhalation Exposure of Rats to Beryllium Sulfate Aerosol," Cancer Research 27 (1967), 439-445.

(2) A.L. REEVES and A. J. VORWALD, "Beryllium Carcinogenesis: II. Pulmonary Deposition and Clearance of Inhaled Beryllium Sulfate in the Rat," Cancer Research 27 (1967), 446-451.

(3) A.L. REEVES and D. DEITCH, "Influence of Age on the Carcinogenic Response to Beryllium Inhalation," in S. HARISHIMA (Ed.), Proc. 16th International Congress Occup. Health. Japan Indust. Safety Assn.; Tokyo, Japan (1969), pp. 651-652.

(4) H.C. SPENCER, S.E. SADEK, J.C. JONES, R.H. HOOK, J.A. BLUMENSHINE and S.B. McCOLLISTER, "Toxicological studies on Beryllium Oxides and Beryllium--Containing Exhaust Products," in Proceedings of the Third Annual Conference on Environmental Toxicology (1972), pp. 1-123.

(5) A.J. VORWALD, A.L. REEVES and H.C.J. URBAN, "Experimental Beryllium Toxicology," in H.E. STOKINGER (Ed.) Beryllium--its Industrial Hygiene Aspects, Academic Press; New York, NY (1966), pp. 201-234.

(6) A.J. VORWALD, "Adenocarcinoma in the Lung of Albino Rats Exposed to Compounds of Beryllium," in Proceedings of the Scientific Session, American Cancer Society Annual Meeting (1953), pp. 103-109.

(7) A.J. VORWALD, "Biologic manifestation of toxic inhalation in monkeys," in H. VAGTBORG (Ed.), Use of nonhuman primates in drug evaluation. Univ. of Texas; Austin, TX (1968), pp.222-228.

(8) C.L. SANDERS, W.C. CANNON, G.J.POWERS, R.R. ADEE and D.M. MEIER, "Toxicology of High-Fired Beryllium Oxide Inhaled by Rodents," Arch. Environ. Health 30 (1975), 546-551.

(9) C.L. SANDERS, W.C. CANNON and G.J. POWERS, "Lung Carcinogenesis Induced by Inhaled High-Fired Oxides of Beryllium and Plutonium," Health Physics 35 (1978), 193-199.

(10) G.W.H. SCHEPERS, T.M. DURKAN, A.B. DELAHANT and F.T. CREEDON, "The Biological Action of Inhaled Beryllium Sulfate," AMA Arch. Industrial Health 15 (1957), 32-58.

(11) G.W.H. SCHEPERS, "Neoplasia Experimentally Induced by Beryllium Compounds," Prog Exp. Tumor Res. 2 (1961) 203-244.

(12) G.W.H. SCHEPERS, "Lung Tumors of Primates and Rodents," Part II: Ind. Med. 40 (1971), 23-31.

(13) W.D. WAGNER, D.H. GROTH, J.L. HOLTZ, G.E. MADDEN and H.E. STOKINGER, Title of Article: "Comparative Chronic Inhalation Toxicity of Beryllium Ores, Bertrandite and Beryl, with Production of Pulmonary Tumors by Beryl," Toxicol. Applied Pharmacol. 15 (1969), 10-29.

(14) H.A. SCHROEDER and M. MITCHENER, "Lifetime Studies in Rats: Effects of Aluminum, Barium, Beryllium and Tungsten," J. Nutr. 105 (1975), 421.

(15) H.A. SCHROEDER and M. MITCHENER, "Lifetime Effects on Mice: Mercury, Methylmercury and Nine Other Trace Metals," J. Nutr. 105 (1975), 452.

(16) T.A. McMAHON, J.D. BRAIN and S. LEMOTT, "Species Differences in Aerosol Deposition, in W.H. WALTON (Ed.), Inhaled Particles IV: Part 1, Pergamon Press; Oxford (1977), pp. 22-32.