

APPENDIX B

October 13, 1978

Dr. William H. Foege
Director
Center for Disease Control
Atlanta, Georgia 30333

Dear Dr. Foege:

In response to your request for written answers to the queries concerning the carcinogenic potential of beryllium and its compounds, the following answers are submitted. These answers are the result of careful review of all documents, publications, and reports furnished to us concerning the effects of beryllium exposures in animals and man. In review and discussion of this material at the meeting of consultants in Atlanta on October 9, 1978, our individual conclusions were found to form a consensus which follows:

Question 1:

Are the animal studies credible in showing beryllium carcinogenicity in at least two species?

Answer:

Yes, with the following qualifications. Lung cancers have been recorded in rats and monkeys following the introduction of beryllium salts, usually beryllium sulfate or beryllium oxide, into lungs by direct instillation or by inhalation. Many of the studies reported lack rigorous analysis, are often poorly controlled, suffer from inconsistent protocol and exposure periods, and frequently lack statistical justification. Some of the studies reviewed were unpublished agency reports and have not been subjected to critical peer review. The compounds of beryllium used in these studies are not among the most common to which man is exposed in industrial environments. There are no reports that beryllium copper alloys are carcinogenic, although these alloys have not received adequate study. The concentration and duration of exposures in which lung carcinoma develops in animals following beryllium exposures varies greatly, but is usually associated with a long latent period. There is some unpublished evidence indicating that even a single exposure by intratracheal injection may after a long latency produce lung cancer in animals. There have been pitifully few studies of particle size of the beryllium agent used in the inhalation studies. Little reliable information exists concerning the amounts of beryllium retained in the lungs after these exposures, or the time course of clearance of the beryllium materials from the lungs. Adequate data for the development of dose time response patterns are not available. In addition to a development of lung cancers in animals exposed to beryllium by inhalation or intratracheal instillation, the introduction of some beryllium compounds intravenously or directly into bone produces osteogenic sarcoma, which is a malignant bone tumor in rabbits and rats. One unconfirmed report documents the development of this malignant bone tumor in a single rabbit after exposure to beryllium by inhalation. There are no data indicating the development of malignant bone tumors in man following beryllium exposures.

In spite of the deficiencies in the reported studies, the evidence for the carcinogenic potential of beryllium must be accepted. It is strongly recommended that additional well controlled studies of the effects of inhalation of beryllium compounds and beryllium alloys in animals be performed in order to generate data relating to latency, particle size, the effects of copper alloys, clearance, and dose response. These will provide much understanding of the effects of beryllium exposure in man.

Question 2:

Is beryllium copper alloy a carcinogen?

Answer

There are insufficient data available to answer this question. A single animal exposure study had very low dose exposures in a small number of animals.

Since a large number of workers are exposed to this alloy, we recommend that appropriate studies be done to determine the nature and the extent of worker exposures to beryllium copper alloy. We also recommend that this alloy be tested as a carcinogen.

Question 3:

Is there evidence indicating that beryllium is a carcinogen in man?

Answer:

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 definitively excluded. Likewise, the three reports (Wagoner, et al., 1978; Mancuso, 1978; and Infante, et al., 1978) showing a positive statistical association between beryllium exposure and human lung cancer are unpolished drafts, each of which is likely to require some revision after journal peer review prior to publication.

The few epidemiologic studies of beryllium and human cancer are only suggestive that beryllium is carcinogenic in man. While alternative explanations of the observed lung cancer excess have not been rigorously excluded, the association has not been shown to be invalid or biologically implausible. 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.

David P. Discher, M.D.

APPENDIX C

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APPENDIX C

Subsequent to October 13, 1978, the date of the letter set forth in Appendix B, the following have occurred:

- a) The three unpublished reports mentioned in the answer to Question 3 contained in the letter have been published.
- b) NIOSH, the major scientific and technical resource for OSHA, as a result of scientific criticism of the epidemiologic study principally relied on by OSHA in proposing a revised beryllium exposure standard has undertaken an expanded study of the cancer issue.
- c) OSHA has not adopted the proposed revised beryllium exposure standard.
- d) In a proceeding for compensation under the Pennsylvania Workmen's Compensation Act, the hearing examiner made a finding of carcinogenicity on the basis of an opinion of a medical witness in respect of the epidemiologic study referred to by OSHA. The proceeding was settled and the finding was withdrawn.