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#1 YEAR 1978

Dear Dr. Foege:

My response to the three questions addressed by you to each of the members of the beryllium review group at our meeting on October 9, 1978, is as follows:

Question 1 Are the animal studies credible in showing carcinogenicity of beryllium in at least two species?

Response

The animal studies are credible in showing carcinogenicity of beryllium in at least two species. Beryllium sulfate administered experimentally by the inhalation route to rats and monkeys produced pulmonary neoplasms in both species. Beryllium oxide, beryllium hydroxide, beryllium fluoride, beryllium phosphate, beryl ore, beryllium metal and beryllium-aluminum alloy each induced pulmonary neoplasms in rats usually by the instillation of these compounds directly into the trachea. Intramedullary injections of beryllium metal, beryllium silicate or beryllium phosphate produced osteogenic sarcomas in rabbits.

There are limitations to this body of evidence. In some cases, adequate controls were not used. In others, the results were not published in peer reviewed journals. Overall, however, the evidence that some forms of beryllium are carcinogenic in more than one species of animal is convincingly strong.

Question 2 Is beryllium copper alloy a carcinogen?

Response

No, there is no direct evidence concerning the carcinogenicity of beryllium copper alloy. In only one unpublished study was beryllium copper alloy tested in animals (Groth, D.H. et al. 1978); since less than 20 rats were employed for each of two concentrations of the alloy, it is not possible to place any confidence on the negative results of this work.

In the face of the positive experimental carcinogenic findings for many beryllium salts and for the metal alone, I believe that a high concentration of beryllium copper alloy administered to a large number of animals, such as 1000

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exposed and 1000 controls, would be likely to show evidence of carcinogenicity. I make this judgment on the basis of the carcinogenicity of beryllium metal itself. I am also concerned that workers who use beryllium copper alloys may be exposed to beryllium oxide and beryllium metal dusts in the process of grinding, milling or heating the alloy; these workers would then be exposed to forms of beryllium that have been shown to be carcinogenic in animals.

Question 3 Is there evidence indicating that beryllium is a carcinogen in man?

Response

In my opinion as an epidemiologist who has been extensively involved in environmental and occupational health studies, the epidemiological 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; Infante et al. 1978) showing a positive relationship in humans are unpublished drafts, each of which is likely to require some revisions after journal peer review prior to publication.

In the first report by Wagoner et al. (1978), a statistically significant excess of lung cancer (47 observed, 34.3 expected) was reported from a retrospective cohort study of 3055 workers at a beryllium extraction, processing and fabrication facility in Pennsylvania. Among the more important limitations of this study are the following:

(1) The contribution of cigarette smoking to the excess observed lung cancers could not be evaluated because smoking information was lacking. This deficiency is common to retrospective cohort mortality studies, and yet the scientific community has accepted evidence for an association between lung cancer and certain occupational hazards, based upon retrospective cohort mortality studies lacking cigarette smoking data. Examples are studies of uranium miners, rubber workers, asbestos exposed insulation workers and asbestos miners, and acrylonitrile workers. In the Wagoner et al. study (1968), the authors cited evidence that the distribution of histologic types among the 25 lung cancer cases for which tissue specimens could be reviewed was such that exposure factors other than cigarette smoking seemed to be operating. I do not believe it was possible for the authors to be more definitive in evaluating the cigarette smoking contribution, given the retrospective nature of their study.

(2) Nearly the entire excess in lung cancer was distributed among workers who were employed less than one year in the beryllium plant (40 observed cases, 28.6 expected). This finding is disturbing in that we would expect workers employed for 5 or more years to have been exposed to greater cumulative doses of beryllium than those employed less than one year. Yet in the group employed

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for 5 and more years, 7 lung cancer deaths were observed, and 5.7 were expected, yielding a nonsignificant mortality ratio. Even if we consider a minimum follow-up period of 15 years, the group employed for 5 or more years experienced 6 lung cancer deaths against 4.2 expected, a ratio that still is not statistically significant. Many of the workers employed for less than a year apparently worked during the 1940-49 interval, when war time conditions may well have resulted in less controlled exposures and greater job turnover. It is possible that these short-term workers, who went on to experience excess lung cancer rates, were also employed in other industries associated with lung cancer risks, or that they indeed had very high beryllium exposures in a short time. Absence of complete work histories and of exposure data makes it impossible to evaluate alternative explanations for the high lung cancer risks in short-term workers.

(3) In the Wagoner et al. study, expected numbers of lung cancer deaths for the 1968-1975 intervals were calculated by applying U.S. lung cancer death rates for the 1965-1967 period. Since lung cancer rates in the U.S. have continued to increase over the 1965-75 decade, a larger expected value would have been obtained if actual 1968-75 U.S. lung cancer rates were applied, thus decreasing the ratio of observed to expected. In a recent evaluation of the Wagoner et al. study by MacMahon and Roth (1968), 1968-1975 U.S. lung cancer rates were applied to the 1968-1975 experience of the worker cohort, and the expected number of lung cancer deaths was found to be 37.7, as opposed to the 34.3 reported by Wagoner et al. The ratio of 47 deaths observed vs. 37.7 expected is statistically significant at the $p=0.08$ level, a value that most epidemiologists would judge to be of borderline significance. However, there are other factors that may have resulted in an underestimate of the lung cancer risk among the beryllium workers. These, as cited by Wagoner et al., include among others regional differences in lung cancer rates between the Pennsylvania location and the U.S. average, and the consideration of all persons lost to follow-up as being alive (or at least none dead of lung cancer). These techniques are standard protocol in retrospective cohort studies but are known to yield conservative estimates of excess deaths associated with an exposure factor.

The draft by Mancuso (1978) reports a 1.5 to 2.5-fold higher lung cancer rates in a cohort of beryllium workers from two plants, one in Ohio and one in Pennsylvania, compared with rates for workers employed in an Ohio viscose rayon factory. A consistent lung cancer excess is shown for short-term and long-term beryllium workers. Potential confounding factors such as smoking and other job exposures were not evaluated, but it is difficult to account for these factors in retrospective mortality studies. The mortality rates need to be age adjusted, but it is unlikely that age differences were significant enough to account for the 1.5 to 2.5 mortality ratios. The nature of this study is such that no conclusions about a causal relationship with beryllium exposure can be made, but a reasonable suspicion for an association between excess lung cancer and employment at the two beryllium plants is raised. Again, this work has not been submitted for publication.

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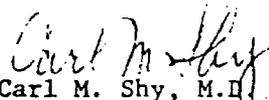
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In the Infante et al. (1978) study, an excess lung cancer mortality is reported for cases entered alive and without lung cancer into the Beryllium Case Registry. Expected numbers of lung cancer deaths are computed from the U.S. white male mortality experience for the follow-up period. Interpretation of the reported excess is severely limited due to the highly selective nature of the study cohort. This group was entered into the Registry because of the presence of lung disease; it is not improbable that this group smoked more than average and that they were therefore at greater risk of lung cancer, independently of other exposures. I do not feel that this study adds to our index of suspicion concerning the carcinogenicity of beryllium in man.

In sum, the few epidemiologic studies of beryllium and human cancers are only suggestive that beryllium is carcinogenic in man. While alternative explanations of the observed lung cancer excess have not been rigorously excluded, the associations have 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 were completed. In my opinion, beryllium should be considered as a suspect carcinogen for exposed workers.

Sincerely,



Carl M. Shy, M.D.
Professor of Epidemiology and
Director, Institute for Environmental Studies

CMS/bs

cc: William A. Felsing, Jr.

Enclosure (References)

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