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Critical Review of Data Relating to Possible Cancer  
Effects from Beryllium

The papers and documents which were studied for the review consisted of several papers on animal experiments relating to the toxicity of the metal, industrial hygiene reports, recent epidemiological studies of possible carcinogenic effects, and numerous documents from several sources containing background information on the controversy which surrounds the human studies. The latter group of papers will only be referenced when they contain information which is not available elsewhere.

The first question which was addressed to the consultants referred to the evidence on carcinogenicity which was available from animal experiments. There is a large body of experimental data which has tested the carcinogenicity of beryllium using many different animal species, different beryllium-containing materials, various routes of administration, and varying doses of the metal. These experiments, in general, were done in the early fifties and into the sixties and were less rigorously controlled than acceptable by current standards. They also placed great emphasis on the production of chronic lung disease as seen in human populations when exposed to the phosphor (a beryllium manganese zinc silicate material). Many experiments have concentrated on soluble agents, probably because they were easier to handle and perhaps less toxic to the animals. Since many of the materials caused death early in the experiment, the investigators were frequently left with very few animals followed by a long enough period to detect cancers. In general, the small animals had to be followed for ten or more months, and the larger animals for six to ten years in order to detect the tumor formation.

The two animal species with the most consistent and most comprehensive data on carcinogenic effects are the inhalation experiments in rats and the intravenous experiments in rabbits. The rats were exposed by intratracheal administration or inhalation to  $\text{BeSO}_4$  aerosol, bertrandite ore, beryl ore dust,  $\text{BeF}_2$ , Bephisphate, phosphor and  $\text{BeO}$  (prepared at different heat levels). Tumor formation occurred in these experiments at levels from about 16 to almost 100 percent depending on duration of followup. It is very difficult to identify any consistent dose levels to compare and most experiments included high levels of Be. Some investigators indicated that tumors were metastatic and transplantable.

Several interesting observations have been made concerning the neoplastic changes in this model system. The initial lesions according to some appear to be a proliferation and epithelialization which occurs at the bronchioles and alveolar ducts, and this progresses to tumor formation. The final tumors are most frequently adenocarcinomas and epidermoids. Schepers (1955) noted the similarity of these lesions to those of the epithelialization of alveolar walls noted in human lungs with berylliosis. This is not similar to the bronchogenic reaction seen with smoking.

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There were some data on the deposition of Be in lungs of rats but it is somewhat conflicting. Reeves et al (1967) indicated that the rate of lung uptake of  $\text{BeSO}_4$  decreased with continued exposure, whereas Schepers et al (1957) had previously indicated a continuously increasing level of Be in the lung even two months after exposure ceased.

The rabbit is the second animal system in which osteogenic sarcomas and bone tumors exclusively have been produced from intravenously administered Be products or from direct intramedullary injection into bone. The materials used were  $\text{Zn Be Si O}_4$ ,  $\text{Be Si O}_4$ , Be O, phosphor, and Be phosphate. Some investigators did report negative results with Be O and Be phosphate. Direct injection into the bone did not produce tumors at the local site. These are, in general, early experiments and the controls were few and often received injections of  $\text{Zn Si O}_4$ .

The tumors which were produced included osteosarcomas, chordiosarcomas, chondromas, and others. They were usually metastatic, especially to the lung and other viscera. Investigators commented that the tumor generally contains little Be, although the metal can be found elsewhere in the bone.

Other animal systems have been tested, especially mice, guinea pig, and monkeys. For most of these the experimental evidence is minimal. Two monkey species, the squirrel and Macacus mullata showed no effect from exposure to Be products. However, Vorwald using Rhesus monkeys did show tumors in eight of nine animals exposed to  $\text{Be SO}_4$  and followed for six to ten years.

As can be seen, few animals have been exposed to pure Be metal or to its alloys. We were specifically asked to address the issue of carcinogenic effects of copper alloys. Most of the data in this area are from a single experiment by Groth done several years ago, but soon to be reported as part of a review. Although he found evidence of carcinogenicity of Be metal, passivated Be and Be Al alloy he found no cancers in a few animals exposed to very low doses of Be in the copper, nickel, and copper cobalt alloys.

The experimental data in animals have demonstrated a probable carcinogenic effect in rats by inhalation and in rabbits by intravenous or bone injection in response to various Be-containing material. Most of the experiments have been poorly controlled, have used different agents, and have not given us much data on changing dose levels under constant experimental conditions. There is virtually no information on the effects of exposure to alloys.

The final question is whether there are human data suggesting a carcinogenic effect. There are in general three sources of human data - the Wagoner and Bayliss cohort of workers from the Pennsylvania Be plant, Mancuso's data which contains information from Social Security quarterly reports on employees in both the same plant and an Ohio Be operation, and data from a nonpopulation

ed, voluntary registry of known cases of beryllium-induced lung disease. ly authors had noted that there were no signs of an increased risk of cer despite their fears that animal data suggested a possible hazard. se observations included the evaluation of the registry data in 1966 Hardy and the study of patients with chronic beryllium disease followed ough 1969.

1969, Mancuso and El-Attar concluded that there were no signs of a cinogenic effect from exposure to Be. However, by 1970, Dr. Mancuso further observations about the cohort of workers exposed to Be in the plants noted that the lung cancer death rates were higher for individuals sed to Be work for a short period of time. He also noted that the lung cer mortality was higher in individuals who had previously been registered having berylliosis. The paper had no comparison rates from other groups, so one could not evaluate whether these rates represented an excess risk whether there were significant differences in this observed mortality. a recent paper which was submitted for our review, Mancuso has followed s 1937-48 cohort of employees through 1976 and compared their mortality arience to a group of rayon workers. This study design should be the imum method for showing a carcinogenic risk. The data do suggest a ner lung cancer risk in Be workers, but the analysis is incomplete. The a are not age-corrected and there is no indication as to the significance the findings by mathematical test. There are also discrepancies in the pers of individuals included in successive age-groups and the numbers of ths which are included. The design of this study should be useful in onstrating any effect when it is completely edited and analyzed and the a are age-and time-corrected. The older age distribution of Be workers ed in Mancuso's paper of 1970 make such adjustments imperative.

second paper of Mancuso's has compared the data from each Be plant to : of the U.S. white males using the NIOSH life table. The data suggest increased risk of mortality in the short-term employees with the longest ation of followup in both facilities.

other set of papers which we reviewed were those of Wagoner et al who : used the same Pennsylvania plant as Mancuso but obtained their data ough industry sources. One of their cohorts, which encompasses a 10-year od from 1940-49, includes the same 7-year cohort from 1942-48 which usoso has used. It should be noted that Wagoner has fewer individuals he group despite the additional three years of employee identification, aps because of his method of population ascertainment or because of ction of individuals for inclusion in the cohort. However, the conclusions hed by the two studies are the same. The risk of lung cancer mortality igher than expected, and most of this risk occurs because of deaths in t-term employees who were followed for over 25 years.

one criticism which can be levied at this study is that the U.S. popu- on is not an appropriate control group and that local state and county arisons should be included in order to verify the significance of the lings. Part of the controversy which has arisen about this paper stems

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indicated in these two studies and after additional more appropriate populations are selected for comparison in the Wagoner study, we would have suggestive evidence of a risk of lung cancer from Be exposure. To substantiate the finding, however, we would need another independent study since 85% of the lung cancer deaths which are in the Wagoner study are common to the Mancuso studies. A careful examination and comparison of the history of these workers is also warranted.

As noted in several commentaries, the demonstration of similar risks in two independent populations with similar exposures provides strength to the proposed causative association.

Infante's study of mortality of Be registry patients does not serve to substantiate a risk in exposed individuals. Since these workers constitute an unusual group of selected patients with lung disease, we cannot compare them to the general population. They would need to be compared to similar types of patients, all of whom may have an increased risk of lung cancer, not just patients exposed to Be. This could be done by comparing them to hospital populations with lung disease which ideally would be another type of chemical pneumonitis, or an interstitial pneumonia or chronic pneumoconioses.

If the first two cohort studies continue to indicate a significant difference after minor corrections, the data are highly suggestive of a risk of lung cancer from Be exposure. A second study in another population which is large enough so that it might have significant results with a relative risk of two-fold or less is warranted. Further studies to try to identify any specific factors which might have contributed to the possible epidemic risk of lung cancer in the short-term workers from the early 1940 cohort should be undertaken.

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