COMMENTS OF BRUSH WELLMAN INC.

ON THE DRAFT REPORT ON CARCINOGENS BACKGROUND DOCUMENT FOR BERYLLIUM AND BERYLLIUM COMPOUNDS PREPARED FOR THE NATIONAL TOXICOLOGY BOARD OF SCIENTIFIC COUNSELORS

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Introduction

Technology Planning and Management Corporation has prepared for the National Toxicology Program ("NTP") of the U.S. Department of Health and Human Services, Public Health Service, a Draft Report on Carcinogens Background Document for Beryllium and Compounds to be reviewed by the NTP Board of Scientific Counselors on January 20-21, 2000. Brush Wellman Inc. ("Brush Wellman") submits these comments on Chapter 3, Human Cancer Studies, of the Draft Report.

Brush Wellman is a leading international supplier of high performance engineered materials. It is the only fully integrated supplier of beryllium, beryllium alloys and beryllia ceramic in the world. Since its founding in 1931, Brush Wellman has concentrated its operations and skills on advancing the unique performance capabilities and applications of beryllium-based materials. As the world leader in beryllium production and technology, Brush Wellman strives to remain the leader in medical knowledge of beryllium and in the environmental, health and safety aspects of the material as well. Brush Wellman has sponsored basic research concerning the environmental and health effects of beryllium. A special focus of Brush Wellman's medical and research efforts has been on lung diseases associated with inhalation of beryllium.

Summary

Beryllium and beryllium compounds do not meet the NTP criterion for classification as known to be human carcinogens.

- The human studies that do exist report slight relative cancer risk elevations that are confounded by exposure to other carcinogens and are not significant. Taken as a whole these studies do not reflect an excess risk that is sufficiently high to justify the known human carcinogen classification for beryllium.

- The principal studies inadequately adjust for smoking,

- The principal studies do not adjust for exposure to sulfuric acid mists, which have been classified as known human carcinogens.

- For most beryllium compounds, the criterion is not satisfied because there are no studies of human carcinogenic response.

Beryllium and Beryllium Compounds Do Not Meet NTP's Criterion For Classification As Known To Be Human Carcinogens

The NTP has proposed that in the Tenth Report on Carcinogens that the classification for beryllium and beryllium and compounds be changed from "reasonably anticipated to be human carcinogens," originally assigned in the Second Report, to "known to be human carcinogens." NTP should not change the classification for beryllium and beryllium compounds as these

substances do not meet NTP's criterion for classification as "known to be human carcinogens." That classification requires sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

The proposed reclassification of beryllium and beryllium compounds (referred to hereinafter as "beryllium" for brevity) rests primarily on two studies of beryllium workers (Steenland and Ward 1991 and Ward et al. 1992).[1] The results of these studies and their significant limitations preclude them from constituting "sufficient evidence of carcinogenicity in humans."

Both studies evaluated overlapping sets of workers at seven plants. However, their findings of excess cancers are attributable almost exclusively to a single plant, located in Lorain, Ohio. Steenland and Ward (1991) concluded there was increased lung cancer among the members of the Beryllium Case Registry. The authors concluded that persons with acute beryllium disease were at greater risk of lung cancer than those with chronic beryllium disease. As pointed out by Eisenbud (1993), all 17 of the lung cancer cases with acute beryllium disease had been employed at one plant (Lorain), while none of the 90 persons with acute beryllium disease from other plants had lung tumors (145 persons from Lorain were listed with acute beryllium disease). Comparison of smoking among beryllium workers to the general population rates did not include an assessment of the smoking status of any of the workers at the Lorain plant (MacMahon, 1994). This study indicates that workers at the Lorain plant may have had an increased incidence of lung cancer; however, the cause cannot be ascribed to beryllium rather than sulfuric acid mist, smoking or a combination (Eisenbud et al., 1997).

Ward et al. (1992) analyzed tumor rates among a cohort of more than 9000 males employed for at least 2 days between January 1, 1940 and December 31, 1969 at any of seven beryllium processing plants. Survival was ascertained through December 31, 1988. They calculated a lung cancer SMR of 1.26 (95% CI = 1.13-1.42) without any adjustment for smoking effects. After adjusting for smoking by an indirect method (Axelson and Steenland, 1988), there was no significant increase in lung tumor rates, SMR = 1.12; 95% CI = 0.99-1.26). Of the seven plants, only two had SMRs above 1 (Reading 1.09, 95% CI = 0.91-1.31 and Lorain 1.49, 95% CI = 1.13-1.93) and the SMR was statistically significantly increased only in the Lorain plant after adjusting for smoking effects. IARC (1993) concluded that this study supported beryllium as the cause of lung cancer in the workers because the greatest risk was among those with the greatest

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[1] In addition to citing Steenland and Ward (1991) and Ward (1992) as supporting the classification as known to be human carcinogens, the Draft Report also cites "supporting animal data (IARC 1993; Finch et al. 1996)." Animal data, however, cannot replace human data in satisfyng the "known to be human carcinogens" criteria. NTP's own clarification of this criteria states:

> The "known human carcinogen" category requires evidence from studies of Humans. This can include traditional cancer epidemiology studies, data from Clinical studies, and/or data derived from the study of tissues from humans Exposed to the substance in question, and useful for evaluating whether a Relevant cancer mechanism is operating in people.

Hence, animal studies cannot elevate a substance to the level of a "known to be human carcinogen." Animal data are relevant as to the criterion for "reasonably anticipated to be human carcinogens."

potential exposure; those hired before the 1950s, those with acute beryllium disease, those in the Beryllium Case Registry, and because the highest risk occurred among those in the plant with the greatest proportion of pneumonitis. Ward et al. (1992) reported that the SMR was greatest (1.42) for workers first employed before 1950 when exposures were the highest and cites this as evidence of beryllium as the causative agent. This increase is largely due to lung cancer among workers at the Lorain plant which burned and was closed in 1949 (MacMahon, 1994). It should be noted that for workers first exposed since 1960, there is a significant deficit in lung cancer incidence (SMR = 0.62, CI = 0.36-0.95, MacMahon, 1994).

Excess Cancers Have Not Been Consistently Found in the Populations Studied

As part of its beryllium classification rationale, the Draft Report states: "An association with lung cancer has been consistently observed in several populations, with an excess risk of 1.2 to 1.6." This statement is not true, as shown by the population studied by Ward et al. (1992). Of the seven plants, only three had an SMR of 1.2. These data also show to be incorrect a similar statement, which is made on page 39 of the Draft Report, that the reported increases in cancer risk "have been observed consistently in most locations studied."

Excess Cancers Are Largely Attributed to the Lorain Plant
Where There Was Exposure to Sulfuric Acid Mist

As noted in the Draft Report, workers at the Lorain plant were exposed to sulfuric acid mists, and sulfuric acid has been designated as a human carcinogen by IARC. Indeed, NTP itself has also proposed to designate sulfuric acid as a known human carcinogen. The Draft Report attempts to dismiss the confounding effect of sulfuric acid mist in two ways. First, it argues that "excess" lung cancer was also observed in facilities that did not employ the sulfuric acid process, citing Ward et al. (1997) and Wagoner (1980). This argument is flawed because, if the Lorain study is ignored, only two of the seven plants in Ward et al. indicates "excess" lung cancer, and that that excess is not statistically significant. The same is true of the Wagoner (1980) study which showed no statistically significant excess after adjusting for smoking, as noted by EPA (1987), Health Assessment Document for Beryllium at 2-7, Office of health and Environmental Assessment, Environmental Criteria and Assessment Office, EPA 600/8-84-026F.

Equally unpersuasive is the other argument which is made by the Draft Report to dismiss the confounding effect of sulfuric acid mist exposure at Lorain, which is that "the evidence supporting a relationship to lung cancer is weak" (p. 39). This statement may be true, but the reasoning is not, because the fact is that the evidence of a relationship between beryllium and lung cancer is equally weak. Steenland and Beaumont (1989) reported on SMR of 1.5 (95% confidence interval of 1.05-2.27) for lung cancer, after adjusting for smoking, in a cohort of 1,165 steelworkers exposed to sulfuric acid mists. Steenland, K., Beaumont, J. 1989. Further follow-up and adjustment for smoking in a study of lung cancer and acid mists. Am. J. Med. 16:347:354. This SMR of 1.5 for sulfuric acid is almost identical to the adjusted SMR of 1.49 that Ward et al. (1992) reported for Lorain. In light of this sulfuric acid data, lung cancers at Lorain can be as readily attributable to sulfuric acid mists as beryllium dust.[2]

[2] If one believes these SMRs as sufficiently indicative of cancer, the process and circumstances of the Lorain plant, not just the beryllium exposure, should be identified as the carcinogenic agent.

The Studies Inadequately Adjusted for Smoking

The Draft Report dismisses as "speculative" the views of MacMahon (1994) and BISAC (1997) that smoking accounts for the excess cancers reported by Ward et al. (1992) and Steenland and Ward (1991), because "no evidence has been presented to indicate that the prevalence of smoking in any of the exposed cohorts was substantially greater than in the referent population" (p. 38). This statement is not true. Ward et al. (1992) presents evidence that the exposed cohorts did smoke at a substantially greater rate than in the referent population.

In Ward et al. (1992), it is assumed that smoking rates among the workers are similar to those obtained from a limited survey of workers at some of these plants in 1968 or to US rates, which are taken from two surveys, one in 1965 and one in 1970. The assumption that 1968 survey results for a few plants can be applied to all for those working much earlier in the 1940s and 1950s is questionable. The first Surgeon General's report on smoking was issued in 1965; hence, survey results obtained after that date likely reflect some reduction in smoking motivated by the report. Hence, the 1968 survey and the 1965 and 1970 US rates likely underestimate the prevalence of smoking by workers during the 1940s and 1950s.

As noted, Ward et al. (1992) used a 1968 study to estimate the likely effects of smoking for the beryllium plant workers. Use of other studies would have given alternative results. We used the results of a study of US veterans. (Kahn, The Dorn study of smoking and mortality among U.S. veterans; report on 8 _ years of observation. In: Haenzel W ed. *Epidemiological Approaches to the study of Cancer and Other Chronic Diseases*: National Cancer Institute Monograph 9. Bethesda Maryland: U.S. Department of Health Education and Welfare 1966: 1-25.) the results are given in Table 1. They show only the Lorain plant having an SMR that is statistically significant from one. We note that for several plants the best estimate for the SMR is less than one, suggesting that the lung cancer rate among workers at these plants is less than that of a comparable population. Overall the results indicate that the SMR for lung cancer is not statistically significant from one; hence, one cannot reject scientifically the hypothesis that there is no difference in lung cancer rates between the workers in these plants and comparable populations unexposed to beryllium.

Table 1. Standard Mortality Ratios for Malignant Neoplasms
Of the Traches, Bronchus, and Lung Adjusted for Smoking
Using Two Sets of Lung Cancer Risk Factors

SMR's (95% CI) for Malignant Noeplasms of the
Trachea, Bronchus, and Lung

Plant	**Unadjusted SMR**	**SMR Adjusted for Smoking Using ACS Risk Factors**	**SMR Adjusted for Smoking Using U.S. Veterans Risk Factors**
1. Lorain	1.69 (1.28-2.19)	1.50 (1.08-1.98)	1.46 (1.05-1.88)

2. Reading	1.24 (1.03-1.48)	1.10 (0.87-1.35)	1.07 (0.84-1.30)
3. Luckey	0.82 (0.37-1.56)	0.73 (0.26-1.39)	0.71 (0.24-1.18)
4. Cleveland	1.08 (0.78-1.45)	0.96 (0.66-1.31)	0.94 (0.64-1.23)
5. Elmore	0.99 (0.55-1.63)	0.88 (0.43-1.46)	0.86 (0.41-1.30)
6. Hazelton	1.39 (0.74-2.38)	1.24 (0.56-2.12)	1.20 (0.54-2.07)
7. Multiple	1.67 (0.89-2.86)	1.49 (0.67-2.55)	1.45 (0.65-2.48)
8. Unknown	1.33 (0.61-2.42)	1.18 (0.42-2.25)	1.15 (0.40-2.19)
9. Total	1.26 (1.12-1.42)	1.12 (0.94-1.31)	1.09 (0.91-1.28)

There is further evidence that the workers in Ward et al. (1992) had a greater rate of smoking than the referent population. The paper used two referent populations to calculate the expected rates of lung cancer, lung cancer rates of the US population and those of the counties in which the plants were located.

The paper acknowledges that most of the workers lived in cities in the counties in which the facilities with the highest rates of lung cancer are reported, Lorain and Reading. Yet these counties are largely rural. It is also acknowledged that lung cancer rates are higher in urban areas than in rural areas. See Weinberg et al. 1982 Am. J. Epidemiol 115:40-58. Hence, use of the county data by Ward et al. likely biases the results in favor of finding larger SMRs for the workers in those plants who largely lived in counties.

We correct this deficiency by using the respiratory cancer rates for the cities rather than the counties that the Lorain and Reading plants are located. These rates are clearly more appropriate than those used in the study. Use of these rates results in dramatic reductions in the SMRs for these two facilities. (See Table 2.) The SMR for Lorain drops from 1.69 or 1.60 when US or county rates are used to 1.14 when city rates are used. This number is not statistically significant from unity and does not allow one scientifically to reject the hypothesis that the number of lung cancers among workers at the Lorain plant is any different from a similar demographic group. The Reading SMRs are reduced similarly, from 1.24 or 1.42 (based upon US or county rates) to 1.07 based upon city rates. This estimated SMR is also not statistically significant from unity.

Table 2. Standard Mortality Ratios (SMRs) for Malignant Neoplasms Of the Traches, Bronchus, and Lung for Workers in Lorain And Reading Plants 1950-88 Using U.S. Death Rates (1950-88), County Rates (1950-1983), and City Rates (1950, 1960, and 1970) for Comparison

Deaths from Malignant Neoplasms of the Trachea, Bronchus, and Lung

Plant Location	**Observed**	**SMR Based on U.S. Rates (95% CI)**	**SMR Based on County Rates (95% CI)**	**SMR Based on City Rates (95% CI)**
Lorain	57	1.69 (1.20-2.26)	1.60 (1.15-2.16)	1.14 (0.87-1.48)
Reading	120	1.24 (1.03-1.48)	1.42 (1.23-1.86)	1.07 (0.89-1.28)

The Draft Report Improperly Classifies Many Beryllium Compounds For Which No Human Data Exist

Based on the few studies of beryllium manufacturing workers, the Draft Report improperly assigns to all beryllium compounds, both manmade and natural, the same cancer classification. Although the Draft Report lists 20 different compounds, there are no human studies for exposure to most of them. NTP should not classify beryllium compounds as carcinogens for which it has no data.