SUPPLEMENTAL COMMENTS OF BRUSH WELLMAN INC.

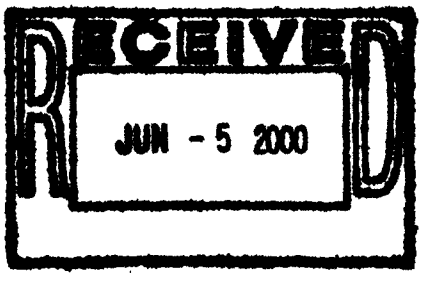
ON THE NATIONAL TOXICOLOGY BOARD OF SCIENTIFIC COUNSELORS

JANUARY 20, 2000 REVIEW AND RECOMMENDATION

REGARDING THE APPROPRIATE CLASSIFICATION OF

BERYLLIUM AND BERYLLIUM COMPOUNDS

June 5, 2000



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On January 20, 2000 the NTP Board of Scientific Counselors accepted the NTP staff recommendation that beryllium and beryllium compounds be classified as a *known human carcinogen.* In large part this decision was based on data presented in the Ward et al. paper reporting an association between exposure to beryllium and lung cancer in six beryllium production facilities. Close examination of the analysis results in the Ward et al. paper, however, indicate that it fails to support the NTP's recommendation because:

- The adjustment for smoking in the Ward et al. paper was not properly performed.
- Ward et al. compared cancer rates in the beryllium facilities to national and county rates and did not take into account the more relevant rates such as city rates.
- The Ward et al. analysis did not consider differences among the plants such as location and years of operation.

These points are demonstrated in the enclosed paper by Levy et al. which is currently going through the peer review process (Attachment A). This paper further demonstrates that correcting for the above factors would show that there is no excess lung cancer deaths among beryllium workers. In the comments below, we address each of the above issues.

Adjusting for smoking alone explains virtually all the excess lung cancers in the Ward et al. study

Members of the Board did not believe that excess lung cancers observed among beryllium workers could be explained by smoking, as indicated by the following comments:

- "...these data indicated that the cohort actually smoked less than the general population, so confounding would not be an issue here." -- Dr Kamel (p. 58, lines 16-18)
- "Smoking did not eliminate the excess risk, particularly at Lorain.....if you look at the subgroups that are high,...smoking is very unlikely to explain the subgroup results that are that high." -- Dr. Zahm (p. 122, lines 4-5, 17-20).

Kamel's comment that it is unlikely that smoking could explain the excess risk because the plant workers actually smoked less than the general population does not take into account that the plant workers had higher rates of *heavy smoking* than the general population. All responsible investigators – Wagoner et al., Ward et al., Levy et al., McMahon, Steenland et al. -- who have analyzed these data have recognized and adjusted for this pattern.

For the following reasons the conclusions of Dr. Zahm are unfounded.

1. Even based on the crude data in the Ward et al. paper, there was no statistically excess risk of lung cancer in four of the six plants studied.
2. After adjusting for smoking, there was no excess risk of lung cancer even in Reading (see attached Levy et al. paper, Table 3). Based on the ACS data, the smoking adjusted rate in Reading is 1.10 with the 95% confidence limits ranging from 0.87 to 1.35; based on the U.S. Veterans Study the rate is 1.07 (0.84 to 1.30).
3. After adjusting for smoking, the combined rate for all plants is far from being significant. Using the ACS data the combined rate for all plants is 1.12 (0.94 to 1.31); using the U.S. Veterans rate is 1.09 (0.91 to 1.28).
4. After adjusting for smoking, three of six plants had SMRs below one (Luckey, Cleveland, and Elmore) – signifying that plant workers had lower lung cancer rates than the general population -- and three had SMRs above one which is exactly what one would expect to find if there is no beryllium effect.
5. Our smoking findings discussed above which are based on the Levy paper are confirmed by a proper analysis of the results in the Ward paper. With respect to the crude data, like Levy et al., Ward et al. reported no lung cancer excess in four of six plants and after adjusting for smoking, no excess in five of six plants. The smoking adjusted result for the Reading plant can be derived from the data in Table XIV of the Ward et al. paper. It can be shown that the odds ratio for Reading is 1.10, with confidence limits 0.90 to 1.29.
6. After the statistical uncertainty associated with Ward's adjustments for smoking is taken into account, even the SMR in Lorain is likely to be insignificant. Ward adjusted for smoking by taking the product of the unadjusted expected values and 1.13, a factor first calculated by Wagoner et al. ("Beryllium: An Etiologic Agent in the Induction of Lung Cancer, Nonneoplastic Respiratory Disease, and Heart Disease among Industrially Exposed Workers", Environmental Research, Vol. 21, pp. 15-34, 1980). The problem is that the 1.13 factor in itself is a statistic that is subject to error. Adjusting for a single multiplier alone in the Ward analysis might indicate that the cancer mortality rates for every plant are far from being statistically significant.

It can be clearly seen from the above that unlike the conclusions drawn by the NTP Board, a proper analysis of the data would show that smoking alone explains virtually all the excess lung cancer deaths.

Choice of a more representative referent population for adjusting lung cancer rates explains virtually all the excess lung cancers in the Ward et al. study

Ward et al.'s use of the county as a referent population is inappropriate, based on data in the paper itself. According to Ward et al. (pages 897-8), 89% of the Lorain plant workers resided in the city, but only 26% of the referent county population actually came from the city. Thus county rates, which reflect a more rural population, are a poor adjustment for city rates (i.e. the location where most of the plant workers resided).

Table 2 of Levy et al. shows the SMRs for the Lorain plant using the city rate. We can see that using the city as the more appropriate referent population to adjust the rate results in having a statistically insignificant SMR even for Lorain (1.14, 0.87 to 1.48). Using the city/county population distributions (89% city and 11% county) also generates an insignificant SMR (1.19, 0.93 to 1.46). [0.89*1.14+0.11*1.60=1.19]

Thus, adjusting for referent population alone shows that the Lorain plant did not have an excess risk of lung cancer deaths.

The data for the cohort as a whole was incorrectly pooled:

By simply pooling data, Ward et al's methodology for combining the data from different plants is incorrect (see Fleiss, Statistical Methods for Rates and Proportions, 1973, Wiley Publication, Section 10.6. *Methods to be Avoided*, pp. 119-124, which includes a discussion of the problems that arise out of using simple summation techniques such as the one used by Ward et al. to combine data from different studies). The correct method for combining is "meta-analysis" which is the method used by Levy et al. (see Table 4).

In addition, it was incorrect for Ward et al. to combine the data from the six plants without considering, at least qualitatively, differences between plants such as: methods of processing the ore (e.g. Lorain was the only plant that used sulfuric acid to extract beryllium); the year the plant operated; the size of the production facility, etc. These factors might provide plausible explanations of why lung cancer rates differed from plant to plant.

Ward et al.'s overall summary of the data was based on faulty statistics.

This submission provides the scientific data to support the following conclusions.

- Crude data show four of six plants with no excess risk.
- A proper summation of the SMR's for the six plants results in no excess risk.
- Correcting for smoking alone results in no excess risk for five and possibly all six plants.

- Correcting the referent population using the more appropriate city data by itself results in no excess risk in any individual plant.
- Correcting for both smoking and the referent population results in no excess risk of lung cancer in any individual plant.

We believe the scientific data does not meet the criteria to support a change in the classification of beryllium and beryllium compounds to a *known human carcinogen.* We encourage the NTP Board of Scientific Counselors to reevaluate their recommendation in light of the above scientific facts.

BERYLLIUM AND LUNG CANCER: A REVIEW AND META-ANALYSIS OF THE NIOSH COHORT MORTALITY STUDY

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BERYLLIUM AND LUNG CANCER: A REVIEW AND META-ANALYSIS OF THE NIOSH COHORT MORTALITY STUDY

ABSTRACT

This report is motivated by recent reviews on the carcinogenicity of beryllium by the International Agency for Research on Cancer, the U.S. Environmental Protection Agency, and the American Conference of Governmental Industrial Hygienists, and reconsideration by the National Toxicology Program on its classification of the carcinogenicity of beryllium. It reanalyzes data from a 1992 publication of a cohort mortality study conducted by the National Institute of Occupational Safety and Health (NIOSH) of workers employed in seven plants producing beryllium in the United States (Ward, E., Okun, A. et al. *American Journal of Industrial Medicine,* 1992; 22:885-904). That publication reported an increased risk of lung cancer in these workers and concluded that it is most likely due to occupational exposure to beryllium compounds. This present report uses: 1) an adjustment for smoking based on more germane estimates of the association between smoking and mortality from lung cancer; 2) computations of expected lung cancer rates based on more relevant comparison populations; and 3) an overall combined estimate of the findings from the individual plants based on meta-analysis. Our findings indicate lower and generally not statistically significant standard mortality ratios that we consider not compatible with the interpretation in the original report of a likely causal association.

I. INTRODUCTION

The National Toxicology Program is considering, as part of its forthcoming Tenth Report on Carcinogens, a change in its classification for beryllium compounds from "reasonably anticipated to be human carcinogens" to "known human carcinogens" [1]. This proposal comes in the wake of recent reviews of the carcinogenicity classification of beryllium by the International Agency for Research in Cancer (IARC)[2], the Environmental Protection Agency (EPA)[3] , and the American Conference of Governmental Industrial Hygienists (ACGIH)[4]. In light of the ongoing regulatory attention to the carcinogenicity of beryllium in humans, an analysis of the published studies on these subjects is both warranted and timely.

While there have been epidemiological studies of cancer in workers employed in the atomic energy production industry and exposed to beryllium along with other putative risk factors[5-7], the major epidemiological information concerning carcinogenicity in humans comes primarily from several published studies of workers at one or more of the seven plants in the United States that have been involved in the production of beryllium[8-14]. As suggested in a review by McMahon[15], these studies represent three separate but overlapping cohorts distinguished primarily by cohort formation methods. The studies conducted by Mancuso[8-10] involved two of the seven plants and defined the cohort on the basis of Social Security earnings reports. The National Institute of Occupational Safety and Health (NIOSH) used plant records to assemble their cohort of workers with their first report including one plant[11], and their most recent report including data from all seven plants[12]. NIOSH also reviewed the Beryllium Case Registry (BCR) which consisted of data on workers with a diagnosis of beryllium related acute or chronic non-neoplastic respiratory disease[13-14]. Based on the earlier studies available at that

time, IARC[16] evaluated the evidence for carcinogenicity in humans as "limited", and EPA[17] evaluated the evidence as "inadequate."

More recently, NIOSH expanded its original cohort of workers described in the earlier report by Wagoner et al.[11] to include workers from all seven beryllium production plants, and updated mortality follow-up to 1988. Based on analysis of mortality data from this expanded cohort, the NIOSH investigators have concluded, "occupational exposure to beryllium compounds is the most plausible explanation for the increased risk of lung cancer observed in this study"[12].

This most recent NIOSH study now represents the largest cohort mortality study of the risk of cancer among workers in the beryllium industry. While the study was generally well designed and well executed, there are problems in the data analysis that forms the basis for the NIOSH conclusion regarding beryllium's causal effect. Our re-analysis of these data indicates that it overestimates the significance of the lung cancer results at the seven plants by failing to account properly for background lung cancer rates in the areas of worker residence. In addition, the publication overestimates the pooled SMR by its use of simple summation to combine the individual plant SMR's. This simple summation implicitly assumes that the worker populations were the same at each plant, and does not utilize the fact that the plants differed with respect to years of operation, location, and other vital factors. Finally, the smoking adjustment used in the publication is based on an estimate of the smoking-lung cancer relationship derived from a population that is perhaps not the most relevant to the population of workers under study.

In this report, we present and interpret findings from a reanalysis that uses what we feel are more appropriate adjustments for smoking and geographic location of worker residences to

obtain improved estimates of the individual plant standard mortality ratios (SMRs). Then, in order to synthesize these plant results, we use meta-analysis methods to pool the individual SMRs into an overall SMR.

II. METHODS

A. The NIOSH Study Design

We will summarize below the main features of the NIOSH study design that are relevant to our subsequent reanalysis. For full details, the reader should consult the original publication.

- This is a mortality study on a population of 9,225 males who worked at least two days between January 1, 1940 and December 31, 1969 at one or more of the seven U.S. plants involved in the production of beryllium and its compounds.
- The vital status of all workers in the cohort was ascertained as of December 31, 1988. Thus, each member of the cohort could contribute a maximum of 49 person-years of observation. Death certificates were requested for all decedents from state vital statistics offices and were coded according to the ICD revision in effect at the time of death.
- The modified life table analysis program (MLTAS) developed by NIOSH[18] was used to estimate standard mortality ratios for the entire cohort as well as for each individual plant. (Two plants located in the Cleveland, Ohio area were owned by the same company and were grouped together in the plant-specific analyses because they kept joint records. Persons working at multiple plants were placed in a separate group for purposes of the site-specific analyses.)

- Two sets of SMRs were presented: one was based on expected values generated from U.S. total and cause-specific death rates for the years of the study, and the other was based on mortality rates that occurred in the counties in which the study plants were located.
- A procedure developed by Axelson and Steenland[19] was used to adjust the lung cancer mortality ratios for confounding due to differences between the smoking habits of the cohort and those of the U.S. population. The adjustment uses data on: 1) the smoking habits of the study population, obtained from a 1968 medical survey conducted by the U.S. Public Health Service in four of the plants representing approximately 16% of the study population; 2) the smoking habits of the U.S. population as a whole, obtained from surveys conducted in 1965 by the National Center for Health Statistics (NCHS)[20], and in 1970 by the Office of Health Research, Statistics, and Technology (OHRST)[21]; and 3) the estimated risk of lung cancer attributable to various smoking categories from a 1966 study by the American Cancer Society (ACS).[22]
- Other than starting and ending dates of employment, there were no occupational history data available. Thus, duration of employment was used as a surrogate for degree of exposure.
- In order to derive overall SMRs for the cohort as a whole, the NIOSH investigators summed the numbers of observed deaths for all plants, and did the same with the expected numbers of deaths. The ratio of these two sums was presented as the estimated SMR for the total cohort.

B. Methods Used in this Reanalysis

1. Estimation of Individual Plant SMRs

Primarily two issues that we raise below with respect to the NIOSH analyses motivate the methods used in the reanalysis of the individual plant data.

The first issue involves the populations used to generate the expected numbers of lung cancer cases to which the observed numbers are compared. The authors present two sets of SMRs, with one set using expected numbers based on U.S. lung cancer rates, and the other using expected numbers based on relevant county-specific lung cancer rates. The second analysis using local county rates was intended to provide a comparison more refined to the study population. The county rates used, however, reflect predominantly rural areas, whereas the bulk of the workers lived in urban areas. Since lung cancer rates are generally higher in urban than in rural areas, the use of county-specific rates probably understates the expected number of cases and results in falsely inflated SMRs.

In this report we calculate correction factors for the plants located in Lorain, Ohio, and Reading, Pennsylvania to adjust for the high background lung cancer rates in these two cities, in which two plants and most of their workers resided. They are derived using U.S. age-specific lung cancer mortality rates among white males for the years 1950, 1960, and 1970[23] as the standard, along with U.S. Decennial Census age-specific population data for the two cities[24], and numbers of lung cancer deaths for white males in those cities for those years (special tabulations provided by the Ohio and Pennsylvania Health Departments). The correction factor for each plant is the ratio of the number of respiratory cancer cases in its host city that is expected on the basis of U.S. rates to the number actually observed. Finally, a "corrected" respiratory cancer SMR is obtained for each of the two plants by multiplying the SMR obtained in the NIOSH report by the appropriate correction factor.

The second issue involves several problems with the adjustment for smoking used in the article. The NIOSH adjustment relies on smoking risk factor estimates obtained from the study conducted by the ACS[22]. There have been, however, several other major smoking studies,

including an update of the ACS study itself, which indicate a higher risk of lung cancer due to smoking than that from the study used. Because the limited smoking data indicate that smoking rates among the workers were higher than in the U.S. population as a whole, use of the 1966 ACS study results in an underestimate of the smoking effect.

In this report we compute for each of the plants a smoking-adjusted SMR for lung cancer that utilizes smoking risk estimates from the major study of smoking and lung cancer in U.S. veterans[25]. We also perform an adjustment based on the risk estimates used by NIOSH. In addition, we will note two other major uncertainties in the smoking adjustment which we were not able to address quantitatively. First, the smoking data on the beryllium workers do not adequately represent the cohort. Second, there appear to have been several important computational errors made in combining the survey and risk estimate data for the adjustment.

2. Estimation of Pooled SMRs for the Entire Cohort

The method used by the NIOSH investigators to estimate the lung cancer SMR for the cohort as a whole was simply to sum the numbers of deaths among workers at each plant, and compare this to the sum of corresponding expected deaths. This procedure treats the data as if it were all derived from the same population, in this case from workers at the same plant in the same time frame. This approach does not take into appropriate consideration differences among the plants with respect to location, years of operation, and several other features.

Here we apply two separate meta-analysis models which are designed to combine results on the same endpoint observed among different populations (see Hedges and Olkin[26] for more complete discussions of these models). In essence, these methods acknowledge that the populations studied were different by not combining results at an individual worker level.

Instead, the combined estimate is obtained by pooling the SMRs found in each individual plant. In each case, the weight given to the SMR from a particular plant is inversely related to its estimated variance; greater weight is thus given to the SMRs based on larger populations which would naturally have smaller variance.

III. RESULTS

A. NIOSH Findings

The findings of the individual plant analyses for lung cancer are shown in Table 1. Of the seven plants studied (with the two Cleveland plants grouped together), only the plants located in Lorain, Ohio and Reading, Pennsylvania had significantly elevated SMRs. The remaining four yielded SMRs ranging from 0.82 to 1.39. In the comparisons based on county rather than U.S. rates, the Reading and Lorain plants again showed significantly high SMRs, while the others did not. After the NIOSH adjustment for smoking, only the Lorain plant showed a significantly elevated lung cancer rate.

Shown in the last row of Table 1 are the NIOSH results for the entire cohort. There was a total of 280 deaths from malignant neoplasms of the trachea, lung, and bronchus among the workers in the total study cohort. Comparison of this number to the sum of expected deaths, based on U.S. rates, at the seven plants yielded a crude SMR of 1.26 ($p < 0.01$). When the numbers of expected deaths were adjusted to reflect the smoking factor derived by NIOSH, however, the resulting SMR was a lower and statistically not significant 1.12.

B. Reanalysis Findings

1. Adjustment for Comparison Populations Used (Lorain and Reading)

The correction factors for the cities of Lorain, Ohio, and Reading, Pennsylvania (representing the ratio of the number of trachea, bronchus, and lung cancer deaths expected on the basis of age-specific U.S. rates to the number actually observed) were 0.676 and 0.861, respectively. (The referent population adjusted rate is the product of either of these two factors and the crude rate.) The effect of incorporating these corrections on the SMRs presented in the NIOSH publication is shown in Table 2. For the cohort in the Lorain plant, the SMR calculated in the NIOSH publication is 1.69 based on U.S. rates with 95% confidence interval not overlapping unity. However, when corrected for city rates, the SMR is a much smaller 1.14 with 95% confidence interval from 0.87-1.48 and overlapping unity. Similarly, for workers employed in the Reading plant, the SMR of 1.24 (95% CI: 1.03-1.48) based on U.S. rates is reduced to a smaller and statistically not significant 1.07 (95% CI: 0.89-1.28) when the correction is made for rates in the city of Reading. In other words, neither the Lorain plant nor the Reading plant respiratory cancer rate was significantly elevated when compared to the rates in the cities in which most of the workers lived.

2. Adjustment for Smoking

The effects of the smoking adjustments on the SMRs for cancer of the trachea, bronchus, and lung are shown in Table 3. These adjustments were made using the methodology described above. We found a correction factor for smoking of 1.124 based on the ACS risk estimates and a correction factor of 1.154 based on the U.S. Veterans Study. (The smoking adjusted SMR is the quotient of the crude SMR and either of these two factors.) As shown in Table 3, no matter which correction factor is used, the smoking-adjusted 95% confidence interval for each plant

other than the one in Lorain, Ohio overlaps unity. In other words, only the Lorain plant showed a significant increase in respiratory cancer after the smoking adjustment.

3. Meta-analysis Results

The overall SMRs derived for the cohort as a whole by the NIOSH summation method and by the two meta-analysis models are shown in Table 4. The first column presents results derived by the simple summation method. With the exception of our smoking-adjusted SMRs (rows 3 and 4), the results in the first column were those reported by the NIOSH investigators. Accordingly, the significance of results is as reported in the NIOSH report -- the overall crude SMRs based on either the U.S. or relevant county lung cancer rates are statistically significant, whereas the reported NIOSH adjustment for smoking resulted in a nonsignificant overall SMR.

Shown in the next two columns are the analogous pooled SMRs derived by respectively using the fixed-effects and random-effects meta-analysis models. It can be seen that the point estimates of pooled SMRs are virtually the same from the two models, although the confidence bands are slightly wider in the random-effects model results. This reflects the assumption that the true underlying SMRs at the individual plants are not necessarily the same. The chi-square tests for homogeneity are not significant, indicating that either model may be appropriately used.

Comparison of the results from these meta-analysis models to those from the summation method does reveal differences in the estimated SMRs. For example, the crude SMR reported by the NIOSH investigators was 1.26, with 95% confidence interval 1.12 to 1.42. On the other hand, both the fixed- and random-effects meta-analysis models yield a lower crude SMR estimate of 1.22, with confidence intervals closer to but not overlapping unity.

A similar pattern is seen in comparing both the smoking-adjusted and the county-adjusted SMRs -- the meta-analysis models yield overall SMR estimates which are somewhat closer to unity than those derived by summation. The practical interpretation is that the simple summation method assigns undue weight to the plants with the largest numbers of observed deaths. While the meta-analysis models also give greater consideration to such plants, the relative weights are appropriately based on the variability of the estimated SMRs.

In summary, the meta-analysis indicated that the summation method used by NIOSH produced overestimates of the pooled SMRs. Because our adjustment for city lung cancer rates was performed for only the Reading and Lorain plants, we did not synthesize our results by meta-analysis. Given that both of these plants showed nonsignificant SMRs after this adjustment, it seems clear that the overall NIOSH result using the county data is particularly inflated.

IV. DISCUSSION

Interpretation of the findings from this cohort mortality study with respect to occupational exposure to beryllium and incidence of respiratory cancer is difficult. Empirically, the SMRs presented in the NIOSH publication (those based on U.S. or county rates) are small, with the highest being 1.69 (for the Lorain, Ohio plant). Only two of the seven plants (Lorain, Ohio and Reading, Pennsylvania) showed 95% confidence intervals not overlapping unity.

When the respiratory cancer rates for the cohort of employees in these two plants are compared to relevant city rates rather than the less relevant county or U.S. rates, the resulting SMRs are dramatically reduced (from 1.69 to 1.14 for the Lorain plant, and from 1.24 to 1.07 for the Reading plant) with neither 95% confidence interval overlapping unity. This sizeable

reduction indicates that residents of both cities had higher risks than the U.S. population as a whole. This decrease does not reflect any further adjustment that might be made for smoking.

In any study having lung cancer as an endpoint, adjustment for smoking is crucial since it is an overwhelmingly dominant risk factor. Based on the prevalence of smoking found in the 1968 survey of some workers, and on smoking-lung cancer risk estimates used in the NIOSH smoking adjustment, our attributable risk computations indicate that 87%, or 244 of the 280 lung cancer deaths among the cohort, might be attributable to smoking. This leaves only 36 projected lung cancer deaths attributable to other factors. This alone would make any finding of an association that does not include direct assessment of the smoking status of the cohort tenuous at best.

In contrast, the attempt to correct for smoking status used both in the NIOSH publication and in our reanalysis is indirect, and is based on a relatively small survey taken in 1968 which does not reflect the smoking status of vital portions of the cohort. Examined at face value, the SMRs adjusted for smoking using the risk factors reported in the U.S. Veterans Study are somewhat lower than those presented in the NIOSH publication. In both instances, only the smoking-adjusted SMR for the Lorain plant remains significantly elevated.

There are at least two additional major uncertainties in the smoking adjustment in the NIOSH publication for which we were not able to correct. First, the smoking data in the cohort were from a 1968 survey representing 16% of the cohort and covering only four of the seven plants. Most notably not in the survey was Lorain, the only plant that showed significantly elevated lung cancer rates after adjustment. Viewed another way, also not well represented in the survey were workers hired prior to 1960 (among which group 93% of all lung cancer cases occurred).

A second major uncertainty is that there appear to be errors in the combining of survey and risk factor data. For example, it is not clear how the investigators combined the U.S. smoking data from 1965 and 1970, particularly since the smoking categories in the two studies were not the same. It seems, however, that the methodology had some inconsistencies. For example, according to the data used by NIOSH for 1965, 39.4% of the white male population smoked fewer than 20 cigarettes per day. According to the document cited by NIOSH, however, only 39.1% (14.8% + 24.3%) smoked fewer than 24 cigarettes per day. The two figures are clearly incompatible.

Finally, it is questionable whether the SMRs for the cohort as a whole are properly derived by simply summing the observed and expected deaths and computing the ratio. The implicit assumption of combining the individual plant SMRs by this procedure is that the workers from the seven plants constituted one population. Because the plants operated during different time periods and in different locations, this seems to be a dubious assumption. Lack of plant-specific smoking data casts further doubt in this regard.

Meta-analysis models have been developed for the purpose of combining results on the same endpoint among different populations. We have applied both fixed-effects and random-effects meta-analysis models to the results from the individual plants; these models appropriately give greater consideration to those results with smaller variance. Both of our meta-analysis models yielded overall SMRs which are even closer to unity than those presented in the NIOSH report.

In summary, the NIOSH investigators report statistically significant crude SMRs which could be attributable to a host of factors. These SMRs are low, and there is no evidence at all of a dose-response relationship. Moreover, if there is an association between beryllium exposure

and lung cancer, it exists only at the mega-levels of exposure present in the plants up until the early 1950's. Only two of the seven plants studied showed significantly elevated crude SMRs for lung cancer, and our reanalysis showed that the rates in these two plants were not higher than the rates in the communities in which these workers lived. Similarly, even indirect adjustments for smoking based on limited data reduced the significance of findings, with only one plant still showing significantly elevated rates. Finally, proper synthesis of the plant SMRs by meta-analysis resulted in pooled SMRs smaller than those reported by NIOSH.

The NIOSH publication, in spite of acknowledging several of the shortcomings in their adjustments for plant location and smoking, still interprets these findings as supportive of the ability of beryllium to induce lung cancer in humans. Our reanalysis of these same data using more appropriate methods of statistical adjustment for smoking and background cancer rates as well as more appropriate methods of synthesizing these data into a combined estimate casts considerable doubt on any such interpretation. Our analyses have shown that the existence of any statistical association at all between beryllium exposure in these workers and lung cancer is at best extremely fragile and does not support the strong extrapolations made in the NIOSH publication.

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TABLE 4. Estimated standard mortality ratios and 95% confidence intervals for the total NIOSH cohort by meta-analysis

SMR Data	Synthesis Method: Addition*	Fixed Effects	Random Effects	Homogeneity
Crude	1.26 (1.12, 1.42)	1.22 (1.08, 1.37)	1.22 (1.07, 1.38)	X27 = 9.36
Smoking-adjusted:				
NIOSH	1.12 (0.99, 1.25)	1.08 (0.95, 1.21)	1.08 (0.94, 1.22)	X27 = 9.41
Reanalysis†	1.12 (0.94, 1.31)	1.09 (0.96, 1.22)	1.09 (0.95, 1.23)	X27 = 9.31
Reanalysis††	1.09 (0.91, 1.28)	1.05 (0.93, 1.19)	1.06 (0.93, 1.19)	X27 = 9.37
NIOSH County-Adjusted	1.32 (1.19, 1.46)	1.27 (1.12, 1.43)	1.26 (1.06, 1.46)	X25 = 8.95

* This was the method used by NIOSH.

† Incorporating lung cancer risk factors from (22)

†† Incorporating lung cancer risk factors from (25)