Inhalation Toxicology, 14:1003–1015, 2002

0895–8378/02 $12.00 + .00
DOI: 10.1080/08958370290084755

Taylor&Francis
healthsciences

BERYLLIUM AND LUNG CANCER: A REANALYSIS OF A NIOSH COHORT MORTALITY STUDY

Paul S. Levy

Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, Illinois, USA

H. Daniel Roth, Peggy May T. Hwang, Timothy E. Powers

Roth Associates, Inc., Rockville, Maryland, USA

This analysis 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 et al., 1992). 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 alternative 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 are not compatible with the interpretation of a likely causal association.

The National Toxicology Program has recommended, 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" (http://ntp-server.niehs.nih.gov/NewHomeRoc/10thConsideration.html). This proposal comes in the wake of recent reviews of the carcinogenicity classification of beryllium by the International Agency for Research in Cancer (IARC, 1993), the U.S. Environmental Protection Agency (U.S. EPA, 1998), and the American Conference of Governmental Industrial Hygienists (ACGIH, 1992). 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.

Animal studies on the relationship between exposure to beryllium and occurrence of lung cancer have been performed in both rats and mice. In

Received 31 January 2002; sent for revision 8 March 2002; revision received 27 March 2002; accepted 2 April 2002.

This article was supported by Brush Wellman, Inc., and NGK Metals.

Address correspondence to Dr. H. Daniel Roth, Roth Associates, Inc., 6115 Executive Boulevard, Rockville, MD 20852, USA. E-mail: n_roth@worldnet.att.net

one study on rats, approximately 64% of the animals exposed to varying burdens of beryllium metal through inhalation developed lung cancer (Finch et al., 1996). In mice studies, however, the results are considerably more ambiguous. Perhaps most important is that it is difficult to extrapolate from these animal data to humans given the difference in pulmonary anatomy between humans and rodents.

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 (Loomis & Wolf, 1996; Wing et al., 1993; Rooney et al., 1993), 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 (Mancuso & El Attar, 1969; Mancuso, 1970, 1980; Wagoner et al., 1980; Ward et al., 1992; Infante et al., 1980; Steenland & Ward, 1991). As suggested in a review by McMahon (1991), these studies represent three separate but overlapping cohorts distinguished primarily by cohort formation methods. The studies conducted by Mancuso (Mancuso & Attar, 1969; Mancuso, 1970, 1980) 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 its cohort of workers with its first report, including one plant (Wagoner et al., 1980), and its most recent report including data from all seven plants (Ward et al., 1992). NIOSH also reviewed the Beryllium Case Registry (BCR), which consisted of data on workers with a diagnosis of beryllium related acute or chronic nonneoplastic respiratory disease (Infante et al., 1980; Steenland & Ward, 1991).

Based on analysis of mortality data from the expanded cohort used in their later study (Ward et al., 1992) which updated mortality up to 1988, 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."

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 reanalysis of these data indicates that it inflates 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, we consider other populations for the smoking adjustment. Finally, the use of summation to combine individual plant standard mortality ratios (SMRs) oversimplifies the situation by assuming all worker populations were the same at each plant.

In this report, we present and interpret findings from a reanalysis that uses what we feel is a more appropriate adjustment for the geographic

location of worker residences to obtain improved estimates of the individual plant SMRs, and alternatives to the smoking adjustment. Then, in order to synthesize these plant results, we use meta-analysis methods to pool the individual SMRs into an overall SMR.

METHOD

The NIOSH Study Design

We summarize next 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 9225 males who worked at least 2 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 (Steenland et al., 1990) was used to estimate standard mortality ratios for the entire cohort as well as for each individual plant. (Two plants located in the Cleveland, OH, 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 (1988) 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 4 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, 1981), and in 1970 by the Office of Health Research, Statistics, and Technology (OHRST, 1979); and (3) the estimated risk of lung cancer attributable to various smoking categories from a 1966 study by the American Cancer Society (Hammond, 1966).

- 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.

Methods Used in This Reanalysis

Two issues exist with respect to the NIOSH analyses that 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. As stated in the original NIOSH paper (Ward et al., 1992), 89% of the workers in Lorain and 68% of the workers in Reading resided in the city. Of the 32% not living in the city of Reading, a recent review of time cards indicates that a large proportion lived in areas just outside of the city limits that are considered by residents to be a de facto part of the city. 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, OH, and Reading, PA, 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 (U.S. EPA & National Cancer Institute, 1985) as the standard, along with U.S. Decennial Census age-specific population data for the two cities (U.S. Department of Commerce, Bureau of the Census, 1983). Also, numbers of lung cancer deaths for white males in those cities for those years were used (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 (i.e., correction factor = number of respiratory cancer cases expected in city/number 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 (i.e., corrected SMR = crude SMR x correction factor). More details of these adjustments and corrections are discussed in the Results section.

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 (Office of Health Statistics, Research, and Technology, 1979). There have been, however, several other major smoking studies, including a reanalysis of the ACS study itself (Wagoner et al., 1980), which indicate a higher risk of lung cancer due to smoking than that from the study used. Because the smoking data available indicate that smoking rates among the workers were higher than in the U.S. population, particularly for heavy smokers, use of the 1966 ACS study results in an underestimate of the smoking effect.

To examine the range of risk estimates, we applied both the 1966 ACS estimates used by NIOSH as well as the risk estimates of Wagoner et al. We called the former the Ward-ACS estimates and the latter the Wagoner-ACS. Except for rounding error and for the risk for former smokers, the Ward-ACS and the Wagoner-ACS risk estimates are comparable. The Ward-ACS risk estimate for former smokers is obviously incorrect because it is solely based on individuals aged 50–69 and not for smokers on all age groups. (We cannot comment on the Wagoner risk for former smokers because we do not have the data upon which it was derived.) We also compute for each of the plants a broader smoking-adjusted SMR for lung cancer that utilizes smoking risk estimates from the major study of smoking and lung cancer in U.S. veterans (Kahn, 1966). Finally, we will note two other major uncertainties in the smoking adjustment that we were not able to address quantitatively. First, the smoking data on the beryllium workers, which represent only 16% of the workers from four of the plants, do not adequately represent the cohort. Second, Ward et al. appear to have made several important computational errors in combining the survey and risk estimate data for the adjustment. For example, the risk estimates of smoking and smoking status are not for comparable age groups.

In addition, there is an issue with NIOSH's analysis of data pooled from all the plants. 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 they 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 that are designed to combine results on the same endpoint observed among different populations (see Hedges & Olkin, 1985, 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.

RESULTS

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, OH, and Reading, PA, had significantly elevated SMRs. The remaining 4 yielded crude 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 7 plants yielded a crude SMR of 1.26 ($p < .01$). 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.

Reanalysis Findings

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

TABLE 1. Summary of NIOSH plant results on malignant neoplasms of the trachea, bronchus, and lung (respiratory cancer)

Plant	Number of deaths from respiratory cancer	U.S.-compared, smoking unadjusted	County-compared, smoking unadjusted	U.S.-compared, smoking adjusted[a]
Lorain	57	1.69[b]	1.60[b]	1.49[b]
Reading	120	1.24[b]	1.42[b]	1.09
Lucky	9	0.82	0.84	0.72
Cleveland	44	1.08	1.05	0.95
Elmore	15	0.99	1.06	0.87
Hazelton	13	1.39	1.50	1.23
Multiple	13	1.67	—	1.47
Unknown	9	1.33	—	1.17
Total	280	1.26[b]	1.32[b]	1.12

[a]Only the results for the Lorain and Reading plants were reported. The others were computed using the NIOSH smoking adjustment factor.

[b]Statistically significant at .05 level.

TABLE 2. Standard mortality ratios (SMRs) with 95% confidence intervals for respiratory cancer in Lorain and Reading plants, 1950–1988, using U.S. death rates (1950–1988), county rates (1950–1983), and city rates (1950, 1960, and 1970) for comparison

Plant location	Observed deaths	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 (1.28, 2.19)	1.60 (1.21, 2.07)	1.14 (0.86, 1.48)
Reading	120	1.24 (1.03, 1.48)	1.42 (1.18, 1.70)	1.07 (0.89, 1.28)

[a]City SMR = U.S. SMR × relevant correction factor. For Lorain, 1.14 = 1.69 × 0.676, and for Reading, 1.07 = 1.24 × 0.861.

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 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 0.86 to 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.

Thus, correcting for referent population alone indicated that there was no statistically significant excess of lung cancer deaths in Lorain because lung cancer rates in Lorain City far exceeded the national average. Given that Lorain City is a highly industrialized area with air pollution levels that also far exceeded national averages, this is not surprising. Based on U.S. EPA national monitored air quality data in 1979, with regards to sulfate levels, Lorain City was in the upper 10th percentile both in the state of Ohio as well as in the United States. In addition, in the late 1970s and early 1980s, Lorain City was in violation of the National Ambient Air Quality Standard (NAAQS) for daily and average PM levels. In such a polluted area it is not surprising to find elevated levels of lung cancer, and it would be biased not to take this into account when studying the possible effects of any substance on lung cancer rates (see McDonnell et al., 2000; Abbey et al., 1999; Beeson, et al., 1998; and Pope, 1996).

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 already described.

TABLE 3. Standard mortality ratios (SMRs) with 95% confidence intervals for respiratory cancer adjusted for various sets of smoking risk factors

Plant	U.S. rates smoking unadjusted	Smoking adjusted		
		Ward-ACS	Wagoner-ACS[a]	U.S. Veterans[b]
Lorain	1.69 (1.28, 2.19)	1.49 (1.13, 1.93)	1.31 (0.99, 1.70)	1.39 (1.05, 1.79)
Reading	1.24 (1.03, 1.48)	1.10 (0.91, 1.31)	0.96 (0.80, 1.15)	1.02 (0.84, 1.22)
Lucky	0.82 (0.37, 1.56)	0.72 (0.33, 1.37)	0.64 (0.29, 1.21)	0.67 (0.31, 1.28)
Cleveland	1.08 (0.78, 1.45)	0.95 (0.69, 1.28)	0.84 (0.61, 1.12)	0.89 (0.64, 1.19)
Elmore	0.99 (0.55, 1.63)	0.87 (0.49, 1.44)	0.77 (0.43, 1.27)	0.81 (0.45, 1.34)
Hazelton	1.39 (0.74, 2.38)	1.23 (0.65, 2.10)	1.08 (0.57, 1.84)	1.14 (0.61, 1.95)
Multiple	1.67 (0.89, 2.86)	1.47 (0.79, 2.52)	1.29 (0.69, 2.21)	1.37 (0.73, 2.34)
Unknown	1.33 (0.61, 2.52)	1.17 (0.54, 2.23)	1.03 (0.47, 1.96)	1.09 (0.50, 2.07)
Total	1.26 (1.12, 1.42)	1.12 (0.99, 1.26)	0.98 (0.87, 1.10)	1.04 (0.92, 1.17)

[a]Lung cancer risk factors from (Mancuso, 1980); uses the relative risk factors of smoking applied by Wagoner et al. (1980) and the percentage distribution of the population by smoking status given in Ward et al. (1992).

[b]Lung cancer risk factors from (U.S. Department of Commerce, Bureau of the Census, 1983).

The smoking correction factor used by Ward et al. was 1.13. Based on the relative risks used by Wagoner et al. we found the correction factor to be 1.29, and based on the U.S. Veterans study we found the correction factor to be 1.21. (The smoking adjusted SMR is the quotient of the crude SMR and one of these three factors, i.e., 1.13, 1.29 or 1.21.) 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, OH, overlaps unity. Furthermore, using the Wagoner correction factor, the confidence interval for even the Lorain plant overlaps unity. In other words, only the Lorain plant showed a significant increase in respiratory cancer after certain smoking adjustments.

Meta-Analysis Results While the summation technique used by NIOSH was oversimplistic, in this instance it did not make a substantial difference when individual plant results were more properly combined using meta-analysis. In addition to the summation model used by NIOSH, we applied both fixed effects and random effects meta-analysis models to the

smoking adjusted data. This generated nine separate results (three smoking adjustments—Ward-ACS, Wagoner-ACS, and U.S. Veterans Study—by three models—NIOSH summation, fixed model, and random model). Eight of these nine scenarios generated statistically insignificant results. (The only exception was applying the fixed model to the Ward-ACS adjustment.) Also, all of the three scenarios (summation, fixed, and random) using the city-adjusted rates for Lorain and Reading were statistically insignificant. Thus under any reasonable adjustment for smoking or referent population, when the data from all plants are aggregated, there is little evidence of statistically significant elevated SMRs in the plants.

DISCUSSION AND CONCLUSIONS

This article is a reanalysis of a very large cohort mortality study that included nearly all of the plants in the United States that manufactured beryllium and covered a period of nearly 50 years. Its major objective was to characterize the nature of the relationship between occupational exposure to beryllium and occurrence of lung cancer.

In both the original article and in our reanalysis of it, duration of employment was used as a surrogate for exposure to beryllium. Recently, a NIOSH investigator constructed an exposure matrix for the Reading plant, which furnishes 42.9% of the lung cancer cases and 40% of the person years at risk (pyar) (Sanderson et al., 2001). Reasons given for not including exposure data from the other six plants were either the paucity of lung cancer cases or inadequacies in the work history or industrial hygiene data from those plants. It is apparent from our examination of data from that article that there are very few exposure measurements available from the Reading plant before 1970, whereas the bulk of the person-years at risk of exposure for the members of the cohort from this plant occurred prior to 1970. Also, there is possibly serious overestimation of exposures owing to the fact that most of the measurements reflect the presence of nonrespirable particles. When personal sampling results were examined against the estimate of exposure derived from the exposure index, it was found that the exposure index accounted for only 24% of the variability in the personal sampling results. These and other problems inherent in the available exposure data pose serious threats to the validity and reliability of this index. Thus, duration of employment currently remains the best method to characterize exposure.

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, OH, plant). Only 2 of the 7 plants (Lorain, OH, and Reading, PA) 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 both 95% confidence intervals overlapping unity. This sizeable reduction is a result of the fact that residents of both cities had higher respiratory cancer rates than the U.S. population as a whole. This high risk for respiratory cancer might reflect the high air pollution levels in the two cities (Page & Asire, 1985). Lorain City is in the upper 10th percentile of polluted areas in the United States, based on 1979 ambient sulfate values (Storage and Retrieval of Aerometric Data, SAROAD, U.S. EPA).

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 85%, or 237 of the 280 lung cancer deaths among the cohort, might be attributable to smoking. This leaves only 43 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 that 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 both the Wagoner et al. paper and the U.S. Veterans Study are somewhat lower than those presented in the NIOSH publication. In both the NIOSH study and our reanalysis based on estimates from the U.S. Veterans Study, only the smoking-adjusted SMR for the Lorain plant remains significantly elevated. When the correction factor based on Wagoner et al. is applied, even the Lorain plant has a statistically insignificant smoking-adjusted SMR.

There are at least two major problems with the smoking adjustment in the NIOSH publication that 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 4 of the 7 plants. Most notably, Lorain was not in the survey, and it is the only plant that in some analyses showed significantly elevated lung cancer rates after adjustment. Viewed another way, workers hired prior to 1960 (the group in which 93% of all lung cancer cases occurred) were not well represented in the survey.

A second major problem is that there appear to be errors in the NIOSH calculation of the factor used to adjust for smoking. In part, this factor was calculated by using the 1968 survey of beryllium workers and the 1965 and 1970 surveys of the general U.S. population to compare the smoking habits of the beryllium workers and the U.S. population. A problem is that the target population in the 1965 survey was aged 20+ yr; in the 1968 survey it was undefined; and in the 1970 survey it was 17+ yr. Also, in the 1965 and 1970 surveys, a heavy smoker was defined as a person who smoked 25+

cigarettes/day, as compared to 20+ cigarettes/day in the 1968 survey. Thus there were incompatibilities in the smoking data used to compare the two populations that could not be corrected because of the form in which the data were collected. For the same reason data in some of our adjustments are also incompatible.

Another key component in the calculation of the NIOSH smoking factor was the lung cancer risk associated with different levels of smoking status (e.g., nonsmokers, former smokers, light smokers, and heavy smokers). For never and current smokers, the risks were estimated based on a population 35–84 yr of age as compared to 50–69 yr of age for former smokers. In addition, it appears that the risk data altogether were unadjusted for age. Furthermore, in many instances, the risk data were applied to the wrong category of data on smoking habits. For instance, NIOSH applied the risk estimate of 20+ cigarettes/day to smoking data on 25+ cigarettes/day. Also, the risk data were based on a population aged 35–84 yr while the smoking data were based on populations aged 17 or 20 yr and above. In other words, the smoking data and risk data in the NIOSH analysis were incompatible with one another.

Compounding the problems just listed, the NIOSH analysis did not take into consideration that its factor for smoking adjustment has statistical variability in its own right. Correcting for this variability alone, if anything, would reduce the significance of any statistical association found between beryllium and lung cancer SMRs. Unfortunately, the data needed for computing the statistical variability of the smoking factor are not available.

Moreover, NIOSH incorrectly combined the data from the different plants without taking into account the difference in the location, time period, or manner of operation of these plants. This, however, made little difference in the result which is that under any reasonable adjustment, there is no statistically significant elevated risk of lung cancer in the plants.

Finally, in the NIOSH analysis, no adjustments were made that simultaneously corrected both for the referent population and for smoking. Results found after correcting for only smoking or only the referent population are thus subject to further adjustment. Unfortunately, the data necessary to make the simultaneous adjustment, that is, the degree of dependence between the referent population and smoking, are not available.

In summary, the NIOSH investigators report two of seven plants with statistically significant crude SMRs that could be attributable to a host of factors. These SMRs are low, and no evidence is presented of a dose-response relationship to beryllium. If there is an association between beryllium exposure and lung cancer, it exists only at the mega-levels of exposure present in the two oldest plants up until the early 1950s. Although our reanalysis of the seven plants studied sometimes showed significantly elevated crude SMRs for lung cancer at the two oldest plants, it 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 and abolished the significance of the findings, with only one plant in some instances still showing significantly elevated rates. The NIOSH publication acknowledged several shortcomings in their adjustments for plant location and smoking. Our reanalysis of these same data confirm the shortcomings in their adjustments, casting considerable doubt on their interpretation of beryllium exposure as "the most plausible explanation for the increased risk of lung cancer observed" in their study (Ward et al., 1992). Our analyses have shown that there is no statistical association between beryllium exposure in these workers and lung cancer when using the most appropriate population cancer rates. There is, at best, an extremely fragile association when the data are corrected for smoking.

REFERENCES

Abbey, D. E., Nishino, N., McDonnell, W. F., Burchette, R. J., Knutsen, S. F., Lawrence Beeson, W., and Yang, J. X. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am. J. Respir. Crit. Care Med.* 159(2):373–382.

American Conference of Governmental Industrial Hygienists. 1992. *1992–1993 Threshold limit values for chemical substances and physical agents and biological exposure indices,* p. 13. Cincinnati, OH: ACGIH.

Axelson, O., and Steenland, K. 1988. Indirect methods of assessing the health effects of tobacco use in occupational studies. *Am. J. Ind. Med.* 13:105–108.

Beeson, W.L ., Abbey, D. E., and Knutsen, S. F. 1998. Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: Results from the AHSMOG study. *Environ. Health Perspect.* 106(12):813–823.

Finch, G. L., Hoover, M. D., Hahn, F. F., Nikula, K. J., Belinsky, S. A., Haley, P. J., and Griffith, W. C. 1996. Animal models of beryllium-induced lung disease. *Environ. Health Perspect.* 104(suppl. S): 973–979.

Hammond, E. C. 1966. Smoking in relation to the death rates of one million men and women. In *Epidemiological approaches to the study of cancer and other chronic diseases,* ed. W. Haenszel, National Cancer Institute Monograph 19, pp. 127–204. Bethesda, MD: U.S. Department of Health Education and Welfare.

Hedges, L. V., and Olkin, I. 1985. *Statistical methods for meta-analysis.* Orlando, FL: Academic Press.

Infante, P. F., Wagoner, J. K., and Sprine, N. L. 1980. Mortality patterns from lung cancer and non-neoplastic respiratory disease among white males in the Beryllium Case Registry. *Environ. Res.* 21:35–43.

International Agency for Research on Cancer. 1993. Beryllium, cadmium, mercury, and exposures in the glass. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 58:41–117.

Kahn, H. A. 1966. The Dorn study of smoking and mortality among U.S. veterans; Report on 8½ years of observation. In *Epidemiological approaches to the study of cancer and other chronic diseases,* ed. W. Haenszel, National Cancer Institute monograph 19, pp. 1–125. Bethesda, MD: U.S. Department of Health, Education, and Welfare.

Loomis, D. P., and Wolf, S. H. 1996. Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947–1990. *Am. J. Ind. Med.* 29:131–141.

Mancuso, T. F. 1970. Relation of duration of employment and prior respiratory illness to respiratory cancer among beryllium workers. *Environ. Res.* 3:251–275.

Mancuso, T. F. 1980. Mortality study of beryllium industry workers' occupational lung cancer. *Environ. Res.* 21:48–55.

Mancuso, T. F., and El Attar, A. A. 1969. Epidemiological study of the beryllium industry: Cohort methodology and mortality studies. *J. Occup. Med.* 11:422–434.

McDonnell, W. F., Nishino-Ishikawa, N., Petersen, F. F., Chen, L. H., and Abbey, D. E. 2000.

Relationships of mortality with the fine and coarse fractions of long-term ambient PM10 concentrations in nonsmokers. *J. Expos. Anal. Environ. Epidemiol.* 10(5):427–436.

McMahon, B. 1991. Assessment of human carcinogenicity. In *Beryllium: Biomedical and environmental aspects,* eds. M. D. Rossman, O. P. Preuss, and M. P. Powers, pp. 97–100. Baltimore, MD: Williams & Wilkins.

National Center for Health Statistics. 1981. *Health-United States 1981.* DHHS Publication No. (PHS) 82–1232, pp. 151–154, National Center for Health Statistics, Maryland.

Office of Health Statistics, Research, and Technology. 1979. Changes in cigarette smoking and current smoking practices among adults: United States. *Advance Data* 52:1–4.

Page, H. S., and Asire, A. J. 1985. *Cancer rates and risks.* NIH Publication No. 85-691.

Pope, C. A. 3rd. 1996. Particulate pollution and health: a review of the Utah valley experience. *J. Expos. Anal. Environ. Epidemiol.* 6(1):23–34.

Rooney, C., Beral, V., Maconochie, N., Fraser, P., and Davies, G. 1993. Case-control study of prostatic cancer in employees of the United Kingdom Atomic Energy Authority. *Br. Med. J.* 307:1391–1398.

Sanderson, W. T., Petersen, M. R., and Ward, E. M. 2001. Estimating historical exposures of workers in a beryllium manufacturing plant. *Am. J. Ind. Med.* 39:145–157.

Steenland, K., and Ward, E. 1991. Lung cancer among beryllium disease patients: A cohort mortality study. *JNCI* 83:1380–1385.

Steenland, K., Beaumont, J., Spaeth, S., Brown, D., Okun, A., Jurcenko, L., Ryan, B., Phillips, S., Roscoe, R., Stayner, L., and Morris, J. 1990. New developments in the life table analysis system of the National Institute of Occupational Safety and Health. *J. Occup. Med.* 32:1091–1098.

U.S. Department of Commerce, Bureau of the Census. 1983. *County and city data book: A statistical abstract supplement,* 10th ed.

U.S. Environmental Protection Agency. 1998. Beryllium and compounds. IRIS Substance File, April 3.

U.S. Environmental Protection Agency and National Cancer Institute. 1985. *U.S. cancer mortality rates and trends.* EPA 600/1:1950-1979 83-015b. Washington, DC: U.S. EPA.

Wagoner, J. K., Infante, P. F., and Bayliss, D. L. 1980. Beryllium: An etiologic agent in the induction of lung cancer, non-neoplastic respiratory disease, and heart disease among industrially exposed workers. *Environ. Res.* 21:15–34.

Ward, E., Okun, A., Ruder, A., Fingerhut, M., and Steenland, K. 1992. A mortality study of workers at seven beryllium processing plants. *Am. J. Ind. Med.* 22:885–904.

Wing, S., Shy, C. M., Wood, J. L., Wolf, S., Cragle, D. L., Tankersley, W., and Frome, E. 1993. Job factors, radiation and cancer mortality at Oak Ridge National Laboratory: Follow-up through 1984. *Am. J. Ind. Med.* 23:265–279.