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Beryllium: An Etiologic Agent in the Induction of Lung Cancer, Nonneoplastic Respiratory Disease, and Heart Disease among Industrially Exposed Workers

JOSEPH K. WAGONER,* PETER F. INFANTE,† AND DAVID L. BAYLISS‡

*Offices of the Assistant Secretary and †Carcinogen Identification and Classification, Occupational Safety and Health Administration, Department of Labor, Washington, D.C. 20210, and ‡Industry-wide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226

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On the basis of the clear demonstration of the carcinogenicity of beryllium in several animal species along with the suggestion of an increased risk of lung cancer mortality in humans exposed to beryllium, an epidemiologic study of workers exposed to beryllium at one production facility was undertaken. Within the limitations imposed by the selection of data for calculation of cause-specific expected mortality (use of U.S. white male cause-specific mortality rates with linear extrapolation of 1965–1967 to 1968–1975 vs use of cause-specific mortality rates for the county in which the study facility and the majority of its workers resided), the study demonstrated a statistically significant increased risk of respiratory disease (neoplastic and nonneoplastic) and of heart disease mortality. A possible explanation other than in terms of beryllium was sought for this excessive risk of cause-specific mortality among beryllium-exposed workers. The excessive risk of lung cancer mortality could not be related to an effect of age, chance, self-selection, study group selection, exposure to other agents in the study facility, or place of residence. On the basis of the frequency of cigarette smoking among those cohort members employed in 1967–1968 and the distribution of histologic types of lung cancer among deceased cohort members, it seems unlikely that cigarette smoking per se could have accounted for the increased risk of lung cancer among beryllium-exposed workers in the study cohort. Lifetime employment histories for members of the study cohort were not available, so that definitive statements about the role of other occupational exposures cannot be made. However, information on usual occupations as indicated on death certificates suggests that it is unlikely that some undefined occupational or environmental exposure other than to beryllium could account per se for the excessive lung cancer mortality. This interpretation is further supported by the residential stability of the study cohort in a county having a lung cancer rate significantly lower than that of the entire United States. The findings of a statistically significant excess of lung cancer mortality among cohort members in general ($P < 0.05$) and among workers observed 25 or more years since onset of beryllium exposure in particular ($P < 0.01$), when taken in context with the results of earlier animal bioassay and recent epidemiologic studies, are supportive of the hypothesis that beryllium is carcinogenic to man.

INTRODUCTION

Probably no compounds known to man give so consistent a carcinogenic response in so many animal species as do the compounds of beryllium (NIOSH, 1977). Numerous studies repeatedly have shown the compounds of beryllium to be carcinogenic by several routes of administration (Araki *et al.*, 1954; Barnes, 1950; Barnes *et al.*, 1950; Cloudman *et al.*, 1949; Dutra and Largent, 1950; Dutra *et al.*, 1951; Gardner and Heslington, 1946; Groth *et al.*, 1980; Hoagland *et al.*, 1950; Janes *et al.*, 1954; Kelly *et al.*, 1961; Komitowski, 1967; Reeves *et al.*, 1967;

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Schepers, 1964; Schepers *et al.*, 1957; Tapp, 1969; Vorwald, 1950, 1953, 1968; Vorwald and Reeves, 1959; Vorwald *et al.*, 1966; Wagner *et al.*, 1969; Yamaguchi, 1963). As indicated in Table 1, reports of experimental studies demonstrating the pulmonary carcinogenicity of beryllium compounds likewise are numerous.

On the basis of one limited experimental study (Groth *et al.*, 1980) some have suggested that beryllium copper alloy is not carcinogenic. However, a review of the study design indicates several limitations for a valid assessment of carcinogenicity, i.e., insufficient dosage, inadequate sample size, incomplete histopathologic evaluation, and low animal survival rate (D. H. Groth, personal communication).

In humans, evidence clearly demonstrates the presence of beryllium related nonneoplastic respiratory diseases (Hardy, 1965; Hasan and Kazemi, 1973, 1974) and their cardiac sequelae (Andrews *et al.*, 1969) among workers employed in industries producing and using beryllium and its compounds. Cases of berylliosis also have been identified among individuals living near these industrial facilities (Hardy, 1965; Hasan and Kazemi, 1974).

TABLE 1
EXPERIMENTAL PULMONARY CARCINOGENICITY OF BERYLLIUM ACCORDING TO ANIMAL SPECIES, COMPOUNDS OF BERYLLIUM AND ROUTES OF ADMINISTRATION

Species	Compounds of beryllium[a]	Routes of administration	Author (year)
Rat	$BeSO_4$	Inhalation	Vorwald, 1953
	$BeSO_4$	Inhalation	Schepers *et al.*, 1957
	$BeSO_4$	Inhalation	Vorwald and Reeves, 1959
	$BeSO_4$	Inhalation	Vorwald *et al.*, 1966
	$BeSO_4$	Inhalation	Reeves *et al.*, 1967
	$BeSO_4$	Inhalation	Vorwald, 1968
	$BeSO_4$	Inhalation	Vorwald and Reeves, 1959
	Beryl ore dust	Inhalation	Wagner *et al.*, 1969
	$BeSO_4$	Intratracheal injection	Vorwald and Reeves, 1959
	BeO	Intratracheal injection	Vorwald and Reeves, 1959
	$Be(OH)_2$	Intratracheal injection	Groth *et al.*, 1979
Monkey	$BeSO_4$	Inhalation	Vorwald *et al.*, 1966
	$BeHPO_4$	Inhalation	Schepers, 1964
	BeO	Intrabronchial injection and/or bronchomural implantation	Vorwald *et al.*, 1966

[a] $BeSO_4$, beryllium sulfate; BeO, beryllium oxide; $BeHPO_4$, beryllium phosphate; $Be(OH)_2$, beryllium hydroxide.

In contrast to the demonstration of beryllium's carcinogenicity in experimental animals, data bearing on the carcinogenicity of beryllium in humans have been less clear. In a review of the United States Beryllium Case Registry data in 1967, Hardy *et al.* reported that there was no evidence to support beryllium as a human carcinogen. However, recognizing major deficiencies in the existing Registry data and the analyses undertaken for the evaluation of carcinogenic risk among Registry enrollees, the authors urged the study of workers employed in the beryllium industry.

In 1969, Mancuso and El-Attar reported, as part of a methodologic development of the Social Security Administration (SSA) data source for the conduct of long-term follow-up investigations, that the study of individuals employed at two beryllium production facilities as undertaken did not permit a valid assessment of the carcinogenicity of beryllium. Recognizing limitations in the study design, the authors expressed the need to update the study of beryllium workers after a longer period of observation (latency). An additional limiting factor of that study was the use of rubber workers as a comparison group. Rubber workers themselves recently have been shown to be at an increased risk of cancer, including lung cancer (Andjelkovic *et al.*, 1976; Fox and Collier, 1976; Monson and Nakano, 1976).

In 1970, Mancuso further reported on the role of beryllium-induced bronchitis and pneumonitis as an etiologic factor in the increased risk of lung cancer among beryllium-exposed workers. In this study, among 142 cases of beryllium-related bronchitis and pneumonitis identified during 1940–1948, Mancuso (1970) reported that six deaths due to lung cancer subsequently occurred, for an age-adjusted lung cancer mortality rate of 284.3 per 100,000 population. This rate when contrasted with 77.7 for all white males employed in the same beryllium production facility during 1937–1948, led the author to conclude "prior chemical respiratory illness influences the subsequent development of lung cancer among beryllium workers."

A study by Bayliss and Lainhart in 1972 suggested that workers employed at two beryllium production facilities were at an increased risk of lung cancer, though this excess was not statistically significant. The authors concluded "it cannot be said that mortality patterns in this population are significantly increased especially with respect to lung cancer from 1942 through 1967." The design and methodology of that study, however, have been considered inadequate to evaluate the true risk of cancer among beryllium-exposed workers (Bridbord *et al.*, 1975; Infante and Wagoner, 1975). By definition, the study cohort provided little opportunity to scientifically assess the potential carcinogenicity of beryllium at 20 or more years since onset of exposure, that time period previously shown in studies of other agents to be associated with a relatively greater sensitivity for the detection of an occupational cancer risk (Hammond *et al.*, 1976; IARC, 1977; Nicholson, 1976). Furthermore, the study group consisted not only of workers directly engaged in the production of beryllium but also of individuals engaged in off-site sales activities.

More recently, Hasan and Kazemi (1974) reported findings suggestive of an increased risk of death due to lung cancer among 53 males who were entered into the Beryllium Case Registry since 1965 with a diagnosis of beryllium disease. Although the authors indicated that beryllium was one of the factors responsible in

the development of lung cancer in beryllium workers, they felt that the small population at risk and the short follow-up period limited the extent of interpretation.

This clear and consistent demonstration of the carcinogenicity of beryllium in several animal species along with the suggestive, but not clearly demonstrable increased risk of lung cancer among humans exposed to beryllium, prompted an investigation of the long-term mortality patterns (neoplastic and nonneoplastic) among workers occupationally exposed to beryllium.

METHODS AND MATERIALS

Selected for study was one major beryllium extraction, processing, and fabrication facility located in Pennsylvania. Study was restricted to this beryllium production facility as other facilities in the United States either had been in operation for too limited a time period or could give no assurance that employment records had been maintained in such a manner (Bayliss, 1977) to permit a valid assessment of the potential carcinogenicity of beryllium to man. Initially, "all" employees who terminated from the study facility sometime during the period of January 1, 1942 through December 31, 1967 had been reported by management to have been identified through a search of available employment files and to have been submitted to the U.S. Public Health Service. During 1968, as part of a medical survey at the study facility, employment histories of current employees were obtained. After excluding all non-white employees, all female employees and all male employees either not directly engaged in the extraction, processing, or fabrication of beryllium or in on-site administrative, maintenance, and support activities, the final study cohort consisted of 3055 white males who were employed sometime during the period, January 1, 1942 through September, 1968. The exclusion from analyses of individuals in these three categories was based on two factors: (1) the low potential for beryllium exposure for individuals whose prime employment was off-site; and (2) the existence of disease differentials by race and sex in combination with the lack of statistical sensitivity for the detection of risk factors based upon analyses of small-sized groups.

For some individuals, exact dates of birth, last employment, or death were not indicated on the company employment records. In 1976, correspondence from the company whose facility was under study indicated intentional and unintentional destruction of employment records since the time of initial submission of the data to the U.S. Public Health Service (Butler, 1976). For those few study cohort members with no indication of birthdate, an age of 20 years was assigned on the date of initial employment and for those deceased individuals with missing dates of death, a date was assigned equal to the last date of the study. For those study cohort members (approximately 60) with incomplete employment histories, determination of the approximate date of termination of employment was achieved through matching against quarterly employment data maintained in the files of the Social Security Administration. For a subset of the 60 having only one-quarter of employment on the basis of SSA records, the date of termination was set to the date of initial employment. It should be noted that employment histories were updated only through September 1968 for these approximately 60 individuals so as not to introduce bias by the differential treatment of this subset of the cohort. It

further should be noted that no additional individuals were entered into the study cohort as a result of data from the SSA. In addition, to estimate the degree of completeness of the study cohort, as defined through the use of company-submitted employment records and employment histories obtained during the 1968 medical survey, a stratified systematic sample with a uniform sampling fraction of 1 in 10, was selected from individuals listed on first-quarter SSA earnings reports from 1942 through 1949 (1946 omitted due to illegibility). This sample (346), when matched against the records submitted by management or obtained as a result of the medical survey, indicated than less than 6.6% (23) could not be accounted for. For these 23 individuals, who were randomly distributed by quarters of employment, a determination could not be made concerning the number who would have met the study criteria of being white males engaged in on-site activities. This was so as the SSA data submitted to NIOSH through management did not contain information specific for race, sex, and job category. Table 2 shows the distribution of duration of employment and the median duration of employment according to the calendar time period of initial employment for the 3055 study cohort members, respectively.

Follow-up of all study cohort members was attempted from the time of termination of employment to January 1, 1976, the cut-off date for analyses of these data. Vital status ascertainment was accomplished through records maintained by federal, state, and local governmental agencies including the Social Security Adminstration, the Internal Revenue Service, state vital statistics offices, and state motor vehicle registration files. For those individuals not located through these conventional data sources, other sources such as city directories and contact with friends, relatives, and neighbors were used.

As a result of this follow-up effort, vital status was determined for all but 79 (3%) individuals (Table 3). Death certificates were obtained for those known to be deceased and causes of death were interpreted by a qualified nosologist according to the revision of the International Classification of Diseases in effect at the time of death. These underlying causes of death were subsequently converted to Seventh Revision codes to facilitate computer processing. In addition, those 12 individuals who had been reported deceased but for whom no death certificates

TABLE 2
DISTRIBUTION OF STUDY COHORT MEMBERS ACCORDING TO CALENDAR TIME PERIOD OF INITIAL EMPLOYMENT AND DURATION OF EMPLOYMENT

Calendar time period of initial employment	No. of employees by duration of employment (months)						Total No.	Medium duration of employment (months)
	<1	1–5	6–11	12–35	36–59	≥60		
1930–1939	0	0	0	7	9	47	63	118.0
1940–1949	469	658	266	298	90	224	2005	3.9
1950–1959	118	137	64	107	38	221	685	14.5
≥1960	22	53	27	115	52	33	302	20.1
All time periods	609	848	357	527	189	525	3055	7.2

TABLE 3
VITAL STATUS AS OF DECEMBER 31, 1975 AMONG WHITE MALES EMPLOYED IN A BERYLLIUM PRODUCTION FACILITY

Status		
Known to be alive	2101	
Known to be deceased	875	
Known to be deceased in U.S.		875
Death certificates obtained		863
Death certificates outstanding		12
Not known to be alive or deceased	79	
Total	3055	

were obtained were considered as deceased, cause of death undetermined. The 79 individuals whose vital status was not ascertained were considered to be alive, thus leading to an underestimate of any finding of increased cause-specific mortality among the study group (MacMahon and Pugh, 1970).

A modified life-table technique, patterned after the technique of Lundin *et al.* (1971), was used to obtain person-years at risk of dying by 5-year calendar time period, 5-year age group, duration of employment (beryllium exposure), and interval since onset of employment. Because of job mobility within the study facility, analysis was not undertaken specific for job category. Table 4 shows the distribution of person-years at risk of dying according to specific age and calendar time-period groups. Members were initially considered at risk of dying either from January 1, 1942, or from the date of first employment, whichever was later in time. Comparison was made between the observed number of deaths among the study cohort members and that number expected on the basis of age, calendar time period, and cause-specific mortality rates for the general white male population of the United States. As published vital statistics data were not readily available for the period 1968–1975, mortality rates for that calendar time period were assumed to be those of 1965–1967. This assumption would underestimate the expected number of lung cancer deaths among the study cohort when using U.S. rates as a basis for comparison. (For a discussion of how the use of U.S. rates would

TABLE 4
PERSON-YEARS AT RISK OF DYING ACCORDING TO AGE GROUP AND CALENDAR TIME PERIOD AMONG WHITE MALES EMPLOYED SOMETIME DURING JANUARY, 1942–SEPTEMBER, 1968 IN A BERYLLIUM PRODUCTION FACILITY AND FOLLOWING THROUGH 1975

	Calendar time period			
Age group	1942–1949	1950–1959	1960–1975	Total
<30	4,883.09	4,979.16	2,018.07	11,880.32
30–44	3,393.98	10,413.58	15,550.85	29,358.41
45–59	2,420.91	4,440.49	15,048.79	21,910.19
60–74	935.01	2,408.07	4,714.84	8,057.92
≥75	14.49	269.32	1,076.04	1,359.85
Total	11,647.48	22,510.62	38,408.59	72,566.69

overestimate the expected number of lung cancer deaths, see below). Consideration was given only to those 875 deaths among study cohort members occurring within the continental United States, so that comparability was maintained with published vital statistics, the basis upon which expected deaths were generated. Furthermore, in the analyses, study cohort members were considered at risk of death (contributing to person-years and expected deaths) during periods of military service overseas. During that same time period, cohort members dying overseas were not allowed to contribute to observed deaths. Such an analytic procedure would further underestimate the risk of any disease category for members of the study cohort.

On the basis of prior evidence, both in experimental animals and in humans, implicating beryllium in the etiology of respiratory diseases and their cardiac sequelae, a one-tailed test was used for determining statistical significance for neoplastic and nonneoplastic respiratory diseases and heart disease. In the absence of information concerning beryllium in the etiology of other fatal diseases, a two-tailed test was used for determining statistical significance for other cause of death categories. The Poisson distribution was used for testing statistical significance when observed deaths were less than 50, and a χ^2 approximation to the Poisson was used when the observed deaths exceeded 50 (Pearson and Hartley, 1958).

RESULTS

As shown in Table 5, during the period of January 1, 1942, through December 31, 1975, a total of 875 deaths occurred among study cohort members as contrasted with 816.86 expected deaths. The distribution of these deaths was such that the only significant excess of mortality occurred for diseases of the respiratory system and of the heart. The excess of respiratory disease deaths was demonstrated for cancer of the trachea, bronchus, and lung (ICD codes 162 and 163), which will be subsequently referred to as lung cancer (47 observed vs 34.29 expected, $P < 0.05$) and for nonneoplastic respiratory disease, excluding influenza and pneumonia (31 observed vs 18.76 expected, $P < 0.01$). A significant excess of deaths also occurred for heart disease (396 observed vs 349.32 expected, $P < 0.05$).

More detailed analyses of respiratory disease (neoplastic and nonneoplastic) and of heart disease mortality according to time interval since onset of beryllium exposure and duration of employment among workers exposed to beryllium appear in Tables 6, 7, and 8.

As seen in Table 6, an excess of lung cancer deaths occurred among beryllium-exposed workers at each interval 15 or more years since onset of beryllium exposure. This excess of lung cancer deaths was most marked after 25 or more years since onset of beryllium exposure (20 observed vs 10.79 expected, $P < 0.01$) and occurred irrespective of the duration of employment, i.e., 17 vs 9.07, SMR = 187 for those having less than 5 years employment, and 3 vs 1.72, SMR = 174 for those having 5 or more years of employment in the beryllium production industry.

The data in Table 7 show an increased risk of deaths from nonneoplastic respiratory disease (less influenza and pneumonia) at each time interval since onset of exposure. Further inspection of the data shows that the excessive risk of non-

TABLE 5

OBSERVED AND EXPECTED DEATHS ACCORDING TO CAUSE AMONG WHITE MALES EMPLOYED SOMETIME DURING JANUARY, 1942–SEPTEMBER, 1968 IN A BERYLLIUM PRODUCTION FACILITY AND FOLLOWING THROUGH 1975

Cause of death	Code No. (ICD)[a]	Observed	Expected
Malignant neoplasms	140–205	143	136.18
Digestive	150–159	43	45.04
Lung	162–163	47	34.29*
Residual	Residual	53	56.85
Cerebral vascular accident	330–334	60	66.52
Heart disease	400–443	396	349.32*
Nonneoplastic respiratory diseases	470–527	48	39.89
Influenza and pneumonia	480–493	17	21.13
Other respiratory disease	470–479, 500–527	31	18.76**
External causes	800–999	82	84.69
All other causes not indicated above		134	140.26
Unknown causes		12	
All causes		875	816.86

[a] International Classification of Disease, 7th Revision Codes.
* Significant at $P < 0.05$; ** significant at $P < 0.01$.

neoplastic respiratory disease was restricted to those workers having been employed for less than 5 years, the maximum risk being evident 25 or more years after onset of employment (12 observed vs 5.62 expected, $P < 0.05$).

For deaths resulting from heart disease (Table 8), an excessive risk likewise occurred at each time interval since onset of employment; this excessive risk

TABLE 6

OBSERVED AND EXPECTED DEATHS DUE TO LUNG CANCER ACCORDING TO DURATION OF EMPLOYMENT AND TIME SINCE ONSET OF EMPLOYMENT AMONG WHITE MALES EMPLOYED SOMETIME DURING JANUARY, 1942–SEPTEMBER, 1968 IN A BERYLLIUM PRODUCTION FACILITY AND FOLLOWING THROUGH 1975

Interval since onset of employment (years)	Duration of employment (years)[a]					
	<5		≥5		Total	
	Observed	Expected	Observed	Expected	Observed	Expected
<15	8	7.95	1	1.48	9	9.43
15–24	15	11.56	3	2.51	18	14.07
≥25	17	9.07*	3	1.72	20	10.79**
Total	40	28.58*	7	5.71	47	34.29*

[a] Employment histories ascertained only through 1967–1968.
* Significant at $P < 0.05$; ** significant at $P < 0.01$.

TABLE 7

OBSERVED AND EXPECTED DEATHS DUE TO NONNEOPLASTIC RESPIRATORY DISEASE (LESS INFLUENZA AND PNEUMONIA) ACCORDING TO DURATION OF EMPLOYMENT AND TIME INTERVAL SINCE ONSET OF EMPLOYMENT AMONG WHITE MALES EMPLOYED JANUARY, 1942–SEPTEMBER, 1968 IN A BERYLLIUM PRODUCTION FACILITY AND FOLLOWING THROUGH 1975

Interval since onset of employment (years)	Duration of employment (years)[a]					
	<5		≥5		Total	
	Observed	Expected	Observed	Expected	Observed	Expected
<15	6	3.57	1	0.66	7	4.23
15–24	11	6.36	1	1.41	12	7.76
≥25	12	5.62*	0	1.15	12	6.77
Total	29	15.55**	2	3.21	31	18.76*

[a] Employment histories ascertained only through 1967–1968.
* Significant at $P < 0.05$; ** significant at $P < 0.01$.

being significant for the total cohort over all duration of employment categories combined (396 observed vs 349.32 expected, $P < 0.05$). The excess of heart disease deaths was contributed to both by those workers having less than 5 years of employment (318 observed vs 288.92 expected) and those workers having 5 or more years of employment (78 observed vs 60.40 expected).

The methodology for previous studies of the assessment of carcinogenic risk among beryllium-exposed populations has been adjudged deficient for not giving adequate consideration to period of follow-up or latency (Bridbord *et al.*, 1975; Hasan and Kazemi, 1974; Infante and Wagoner, 1975; Mancuso and El-Attar, 1969). To evaluate the impact of this adjudged deficiency, analyses of lung cancer risk among study cohort members were undertaken according to two periods of follow-up, i.e., 1942–1967 and 1942–1975. As shown in Table 9, analyses of lung cancer mortality for the total cohort through 1975 demonstrated a significant

TABLE 8

OBSERVED AND EXPECTED DEATHS DUE TO HEART DISEASE ACCORDING TO DURATION OF EMPLOYMENT AND TIME INTERVAL SINCE ONSET OF EMPLOYMENT AMONG WHITE MALES EMPLOYED SOMETIME DURING JANUARY, 1942–SEPTEMBER, 1968 IN A BERYLLIUM PRODUCTION FACILITY AND FOLLOWING THROUGH 1975

Interval since onset of employment (years)	Duration of employment (years)[a]					
	<5		≥5		Total	
	Observed	Expected	Observed	Expected	Observed	Expected
<15	109	100.00	23	18.01	132	118.23
15–24	124	107.73	37	25.59	161	133.32*
≥25	85	81.19	18	16.80	103	97.99
Total	318	288.92	78	60.40	396	349.32*

[a] Employment histories ascertained only through 1967–1968.
* Significant at $P < 0.05$.

TABLE 9
OBSERVED AND EXPECTED DEATHS DUE TO LUNG CANCER FOR WHITE MALES ACCORDING TO PERIOD OF FOLLOW-UP AND TIME INTERVAL SINCE ONSET OF EMPLOYMENT IN A BERYLLIUM PRODUCTION FACILITY

Interval since onset of employment (years)	Period of follow-up				Difference (1942–1967 vs 1942–1975)	
	1942–1967		1942–1975			
	Observed	Expected	Observed	Expected	Observed	Expected
<15	8	8.58	9	9.43	1	0.85
15–24	13	9.95	18	14.07	5	4.12
≥25	2	0.64	20	10.79**	18	10.15*
Total	23	19.17	47	34.29*	24	15.12*

* Significant at $P < 0.05$; ** significant at $P < 0.01$.

excess of lung cancer (47 observed vs 34.29 expected, $P < 0.05$). Analyses of the identical cohort only through 1967, that time period previously studied by Bayliss and Lainhart (1972), demonstrated an excess of lung cancer which was not statistically significant (23 observed vs 19.17 expected). This difference in lung cancer risk according to period of follow-up can be seen to be a reflection of an excessive risk among those beryllium-exposed workers having achieved 25 or more years since onset of employment (Table 9).

Because of an expressed concern restricted solely to beryllium-induced nonneoplastic respiratory disease, the U.S. Atomic Energy Commission in 1949 recommended that "in-plant atmospheric concentration of beryllium should not exceed 2 micrograms per cubic meter, measured as an average concentration throughout an 8-hour day" (Eisenbud, 1955). Thus, analyses were made of the risk of death due to nonneoplastic respiratory disease (less influenza and pneumonia), heart disease, and lung cancer according to date of initial employment at the beryllium production facility, i.e., either prior to or subsequent to 1950. As shown in Tables 10 and 11, an excess of deaths due to nonneoplastic

TABLE 10
OBSERVED AND EXPECTED DEATHS DUE TO NONNEOPLASTIC RESPIRATORY DISEASE (LESS INFLUENZA AND PNEUMONIA) FOR WHITE MALES ACCORDING TO DATE OF INITIAL EMPLOYMENT AND TIME INTERVAL SINCE ONSET OF EMPLOYMENT IN A BERYLLIUM PRODUCTION FACILITY

Interval since onset of employment (years)	Date of initial employment					
	<1950		≥1950		Total	
	Observed	Expected	Observed	Expected	Observed	Expected
<15	7	3.31	0	0.92	7	4.23
15–24	12	6.67*	0	1.09	12	7.76
≥25	12	6.75*	0	0.02	12	6.77*
Total	31	16.73**	0	2.03	31	18.76**

* Significant at $P < 0.05$; ** significant at $P < 0.01$.

TABLE 11
OBSERVED AND EXPECTED DEATHS DUE TO HEART DISEASE FOR WHITE MALES ACCORDING TO DATE OF INITIAL EMPLOYMENT AND TIME INTERVAL SINCE ONSET OF EMPLOYMENT IN A BERYLLIUM PRODUCTION FACILITY

Interval since onset of employment (years)	Date of initial employment					
	<1950		≥1950		Total	
	Observed	Expected	Observed	Expected	Observed	Expected
<15	109	99.68	23	18.33	132	118.01
15–24	151	116.12	10	17.20	161	133.32*
≥25	103	97.76	0	0.23	103	97.99
Total	363	313.56*	33	35.76	396	349.32*

* Significant at $P < 0.05$.

respiratory disease and to heart disease occurred only among those workers initially employed prior to 1950. In contrast, as shown in Table 12 an excess of deaths due to lung cancer occurred for those individuals initially employed either prior to (SMR = 135) or subsequent to (SMR = 152) 1950. However, this excess of lung cancer was statistically significant only for those individuals initially employed prior to 1950.

This pattern of a reduction in risk due to nonneoplastic respiratory disease and heart disease with no commensurate reduction in relative risk of lung cancer is consistent with observations of secular changes in mortality risk associated with another respirable particulate dust, i.e., asbestos. The study of asbestos workers has demonstrated that as dustiness decreased, deaths from nonneoplastic respiratory disease such as asbestosis declined, whereas, no such decline was noted for lung cancer (Nicholson, 1976).

DISCUSSION

Before assessing the role of occupational exposures in the etiology of the increased risk of lung cancer, nonneoplastic respiratory disease, and heart disease

TABLE 12
OBSERVED AND EXPECTED DEATHS DUE TO LUNG CANCER FOR WHITE MALES ACCORDING TO DATE OF INITIAL EMPLOYMENT AND TIME INTERVAL SINCE ONSET OF EMPLOYMENT IN A BERYLLIUM PRODUCTION FACILITY

Interval since onset of employment (years)	Date of initial employment					
	<1950		≥1950		Total	
	Observed	Expected	Observed	Expected	Observed	Expected
<15	6	7.23	3	2.20	9	9.43
15–24	14	11.70	4	2.37	18	14.07
≥25	20	10.76**	0	0.03	20	10.79**
Total	40	29.69*	7	4.60	47	34.29*

* Significant at $P < 0.05$; ** significant at $P < 0.01$.

among workers exposed to beryllium, the role of nonoccupational factors will be considered.

The finding of an excessive risk of total mortality among beryllium-exposed study cohort members raises the possibility that individuals who choose employment in the beryllium industry may have subclinical disease in general, or may be ill at the time of initial employment. Analyses of mortality patterns according to years since onset of employment in the beryllium industry have shown a deficit of "total mortality" during the first two 5-year time intervals since onset of beryllium exposure (<5 years, 71 observed vs 80.49 expected; 5–9 years, 86 observed vs 102.35 expected). For each subsequent 5-year interval since onset of beryllium exposure, an excess of total mortality was observed. These data are not shown in the Tables.

Furthermore, no cause-specific death category, including lung cancer, nonneoplastic respiratory disease, or heart disease demonstrated a significant excess of deaths during the first two 5-year intervals since onset of employment in the beryllium industry. This pattern of mortality is not consistent with self-selection into the beryllium industry of individuals having overt or subclinical disease in general, or heart or respiratory disease, or lung cancer, specifically. This pattern of excessive cause-specific deaths following several years since onset of employment, however, is highly consistent with the healthy worker effect, i.e., healthy workers either self-select themselves into employment or are selected into the place of employment by management following a preemployment physical indicating no clinically apparent adverse health condition.

With reference to the use of the U.S. white male population as the basis for comparison with beryllium workers, consideration was given to the appropriateness of this choice and its effect on detecting an excess of lung cancer mortality among workers at the study facility. Regional differences in lung cancer mortality have been well documented, (Mason and McKay, 1973). More specifically among white male residents of Berks County, Pennsylvania, the county in which the beryllium production facility under study is located, lung cancer mortality is significantly lower than for white males of the entire United States (Mason and McKay, 1973). The average annual age-adjusted lung cancer rate per 100,000 white male population in Berks County during 1950–1969 was 31.8 as contrasted with 38.0 for United States white males, that population used to generate expected deaths in the study cohort. In support of the use of Berks country rates as a basis for comparison is residential information as obtained by personal interview of 379 study cohort members employed at the study facility during a medical survey conducted by the Public Health Service in 1968. Of these 379 individuals, 86% resided in Berks County of whom 54% resided in Berks County outside the city of Reading, the major urban center in Berks County. In further support of the use of Berks County rates is the observation that 38 of the 47 deaths due to lung cancer in the study cohort were known to reside at the time of death, in Berks County. These two observations, regional differences in lung cancer mortality and residential stability of study cohort members in Berks County, indicate that the risk of lung cancer among study cohort members when contrasted with U.S. white males and as shown in Tables 5 and 6 is underestimated by a factor up to 19%.

The role of cigarette smoking in the etiology of the increased risk of lung cancer among beryllium-exposed workers also should be taken into account (Surgeon General's Advisory Committee, 1964). Detailed cigarette smoking histories had been obtained through the 1968 medical survey. For contrast with these beryllium-exposed workers, use was made of cigarette smoking data obtained from U.S. white males during a 1964–1965 Health Interview Survey conducted by the Public Health Service (National Center for Health Statistics, 1967). Whereas, a lower percentage of beryllium-exposed workers were current cigarette smokers (50.4 vs 54.7%) a higher percentage of current cigarette smokers (21.4 vs 15.3%.) smoked more than one pack of cigarettes daily (Table 13). In contrast, however, a higher percentage of beryllium-exposed workers never smoked cigarettes (27.2 vs 24.7%). An evaluation, using the method of Lundin *et al.* (1969) was made of the possible role of this differential smoking pattern in the etiology of the excessive lung cancer risk among beryllium-exposed workers. Standardized Mortality Ratios of lung cancer by smoking category among U.S. white males in 1958 (Haenszel *et al.*, 1962) were weighted by the percentage distribution of workers according to cigarette usage as shown in Table 13 to give lung cancer indices for the U.S. white males and for workers employed in this beryllium production facility. The distribution of smoking habits among workers at the beryllium production facility under study was of a magnitude to increase the lung cancer risk in the absence of beryllium exposure by 14%. In several instances when the risk of bronchogenic carcinoma has been shown to be increased among occupationally exposed groups of workers, there has been an accompanying shift in the distribution of histologic types of tumors. Knowledge of this distribution of histologic types of bronchogenic cancer has provided supportive evidence for the role of an occupational factor in the etiology of the increased risk of cancer. This has been the case for metal miners, uranium miners, copper smelter workers, vinyl chloride polymerization workers, chloromethyl methyl ether production workers, and mustard gas manufacturers (Newman *et al.* 1976; Lundin *et al.*, 1971; Archer *et al.*, 1974, 1976; Waxweiler *et al.*, 1976; Lemen *et al.*, 1976; Yamada, 1963). Therefore, as part of this investigation of cancer among beryllium-exposed workers, pathology specimens were requested for those 47 study cohort members identified by death certificates as having died from lung cancer. Pathology specimens were received

TABLE 13

PERCENTAGE DISTRIBUTION OF BERYLLIUM-EXPOSED WORKERS AND OF AGE-ADJUSTED U.S. WHITE MALE POPULATION BY CIGARETTE SMOKING STATUS

Cigarette smoking status	Beryllium production workers		U.S. population[a]
	No.	%	(%)
Never smoked	103	27.2	24.7
Former smokers	85	22.4	20.5
Current smokers	191	50.4	54.7
<1 pack of cigarettes daily	110	29.0	39.4
≥1 pack of cigarettes daily	81	21.4	15.3

[a] Data source: National Center for Health Statistics, 1967.

for 27 deaths certified as lung cancer. These pathology specimens were subjected to independent histologic examination and classification according to WHO criteria (Kreyberg, 1967). Twenty-five of 27 lung tumor specimens were verified to be primary bronchogenic carcinoma (Smith and Suzuki, 1980). Of these 25 cases of bronchogenic carcinoma, 8 or 32% were histologically classified as adenocarcinoma. Smith and Suzuki (1980) concluded that the prevalence of histopathologic cell types of bronchogenic carcinomas among beryllium-exposed workers could not be presently defined on the basis of an assumption that the distribution of cell type among missing pathology specimens would possibly be different. The authors reported no valid data to support this assumption. Therefore, further analyses of cell type distribution was made under the assumption of no difference between those with and without lung tissue available for independent pathologic evaluation. The 32% relative frequency of adenocarcinoma for lung cancer among beryllium-exposed workers when contrasted with (a) 15.0% (32/214) for a sample of pathologically verified lung cancer deaths among white males in the United States during 1958 (Haenszel *et al.*, 1962) and (b) 15.7% (3716/23,658)[1] for pathologically diagnosed lung and bronchus cancers among white males in the United States during 1960–1973 (Axtell *et al.*, 1976) is statistically significant at $P < 0.05$. This shift of histologic types of bronchogenic carcinoma toward adenocarcinoma among beryllium-exposed workers is consistent with results of experimental studies showing predominately the induction of adenocarcinoma of the lung following inhalation of beryllium (Groth *et al.*, 1980). This significant shift of histologic types of bronchogenic carcinoma toward adenocarcinoma in the study likewise is not consistent with a cigarette etiology as epidemiological studies have repeatedly shown that small cell undifferentiated and squamous cell carcinoma of the lung are the principal types whose frequency is affected by cigarette smoking (Surgeon General's Advisory Committee, 1964). On the basis of these two observations, i.e., frequency of cigarette smoking and distribution of histologic types of lung cancer, it seems unlikely that cigarette smoking per se could account for the increased risk of lung cancer among beryllium-exposed workers in this study.

The absence of a "dose–response relation" in the present study as measured in terms of duration of employment and lung cancer mortality should be interpreted in context with several study constraints. First, it must be recognized that duration of employment in the absence of detailed beryllium environmental concentrations may not be a valid measure of total beryllium exposure. For example, individuals exposed to high concentrations over a short period of time could have as much or more total lung burden of beryllium as individuals exposed over a long period of time to lower concentrations. In support of this are observations in experimental animals demonstrating the long retention of beryllium in body tissue of experimental animals (Stokinger, 1972) and the induction of pulmonary cancer following a single dose of beryllium (Spencer *et al.*, 1968). Also in support of this are observations in humans demonstrating elevated levels of beryllium in lung tissue more than 20 years following termination of short-term occupational expo-

[1] The number of histologic cases specific for males was estimated using sex ratios multiplied by the number of histologic cases for both sexes combined.

sure to beryllium (Sprince *et al.*, 1976). Second, occupational histories in the present study were ascertained only through 1967–1968, the time period of original submission of employment data by plant management or by workers undergoing medical examinations. At a later date, records in the possession of management were reported to have been destroyed thus preventing an updating of employment histories from 1968 to 1975, the study end date. This truncation of employment histories in 1967–1968 could have obscured an exposure–response relation if in fact several individuals dying from lung cancer had accumulated employment subsequent to 1967–1968. Third, as seen in Table 2, among the total of 3055 individuals comprising the study cohort, only 525 had accumulated 5 or more years of employment. Among those 525 study cohort members, less than half (632 person-years at risk) were observed at 25 or more years since onset of employment, a time period adjudged by the International Agency for Research on Cancer (1977) to be associated with a relatively greater sensitivity for the detection of an occupational cancer risk. On the basis of sample-size considerations alone, a true lung cancer risk as large as fivefold could not have been detected among individuals having this duration of employment-latency classification (Cutler *et al.*, 1954). Thus, in the present study the absence of a dose–response relation in terms of duration of employment can reasonably be viewed as a function of small sample size (IARC, 1977).

Consideration should be given to the possibility that occupational exposures other than beryllium may have played a role in the excessive lung cancer risk demonstrated in the study cohort. The facility selected for study produced beryllium copper alloy by reacting beryllium oxide, carbon, and copper in an electric air furnace. The process yielded a beryllium–copper master alloy of approximately 4% beryllium content. The master alloy was diluted with copper to yield alloys of approximately 2% beryllium content. Beryllium oxide used for this reaction was produced by sintering finely ground beryl ore with sodium fluoride. Leaching of the sintered material yielded a beryllium fluoride solution which was further processed to beryllium oxide. These sintering and leaching questions produced potential exposure to beryllium fluoride mists and fumes. The sodium fluoride sintering process for the production of beryllium oxide terminated in the 1970s when an external source became available. During the period 1968–1972, airborne concentrations of beryllium in the study facility were measured in excess of 2 mg/m^3 and some operations in the study facility were found to exceed 1000 mg/m^3 (Chrostek *et al.*, 1976; Knauber, 1977).

In the study facility, no agent inherent in the beryllium production process other than the compounds of beryllium has been associated with the induction of lung cancer, either in animals or in humans (Tomatis *et al.*, 1978). Whereas, no information was available to evaluate the role of prior employment in the etiology of the excessive lung cancer risk, some information was available for post-beryllium employment. A review of usual employment as stated on the death certificate for the 47 deaths due to lung cancer showed that none were employed in occupations or industries (other than beryllium) having a demonstrated lung cancer risk.

The observed excess of lung cancer, nonneoplastic respiratory disease, and heart disease among study cohort members not having been accounted for by

TABLE 14
FACTORS INFLUENCING ESTIMATE OF EXCESSIVE LUNG CANCER RISK AMONG BERYLLIUM-EXPOSED WORKERS

Factor	Underestimate	Overestimate
Smoking		14%
Regional differences in lung cancer mortality	19%	
Secular changes in mortality rates		X
Treatment of lost to follow-up as alive	X[a]	
Deceased with no death certificates	X	
Healthy worker effect	X	
Analytic treatment of military personnel	X	

[a] X, Magnitude of influence not quantified.

factors other than beryllium (Table 14) must now be evaluated in terms of occupational exposure to beryllium and of the known toxicologic and oncogenic properties of beryllium compounds. The excesses of nonneoplastic respiratory disease and of heart disease in the present study are consistent with earlier observations in humans showing beryllium exposure to be associated with respiratory disease (Hardy, 1965; Hasan and Kazemi, 1973, 1974) and its cardiac sequelae (Andrews *et al.*, 1969).

The excess of lung cancer mortality in the present study is consistent with earlier animal bioassay studies demonstrating beryllium to be a pulmonary carcinogen (Groth *et al.*, 1980). This excess of lung cancer mortality in the present study also is consistent with the suggestive results of earlier epidemiologic studies (Mancuso, 1970; Bayliss and Lainhart, 1972; Hasan and Kazemi, 1974) and the more clearly demonstrable results of recent epidemiologic studies of beryllium-exposed populations (Mancuso, 1980a, b; Infante *et al.*, 1980).

Using data ascertained from the Social Security Administration, Mancuso (1980a) identified workers employed during the period 1942–1948 in one beryllium production facility in Ohio or in a second beryllium production facility in Pennsylvania, this latter facility being the same one investigated in the present study. Among workers in each of these facilities, Mancuso (1980a) demonstrated an increased risk of lung cancer mortality as contrasted with that expected on the basis of rates for U.S. white males. The increased risk of lung cancer mortality for the Pennsylvania facility was of an identical magnitude (SMR = 137 for total cohort) using records ascetained either from the Social Security Administration files (Mancuso, 1980a) or from company employment files, as was the case for the present study. This observation argues against a bias in the present study resulting from noninclusion of some individuals in the study cohort as earlier estimated by use of SSA quarterly earning reports. For the Ohio beryllium production facility

studied by Mancuso (1980a), the excessive lung cancer risk was of a higher order of magnitude (SMR = 200 for the total cohort). Each of the studies exhibited the similar trend of an increasing risk of lung cancer with an increasing time interval since onset of exposure. Mancuso (1980b) more recently extended follow-up of these two study cohorts through 1976 and compared the lung cancer risk of beryllium-exposed workers to viscose rayon workers of similar duration of employment categories. Both cohorts of workers (beryllium and viscose rayon) were employed at facilities in the same geographic area and during the same calendar time period and followed over the same period of time. An excessive risk of lung cancer was demonstrated for beryllium-exposed workers at each duration of employment category. This observation is not consistent with the hypothesis that short-term employees, as opposed to exposure to beryllium, are a subset of employees uniquely and exclusively predisposed to an excessive risk of lung cancer. An additional study, by Infante *et al.* (1980), recently found an excess of lung cancer mortality among a cohort of individuals entered into the Beryllium Case Registry with a diagnosis of prior beryllium-related pneumonitis or bronchitis.

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