SECTION VIII
NEOPLASMS

OCCUPATIONALLY INDUCED LUNG CANCER EPIDEMIOLOGY

Richard A. Lemen

INTRODUCTION

It has been estimated that lung cancer will kill approximately 77,000 men and 28,000 women in the United States during 1981 (16). This accounts for 34% of all types of cancer deaths in males and for 15% in females. It is expected that 122,000 new cases of lung cancer will occur in the United States in 1981. This will account for a total of 22% of deaths in males and 8% of deaths in females. The age-adjusted lung cancer death rates have increased steadily in men from 5 per 100,000 deaths in 1930 to about 70 per 100,000 deaths in 1980. In females, the rate did not climb as steadily: from 2 to 3 per 100,000 deaths in 1930 to about 7 to 8 per 100,000 deaths in the mid-sixties. However, from the mid-sixties to 1980, the rate has increased rapidly to approximately 18 per 100,000 deaths. It has been suggested that the rapid rise in lung cancer among females is because of the increasing number of women in the work force and because many more women have taken up smoking (128).

ASBESTOS

Occupational Exposure—Historical Studies

In 1935, 55 years after the usage of asbestos was introduced on a large-scale basis in industry, suspicion of an association between asbestosis and lung cancer was reported by Lynch and Smith (75) in the United States and by Gloyne (38) in the United Kingdom. About 10 years later, case reports of pleural and peritoneal tumors associated with asbestos began to appear (144)(145)(149). Epidemiologic evidence from Doll showed a tenfold risk of lung cancers in the U.K. asbestos textile workers who had been employed from 1930, that was prior to regulations that were written to help workers improve dust conditions in factories (27). Similar findings were reported in the United States in 1961. Mesotheliomas were also detected, but this fact was not published until later (81)(119). Possible variations in risk with other types of asbestos fibers were rarely considered in the earlier reports. Since 1964, following the recommendations of the UICC Working Group on Asbestos Cancers (UICC 1965)(136) for new studies, there has been an expansion of epidemiological studies in many parts of the world.

Epidemiologic Studies—Lung Cancer

Mixed Fiber Types

In most industrial processes different fiber types are mixed, so that pure exposures to a single asbestos type are rare. Mortality studies of defined populations of asbestos manufacturing, insulating, and shipyard workers have provided the most concrete evidence concerning the association between bronchial cancer and exposure to asbestos. Reports received from several countries: England (30)(92), Germany (12), the United States (118), the Netherlands (129), and Italy (112) have confirmed this evidence.

Elmes and Simpson (31) have extended their earlier report (30) to include deaths occurring since 1965 through 1975. The mortality trend has shifted from a preponderance of asbestosis and gastrointestinal deaths to malignancies from lung cancer and mesothelioma, (diseases associated with longer latent periods). These authors report that their findings would suggest any standard based "on the prevention of asbestosis, may not provide adequate protection against neoplasia."

A sevenfold excess of lung cancer was found in a group of insulation workers who had been exposed to chrysotile and amosite asbestos, but not crocidolite (121). Enterline and Henderson reported a 4.4 times increased risk of (respiratory cancer) mortality among retired men who had

worked as production or maintenance employees in the asbestos industry and who had been exposed to mixed fibers (32). Among men with mixed fiber exposure (crocidolite and chrysotile) in the asbestos cement industry, the rate was 6.1 times the expected rate. In a British naval dockyard population, Harries showed that there had been an increased rise in mesotheliomas since 1964 (43). However, the full biologic effects of asbestos in shipyard workers would not have been expected to be detected until the 1970's and thereafter (117).

Edge reported that shipyard workers with mixed asbestos exposure and pleural plaques (without evidence of pulmonary fibrosis) had a 2.5 times increased risk of developing carcinoma of the bronchus, when compared with matched controls without plaques (29). In a study of sheetmetal workers with measurable and mixed asbestos exposure, an excess of deaths from malignant neoplasms (24.7% of the deaths for two cohorts, selected for 5 or more years, who worked in the trade; with 19.1% of deaths for a group where 14.5% was expected) was largely attributed to an excess of malignant tumors of the respiratory tract (21). Of the 307 deaths in the first cohort, 32 lung cancer deaths were significantly in excess (1.7 times the expected level).

Weill et al. reported on the mortality experience of a cohort of 5,645 men employed in the production of asbestos cement products and who had at least 20 years since first exposure (146). These workers were exposed largely to chrysotile with some crocidolite and amosite. Among this group, 601 persons were identified as deceased by the Social Security Administration. The vital status of 25% was unknown, and were assumed to be alive, which probably resulted in underestimation of the true risk. Death certificates were obtained for 91% of the known dead. Dust exposures were estimated, using each worker's employment history in conjunction with historical industrial hygiene data.

Weill et al. observed increased respiratory cancer mortality only among those with exposure in excess of 100 mppcf-year, where 23 cases were observed vs. 9.3 expected (146). The unusually low SMR for all causes in the low-exposure groups suggests the possibility of a selection bias and any interpretation of risks at low exposures should be done with caution. Separating the cohort by fiber type exposure, the authors concluded that the addition of crocidolite to chrysotile enhanced the risk for respiratory malignancy; however, an excess risk was observed among those not exposed to crocidolite with cumulative exposures in excess of 200 mppcf-months. Both average concentration of exposure and duration of exposure were found to be related to cancer risk.

McDonald and McDonald studied the mortality of 199 workers exposed to crocidolite during gas mask manufacture in Canada from 1939 to 1942 (84). This cohort was followed through 1975, when by this time 56 deaths occurred. Out of these 56 deaths, 4 (7%) were from mesothelioma and 8 (14%) from lung cancer.

Chrysotile

McDonald et al. reported an increased risk of lung cancer among men employed in Quebec chrysotile mines and mills (85)(86). The risk of lung cancer among those workers most heavily exposed was five times greater than those least exposed.

Kogan et al. investigated the cancer mortality among workers in asbestos mining and milling industries between 1948 and 1967 (54). The total cancer mortality rate among workers was 1.6 times higher than that found in the general male population; for female workers the rates were 0.8 times higher for those in mines and 1.[illegible] for those in mills. The lung cancer risk for male miners and millers was twice that of the general male population. For females in mines and mills, the risks were 2.1 and 1.4 times that of the general female population, respectively. For workers over 50 years of age, the risk of lung cancer was greater: for men in mining, 4.0; those in milling, 5.9; for women in mining, 9.5; and those in milling, 39.8 times that found in the general population.

Wagoner et al. reported on the cancer risk among a cohort of workers in a major manufacturing complex utilizing predominantly chrysotile asbestos in textile, friction, and packaging products (143). An excess of respiratory cancer occurred among asbestos workers in each duration-of-employment category down to and including one through nine years. They observed statistically significant standard mortality ratios of 122 for all malignant neoplasms of the respiratory system. The asbestos workers in this study were located in the area of predominantly Amish dutch population with known low frequencies of smoking. The authors, nevertheless,

used the general white male U.S. population as a control group, which most likely resulted in an underestimation of the degree of risk.

Robinson et al. (106) reported an additional 8 years of observation and 385 deaths to the Wagoner et al. (143) study of mortality patterns of workers among one facility manufacturing asbestos textile, friction, and packing exposed predominately to chrysotile. Except for 3 years (during World War II), chrysotile constituted over 99% (per year) of the total quantity of asbestos processed. During those 3 years, amosite was selectively used to a limited extent because of Naval specifications and accounted for approximately 5% of the total asbestos used per year. Crocidolite and amosite (for the other years) accounted for less than 1% of the total usage in very selected areas. Exposures to these two types may have played a role in the etiology of disease; however, due to the overwhelming exposure of the cohort to chrysotile, it is likely that the other exposures played a minor role in the overall mortality patterns. Robinson et al. confirmed the observations of Wagoner et al. that statistically significant excess deaths were due to bronchogenic cancer.

Weiss reported no unusual mortality experience over a 30-year period for a cohort of workers employed in a paper and millboard plant, reported to be using only chrysotile (147). The author concluded the study results were suggestive of a minimal hazard from chrysotile. This conclusion must be viewed in light of the limitations inherent in the study. First, the population studied was small (n = 264) and only 66 workers had died at the time of the analyses. Moreover, the unusually low SMR for many of the contrasts in the Weiss et al. paper suggests the possibility of a selective bias greater than usually seen when contrasting industrial populations are contrasted with the general population.

Enterline and Henderson found that retired men who had worked as production or maintenance employees in the asbestos industry, and had been exposed only to chrysotile, and who had reached 65 years of age, had a respiratory cancer risk 2 to 4 times greater than that expected (32). Among men within the asbestos cement industry exposed only to chrysotile, a one- to four-fold excess of respiratory cancer was found.

Anthophyllite

In Finland, anthophyllite mining has been associated with an excess bronchial cancer risk of 1 to 4 times the overall expected and about double this figure for those with more than 10 years' exposure time (53)(87)(88).

Synergism

There is marked enhancement of the risk of lung carcinoma in those workers exposed to asbestos who smoke cigarettes (11)(25). Hammond and Selikoff interpret the excess lung carcinoma risk from asbestos in nonsmokers to be small (41). No link between cigarette smoking and mesotheliomas has been observed in a prospective study by Hammond and Selikoff (41). A preliminary study on female workers employed between January 1940 and December 1967, in a predominantly chrysotile asbestos textile plant, revealed 7 lung cancer deaths among 580 women when only 0.63 deaths were expected ($p<0.01$) (64). One lung cancer death was observed in a smoker, two in women of undetermined smoking history, and four in women who "never" smoked cigarettes (as determined from hospital admission charts).

It is important to note that the historic documentation of cigarette consumption patterns is lacking for most retrospective cohort studies done on asbestos workers. It is also important to note that a sizable portion of the general population, the group usually selected for comparison in these studies, are cigarette smokers. Therefore, the risk of lung cancer demonstrated for these industrial groups exposed to asbestos is of such magnitude that it precludes the identification of an independent etiologic role for cigarette smoking.

Hammond et al. have attempted to correct this methodological problem by comparing 12,051 asbestos insulation workers having complete smoking histories to a control population, with no smoking histories (42). Their control population consisted of 73,763 men from the American Cancer Society's prospective cancer prevention study who were similar to the asbestos workers in that they were white males; nonfarmers; had no more than a high school education; a history of occupational exposure to dust fumes, vapors, gases, chemicals, or radiation; and were alive as of January 1, 1967. Non-smoking asbestos workers showed a five times greater risk of dying from lung cancer than their smoking controls. Both smokers and nonsmokers exhibited a fivefold relative risk; however, the attributable risk was greater among the smokers. This higher attributable risk can be accounted for by the large

number of smokers in the asbestos-exposed population and the comparison population.

Liddell et al. has also studied the smoking patterns among asbestos workers through administering questionnaires to living workers or relatives of deceased workers, who died after 1951 (68). The authors report SMR's of 48 and 46 for nonsmokers and ex-smokers, increasing to 206 for heavy smokers. This study is unreliable however, because specific smoking death rates were not used for the calculation of expected lung cancer deaths, and this underestimated the risks among nonsmokers.

ARSENIC

Lung cancer was first observed to be excessive in a proportionate mortality study of workers exposed to sodium arsenic in the manufacture of sheep dip (45). Roth reported that 18 of the 47 autopsies done on German vinegrowers exposed to arsenical insectides, died of lung cancer (111). Roth then compared lung cancer mortality rates of six rural and urban districts of the Moselle and one district of the Ahv (110). He found that the vineyard districts of the Moselle, using arsenical insecticides, had a higher proportionate mortality rate from lung cancer than did the urban and nonvineyard areas. The district of Ahv, however, had a lower incidence of lung cancer which Roth attributed to the non-use of arsenical insecticides. The autopsy results and the comparison of the vine-growing districts caused Roth to suggest an etiological link existed between arsenic insecticide exposure and an excess of lung cancer.

Pinto and Bennett studied 229 active copper smelter workers and pensioners (97). The pensioners were at least 65 years of age with 15 years or more of service in the plant. The authors concluded that there was no excess lung cancer in the smelter population. However, there was some indication that the nonexposed group had arsenic exposure because the urinary arsenic levels reported by Pinto et al. (98) and cited by Pinto and Bennett (97), indicated such exposure. Even though the overall cancer mortality rate was not statistically significant, the lung cancer mortality rate in the smelter group, 18 of 229 deaths or 7.9%, was greater when compared to the state as a whole, 518 of 13,759 (3.0%). Milham and Strong, in an examination of death certificates from the county where the smelter was located, found 39 deaths due to lung cancer among county residents who had been employed at the smelter and 1 lung cancer death in an employee who was not a resident (90). Based upon the general United States population, the 40 deaths were statistically higher than the expected death rate of 18.

In another study of 8,047 white male U.S. copper smelter workers exposed to arsenic trioxide during 1938 to 1963, Lee and Fraumeni found that observed deaths ranged 6.0 times as high as expected when compared to their appropriate statewide population rates (63). The risk was also greater in those workers exposed to sulfur dioxide. In Japan, a case controlled study of 19 males who died of lung cancer, and of controls dying of other than lung, urinary, bladder, or skin cancer, Kuratsune et al. found that 11 of the lung cancer deaths occurred in men formerly employed at copper smelters—which was statistically in excess—compared to only 3 deaths in former copper smelter workers in the controlled group (60). Another study of 965 deaths, based on records at a Utah Copper Company, indicated that the smelter workers had the highest percentage of lung cancer deaths, 7.0% as compared to 2.2% among other employees or 2.7% when compared to the state as a whole (105). The authors concluded that both smoking and nonsmoking smelter workers experienced a higher frequency of lung cancer deaths than other workers in the company. The average duration of employment at the smelter was approximately 29 years. Although no in-plant arsenic measurements were taken prior to 1959, stack emissions for each year back to 1944 indicated levels three times those measured in 1959.

Baetjer et al. (9), Mabuchi et al. (76), and Ott et al. (94) also found excess lung cancer in workers handling arsenic in the manufacture of pesticides and herbicides. This information is important because, unlike the copper smelter, workers' contact with arsenic was not associated with additional exposure to other substances such as sulfur dioxide. Newman et al. indicate that in at least one study of copper mining and smelting communities, the predominate lung cancer cell type in persons exposed to arsenic was poorly differentiated epidermoid carcinoma; the second most common cell type was adenocarcinoma (93). Wicks et al. (148), however, suggests that the predominate cell type is in fact adenocar-

cinoma, a finding inconsistent with the hypothesis of Kreyberg (58) which states that small cell undifferentiated and epidermoid carcinomas are the only cell types that increase with exposure to inhaled carcinogens. Hood et al. (46) and Fern (33) were unable to demonstrate that arsenic was carcinogenic in the animal species they studied. Arsenic did, however, have teratogenic effects in this study.

BIS(CHLOROMETHYL)ETHER (BCME)

Alkylating agents have been used increasingly in industrial processes as intermediates in organic synthesis, organic solvents, bactericides, fumicides, and cross-linking agents. During recent years, alkylating agents have come under intense scrutiny because of their mutagenic and tumorigenic activities.

One such alkylating agent is bis(chloromethyl)ether (BCME). It is also known as dichlorodimethyl ether and is frequently encountered as a contaminant of chloromethyl ether in concentrations up to 7%.

The carcinogenicity of BCME was first demonstrated in 1968 with skin painting in mice and subcutaneous injection in rats as the bioassay system. It was observed that of 20 mice treated with BCME, 13 developed papilloma, 12 of which progressed to squamous cell carcinoma. This was confirmed by additional experiments using subcutaneous injections of BCME in newborn mice (37).

Because industrial exposure to BCME is more likely to be respiratory than cutaneous, several animal inhalation experiments were undertaken. In 1971, Laskin et al. reported on 30 rats subjected to inhalation of BCME for 101 exposures at a concentration of approximately 0.1 ppm (61)(62). Five of the 19 rats autopsied revealed squamous cell carcinoma of the lung and five revealed esthesioneuropithelioma arising from the olfactory epithelium.

Epidemiologic Studies

Lemen et al. studied the sputum of workers exposed to BCME and compared it to above ground uranium miners since this group was known to experience no unusual lung cancer risk (65). At the time of sputum collection from the 115 workers, a questionnaire was completed to obtain information on the history of tobacco usage. Occupational histories were obtained on all current and past employees at the same time.

Because of the association between age, tobacco usage, and degree of atypia in the sputa, it was deemed necessary to control for these confounding variables in evaluating the role of BCME in the etiology of lung cancer. Because the abnormal epithelium induced by cigarettes undergoes repair only after a substantial period of nonsmoking, an interval of five years or more of nonsmoking was defined as "former smoking." Cigar and pipe smoking was regarded as "nonsmoking" because their role in the etiology of lung cancer is very small, as compared to cigarette smoking.

BCME workers were matched sequentially with the use of a random list of surface miners based on similar cigarette usage (6 cigarettes/day, age at time of sputum collection, for five years).

Evaluation of cases and matched controls was undertaken separately for two groups: 1) male office employees and production and maintenance operation employees exposed less than five years; and 2) males employed for five or more years in the production and maintenance of anion-exchange resins.

The dichotomization was based on the observation that the prevalence of abnormal sputum rises with increasing years of exposure to a carcinogen, and on the theory that there is a latent period after exposure to a carcinogen before abnormal cells appear, although it appears to be shorter than the latent period before the induced carcinoma appears. This dichotomization was made after observation of the industrial hygiene survey was conducted at the facility.

Table VIII-1 shows the distribution of sputum cytology among those anion-exchange employees with the least or no exposure to BCME. So far, there is no association between type of work and degree of abnormal cytology (17% anion-exchange workers vs. 15% controls). Lemen et al. (65) also evaluated the incidence of lung cancer among BCME exposed workers.

By contrast, however, Table VIII-2 demonstrates the statistically significant association of abnormal cytology associated with exposure to BCME for five or more years. As listed in Table VIII-2, 34% of anion-exchange workers in this group had abnormal cytology, in contrast to only 11% for uranium surface miners.

Table VIII-3 shows that whereas only 0.54 cases of lung cancer would have been expected to occur in the plant population, five cases actu-

Table VIII-1

DISTRIBUTION OF SPUTUM CYTOLOGY

Sputum Cytology: All Male Office Employees and Those Males Employed Less Than Five Years in the Production-Maintenance of Anion-Exchange Resins as Contrasted with Age-Cigarette-Matched Uranium Surface Employees

		Uranium Surface Employees		
		Normal, Metaplasia, Mild Atypia	Moderate to Marked Atypia	Total
Anion-Exchange Resin Employees	Normal, Metaplasia, Mild Atypia	49	10	59 (83%)
	Moderate to Marked Atypia	11	1	12 (17%)
	Total	60 (85%)	11 (15%)	71

*$x^{(2)}$ = Not significant.

Source: Lemen et al. (65)

Table VIII-2

RETROSPECTIVE COHORT INVESTIGATION OF LUNG CANCER INCIDENCE

Sputum Cytology: Males Employed Five or More Years in the Production-Maintenance of Anion-Exchange Resins as Contrasted with Age-Cigarette-Matched Uranium Surface Employees

		Uranium Surface Employees		
		Normal, Metaplasia, Mild Atypia	Moderate to Marked Atypia	Total
Anion-Exchange Resin Employees	Normal, Metaplasia, Mild Atypia	13	2	15 (34%)
	Moderate to Marked Atypia	26	3	29 (66%)
	Total	39 (89%)	5 (11%)	44

*$x^{(2)}$ = Significant $p < .025$.

Source: Lemen et al. (65)

Table VIII-3

PRODUCTION AND MAINTENANCE WORKERS WITH FIVE YEARS EXPOSURE TO BIS(CHLOROMETHYL) ETHER IN AN ANION-EXCHANGE RESIN OPERATION*

Age	Person-Years	Expected	Observed
20-29	64	.01	0
30-39	198	.01	1
40-49	237	.09	2
50-59	106	.16	1
60-69	82	.23	1
70+	15	.05	0
Total	702	.55	5

$SIR = \frac{5}{.54} \times 100 = 924 \quad p<0.01$

*Expectation based on respiratory cancer age specific incidence rates for white Connecticut males 1960-1962.

Source: Lemen et al. (65)

ally occurred, representing a significant excess ($p<0.01$), and a ninefold increased lung cancer risk.

Pertinent data on these five cases are given in Table VIII-4. Since the exposure of all cases was intermittent over a period of time and the actual point of time when induction of the carcinomas occurred cannot be known, the period between first exposure and development of cancer is termed the induction-latency period.

DISCUSSION

The results of both the sputum cytology investigation and the lung cancer incidence study indicate that the workers of the plant studied by Lemen et al. have an unusually high cancer risk (65).

The distribution of sputum classes among production and maintenance workers with greater than five years' exposure is definitely different from the nonexposed group. The distribution of cytology findings in the nonexposed group is very similar to that in the control population. Since the controls do not differ significantly in other parameters such as age, sex, or cigarette smoking habits, it may be presumed that persons in the exposed group were exposed to a pulmonary irritant to which the controls and the in-plant contrast group were not. It is reasonable to attribute this risk to airborne BCME.

In the Lemen et al. study, three of nine recorded deaths were due to respiratory cancer, with four of nine recorded deaths due to malignancies (nodular histiocystic lymphoma and respiratory cancer) (65). This appears lower than the number reported in 1973 by Thiess et al. (133) (Table VIII-5), who reported 8 of 14 deaths were due to respiratory cancer, and 12 of 14 deaths were due to all malignancies (cancer of bladder, testes, respiratory system, and stomach). Six of Thiess' reported cases occurred among 18 experimental technical department workers, a group known to experience very high exposures, as opposed to the group in the present study. When looking at only manufacturing workers, two lung cancer cases among 50 workers were reported by Thiess, a finding similar to the present study where 4 cases occurred among 136 manufacturing workers.

Examination of the data in Table VIII-6 indicated that the reported cases of bronchogenic cancer were among relatively young persons with a mean age of 47 years and that the induction-latency period had a mean of 15 years and is consistent with that of other reported cases of occupational lung cancer. The predominant histologic type of carcinoma found was small cell undifferentiated, and exposure ranged from 7 years, 7 months to 14 years with a mean of 10 years. The majority had smoked cigarettes. Considering that less than 40% of the person-years at risk of developing lung cancer among study cohort members occurred after 10 years since onset of employment, and indeed only 8% occurred after 15 years since onset of exposure, a vast majority of these workers have not yet developed sufficient latency for disease manifestation.

As shown in Table VIII-6, Figueroa et al. (34) reported that among 125 workers in a

Table VIII-4

BRONCHOGENIC CANCERS AMONG BCME WORKERS

Case	Age at Cancer (years)	Years of Possible Experience	Induction Latency Period (years)	Cigarette Usage	Histologic Type of Cancer
1	61	11yr, 3 mos	13	10/day-40 yr	large cell — undifferentiated
2	35	7 yr, 7 mos	8	unknown	small cell — undifferentiated
3	48	9 yr, 5 mos	10	40/day-25 yr	small cell — undifferentiated
4	40	12 yr, 10 mos	16	current smoker	small cell — undifferentiated
5	50	11 yr, 2 mos	26	heavy smoker	small cell — undifferentiated

Source: Lemen et al. (65)

Table VIII-5

BRONCHOGENIC CANCERS AMONG BCME WORKERS

Case	Age at Cancer (years)	Years of Possible Experience	Induction Latency Period (years)	Cigarette Usage	Histologic Type of Cancer
1	59	6	8	Smoking histories not given	Five of them were reported to have small cell undifferentiated carcinoma.
2	53	6	10		
3	31	8	8		
4	52	9	9		
5	65	6	15		
6	42	6	16		
7	58	6	16		
8	60	6	16		

Source: Thiess et al. (133)

chemical plant participation in a program designed after the Philadelphia Pulmonary Neoplasm Research Project, (13) 4 cases of lung cancer occurred during the first 5-year period of observation. Considering that age, sex, and smoking habits were not significantly different, his observation of a 4.54% occurrence among the workers vs. only 0.57% among participants of the Philadelphia Pulmonary Neoplasm Research Project, is significant because it represents an eightfold excess. After further retrospective observation, 10 additional lung cancer cases among individuals working in the plant were identified. No population figure or time period was given to determine the incidence.

Table VIII-7 shows that in 1973 Sakabe reported 5 cases of lung cancer among 32 employees exposed to BCME in a dyestuff factory in Japan (114). Four of the workers exposed were involved in the synthesis of onium dyestuff, but the fifth case was exposed only in the laboratory.

In the present study, as well as in the studies completed by Thiess et al. (133) and Figueroa

Table VIII-6

BRONCHOGENIC CANCERS AMONG BCME WORKERS

Case	Age at Cancer (years)	Years of Possible Experience	Induction Latency Period (years)	Cigarette Usage	Histologic Type of Cancer
1	37	7		none	unknown
2	33	8		20/days-20 yrs.	small cell—undifferentiated
3	39	8		20/days-20 yrs.	small cell—undifferentiated
4	47	10		20/days-0 yr.	small cell—undifferentiated
5	52	4		20/days-10 yrs.	small cell—undifferentiated
6	47	3		20/days-21 yrs.	small cell—undifferentiated
7	43	14		20/days-20 yrs.	small cell—undifferentiated
8	53	10		40/days-20 yrs.	small cell—undifferentiated
9	48	5		20/days-33 yrs.	small cell—undifferentiated
10	50	0-1		20/days-30 yrs.	epidermal
11	55	12		20/days-40 yrs.	small cell—undifferentiated
12	43	12		pipe only	small cell—undifferentiated
13	37	14		none	small cell—undifferentiated
14	44	12		none	small cell—undifferentiated

*Source: Figueroa et al. (34)

et al., (34) the incidence of lung cancer among manufacturing workers, approximately 3 to 5%, were similar. This is contrasted with more than 12% found in Sakabe's study (114). His observation probably reflects the nature of the dyestuff plant, where those at risk could be specifically identified. In the other studies it was extremely hard to determine those workers actually exposed to BCME: the entire production force had to be considered at risk, thus making the incidence conservative. In all four studies the ages, years of exposure, and induction-latency periods are not significantly different as tested by an analysis of variance.

The predominance of small cell-undifferentiated or oat cell carcinomas noted in all four reports is noteworthy. A similar predominance of this histologic type has been noted for bronchogenic cancers associated with radon daughters (113) and with nitrogen mustard (150), a radiomimetic substance. Since the same histologic type is associated with BCME exposure and since there are similarities in the properties of BCME and nitrogen mustard, this predominance suggests that BCME may also be radiomimetic.

It is also noteworthy that most, but not all,

Table VIII-7
BRONCHOGENIC CANCERS AMONG BCME WORKERS

Case	Age at Cancer (years)	Years of Possible Experience	Induction Latency Period (years)	Cigarette Usage	Histologic Type of Cancer
1	47	9	14	moderate	unspecified
2	37	5	12	moderate	oat cell
3	41	9	13	moderate	unspecified
4	38	7	9	heavy	unspecified
5	45	4	13	moderate	adenocarcinoma

*Source: Sakabe. (114)

of the men who developed lung cancer had smoked cigarettes. This suggests that cigarette smoking may interact with the primary carcinogen in a promotional or synergistic fashion just as it does with asbestos (120) and radiation cancers (4). The fact that some nonsmokers are in the group and that the lung cancers occur at much younger ages and are of a different cell type than normally found with cigarette-induced lung cancers, provides further evidence that BCME is the primary agent, rather than cigarette smoke.

COKE OVENS

The long delay between the first observation of human cancers induced by the combustion products of bituminous coal and the development of evidence describing the cancer risks among men employed at coke plants in the steel industry has covered a period of two hundred years.

In 1962, the United States Public Health Service, in collaboration with the Department of Biostatistics, University of Pittsburgh School of Public Health and three major steel firms, initiated a study to analyze the mortality experience of men employed in the steel industry in 1953. The purpose of this study was to determine whether particular patterns of mortality among workers employed at certain trades or at certain work processes might provide leads to causative agents for occupational diseases. The methodological approaches to this study and many of the findings have been presented in a series of papers published in the *Journal of Occupational Medicine* (52)(108).

Using detailed work histories, going back to original employment with the steel firms, it was possible to determine cause-specific rates of mortality for more than 60 work areas within the industry and for a great variety of trades. As shown in Table VIII-8, unusual patterns of site specific cancer have been noted for several work areas. Because of the unusually high lung cancer risk observed among coke plant workers and the variety of cancer sites in excess for men employed in this area, more detailed analysis of this experience was undertaken. As seen in Table VIII-9, the greatest risk is noted for those with the longest exposure and those employed where exposure to emissions is greatest on the topside. The United States Department of Labor has now proposed a standard to protect workers from these emissions. The detailed evidence indicating the high risk of specific cancers among men employed at the coke plant, and the demonstration of a relationship between the level of disease response, was crucial in reaching this decision.

As noted previously, the initial evidence suggesting that carcinogenic agents are produced during the carbonization or combustion of bituminous coal was presented by Percivall Pott in 1775. Since that time, a great amount of information indicating excess cancer of several sites among workers in other coal combustion or carbonization occupations has been noted and, in fact, a report of official statistics from England and Wales for the years 1921 to 1938 showed an excess lung cancer mortality for gas producermen, chimney sweeps, and several categories of gas works employees (52). The excess indicated for gas stokers and coke oven chargers was approximately threefold.

ALUMINUM

In trying to assess the extent of the lung cancer problem in the aluminum industry, a similar situation as seen for gas workers and coke oven

Table VIII-8

OBSERVED AND EXPECTED CANCER AND RELATIVE RISKS BY CANCER SITES FOR WORKERS EMPLOYED FIVE OR MORE YEARS IN SPECIFIED WORK AREAS ALLEGHENY COUNTY STEELWORKERS, 1953 - 1966

Site	I.C.D List Numbers	Work Area	Obs.	Exp.	Relative Risk
All Cancers	140-205	Coke Plant	119	91.9	1.51**
Digestive Organs	150-159	Stainless Annealing	6	2.3	2.80*
Esophagus	150	Open Hearth	13	6.6	2.41*
Stomach	151	Blast Furnace	17	12.3	1.45
Large Intestine	153	Coke Plant	12	7.8	1.77
Rectum	154	Machine Shop	6	2.5	2.55
Respiratory System	160-164	Coke Plant	45	24.9	1.81**
		Mason Department	17	11.0	1.57
		Blacksmith Shop	8	3.8	2.16
		Machine Shop	24	16.6	1.48
Genito-Urinary	177-181	Coke Plant	17	10.4	2.01*
Organs		Janitors	7	3.4	2.28
Prostate	177	Janitors	6	2.3	3.11*
Kidney	180	Coke Plant	6	1.5	15.20**
Leukemia & Lymphoma	200-205	Heat Treating & Forging	5	2.2	2.87

*Significant at 5% level.
**Significant at 1% level.

Source: Redmond (100)

workers thirty years ago, is observed. That is, a review of death certificates shows that persons employed in the industry are at a high risk of developing cancer. Furthermore, men employed in certain work areas with exposures related to those found at the coke plant appear to be at the greatest risk.

During the electrolytic reduction of alumina to aluminum a variety of toxic substances are released which may contaminate the workroom air. Among these substances are: hydrogen fluoride, fluoride fume, dust, and carbon monoxide which are potential contaminants whose biological effects are recognized. In addition, coal-tar-pitch volatiles are also released in the process, either in the anode preparation area for pre-baked anodes, or in the pot lines where Soderberg self-baking cells are used.

Investigators from the Soviet Union have reported a significantly higher mortality for all cancers and for specific sites such as lung, bronchi and pleura, and have reported an increased incidence of skin cancer among workers in the aluminum "electrolyzer shops" in comparison with the general population in the same cities (57)(69). Unfortunately, neither of these studies is sufficiently documented to allow firm conclusions.

Milham has reported an increase in proportionate mortality from total cancer, cancer of the pancreas, respiratory system, and malignant lymphomas among aluminum workers in Washington State (Table VIII-9) (89).

The National Institute for Occupational Safety and Health (NIOSH) has conducted environmental surveys of aluminum reduction facilities in the East and Northwest United States, monitoring for coal tar pitch volatiles and a variety of other potentially hazardous substances (125). These surveys included reduction plants using pre-baked anodes, the vertical pin Soderberg anodes, and horizontal pin Soderberg anodes. The findings indicate that the concentration of coal-tar-pitch volatiles (CTPV), as measured by the benzene soluble fraction technique, were almost all elevated above the current OSHA Standard of 0.2 mg/M CTPV for an 8 hour time-weighted-average. The levels were highest in the Soderberg potrooms, presumable because the pitch is heated and "baked off" the

Table VIII-9

PROPORTIONATE MORTALITY RATIOS (PMR's)
WHITE MALE DEATHS IN WASHINGTON STATE, 1950-1971

Aluminum Workers

Cause of Death	*I.C.D. Number**	*Deaths*		
		Obs.	*Exp.*	*PMR*
All Malignant Neoplasms	140 - 204	129	103	126**
Cancer of Esophagus	150	5	2	232
Cancer of Pancreas	157	13	6	204**
Cancer of Respiratory System	160 - 165	40	31	128
Cancer of Testis	178	3	1	251
Cancer of Brain	193	6	4	155
Malignant Lymphoma	200 - 202	10	4	250**
Hodgkin's Disease	201	4	2	164

*I.C.D. = International Classification of Diseases, 7th Revision.
**$p \leq .05$

Source: Milham (89)

anode in these potrooms. In contrast, the lowest measurements were in the potrooms using prebaked anodes. This type of carbon anode already has the pitch "baked off" before being used in the reduction area.

In a 1976 study of chronic respiratory disease among aluminum reduction workers, sputum cytology was utilized to determine the degree of abnormal cells in the respiratory tract as an early indication of cancer (24). Because of certain limitations of that study, the authors were unwilling to draw any conclusions regarding the carcinogenic risks among the study group as compared to matched controls. However, review of the results from that study leads us to conclude that the evidence of potential carcinogenic risk for potroom workers is certainly quite consistent with the previously mentioned mortality observations. When consideration is given to the sputum cytology classification of moderate atypia or higher, a significant ($p<0.01$) difference is observed between the study group (30/390) and the control group (5/195). Moreover, when consideration is restricted to causes of suspicious and positive cancer, there are 6/390 meeting such criteria in the study group, compared to 0/193 in the control group. It also should be noted that the control group in this study had a greater exposure to known carcinogens, according to prior work history, so that difference in cancer risks are underestimated. Other studies on workers exposed to recognized pulmonary carcinogens have used sputum cytology and demonstrated its validity as an early indicator of cancer (35)(65).

CHROMIUM

In 1946, an early association of lung cancer with exposure too chromium was made by Alwens and Jonas, when they noted an excessive frequency in workers involved with the heavy chemical industry in two German towns (2). It was concluded that the causal agent was chromate dust. These observations were followed by Machle and Gregorius in the United States where a study of 6 chromate plants revealed 32 cases of cancer of the bronchis and lung an estimated relative risk of 25% (77). Looking at 290 lung cancer patients from two hospitals near a chromate-producing plant, Baetjer found that 3.8% were chromate workers, a rate significantly higher than among a random sample of other hospital admissions (8). Mancuso, looking at a chromate-producing plant in Ohio, found a ratio of lung cancer deaths to all deaths of chromate workers approximately 15 times greater than that of the general population of the same county (78). In another study of chromate workers over an 11-year period, based upon deaths reported for those enrolled in sick benefit associations, Brinton et al. reported 29 times as many respiratory cancer deaths as would have been expected from the general population (15). A United States

Public Health Service survey by Gafafar of death claims submitted to the sick-benefit plans of seven U.S. chromium manufacturing plants, found for white employees an excess of 10 lung cancer deaths observed as compared to 0.7 expected (SMR = 1429) (36). Black employees had 16 observed lung cancer deaths as compared to 0.2 expected (SMR = 8000). In the cross-sectional medical portion of this study, 897 workers were examined and 10 were found to have bronchogenic carcinoma. When compared to another cross-sectional x-ray survey in Boston, the 10 cases of bronchogenic carcinoma among chromium workers accounted for a prevalence rate of 115 per 100,000 compared to that in the Boston survey of 20.8 per 100,000.

Continued evidence has accumulated from epidemiologic studies in the chromate-producing industries around the world as can be seen in Table VIII-10. Work has also continued to look at various other types of exposure to chromium in the pigment industry, plating industry, ferrochromium industry and other industries where exposure to chromium compounds occur and are summarized in Tables VIII-11, VIII-12, VIII-13, VIII-14.

In conclusion, the data are sufficient proof that respiratory carcinogenicity does occur in excess in men exposed during chromate production, and suggestive of excesses during other exposures to chromium or its compounds. The data from rat studies tend to incriminate chromium as the causative agents (47). The data appear inadequate at the present time to evaluate the carcinogenic potential of the other chromium compounds.

NICKEL

In 1932, the first human evidence of an association of nasal cancer among workers exposed to nickel was described in the report of the Chief Inspector of Factories (18). In this report, 10 cases of nasal cancer were described in refinery workers in Wales. Further follow-up from this same refinery in 1950 reported 52 cases of nasal cancer and 93 cases of lung cancer (19). In 1970, Doll et al. studied 845 men employed in the same refinery who had been employed 5 years or more and had been hired prior to 1971 (28). In men hired prior to 1925, deaths from lung cancer were 5 to 10 times higher than expected when compared to overall British Mortality rates. The deaths from nasal cancers were 100 to 900 times of that which was expected. This was in comparison to men employed after 1925, who showed no signs of excess from these cancers. These results suggest that the carcinogenic hazard in the refinery had been removed by 1925 (26)(91). Doll, et al. observed that by 1970 nasal cancer still persisted essentially unchanged even after the carcinogen was eliminated whereas the lung cancer incidence had decreased over a period of time (28).

Nasal cancer excessed have also been reported in nickel refineries in Canada (20)(82)(137), in Norway (73) (95), the German Democratic Republic (55)(56)(109), Japan (135), in the USSR (115)(116)(131)(132)(151), and in New Caledonia (67).

Kreyberg (59) further evaluated the lung cancer deaths, including those reported by Loken (73) and Pederson et al. (95), with specific emphasis on tobacco consumption, occupation, and cell type. He confirmed that Nickel refinery workers experienced an excess of lung cancer when compared to a reference population not so exposed. In addition, he showed that the majority of lung cancers were of the small cell anaplastic carcinoma and epidermoid carcinoma cell types and that the victims had a history of tobacco consumption. Kreyberg concluded that nickel induced lung cancer is higher than the risk found in the general population, but that the true risk of nickel exposure alone will not be known until a suitably large number of nonsmokers exposed to nickel can be studied. He did not attempt to estimate the magnitude of the synergism, if any, between tobacco and nickel in inducing lung cancer.

Doll et al. indicate that the exact nature of the carcinogenic agents in nickel refineries are not known and that the cancer risk is associated mostly with the earlier stages of nickel refining (28). Some suggestions are that respirable particles of nickel subsulphide and nickel oxide are most suspect (20).

Recently, Costa and Mollenhouer have demonstrated that particles ≤ 5 μm of crystalline nickel subsulfide were actively phagocytized by cultures of Syrian hamster embryo cells and Chinese hamster ovary cells (22). While cells did not take up significant quantities of similar sized particles of amorphous nickel monosulfide, this does suggest that carcinogenic activity is associ-

ated with cellular uptake. Animal studies support inhaled nickel subsulfide has produced lung cancer in rats. Inhalation exposure in rats to nickel carbonyl was also associated with several pulmonary malignancies (49). Three case reports of lung cancer occurred in workers during nickel plating and grinding operations (14)(130)(134).

BERYLLIUM

It has been shown that beryllium is carcinogenic in many animal species (48). Mancuso, in a study of 1,222 white male beryllium production workers employed between 1942 to 1948 in Ohio and Pennsylvania, found an excess of lung cancer when compared to the United States white male population (80). In Ohio, 25 lung cancers were observed as compared to 12.52 expected for a statistically significant excess, and in Pennsylvania, even though not statistically significant, there was an excess of lung cancer (40 cases observed vs. 29.11 expected) when followed through 1977. In 1980, Mancuso compared the mortality experience in a beryllium cohort of 3,685 white males employed between 1937 and 1948 and followed through 1976 with viscose rayon workers and found a statistically significant excess of lung cancer (80 observed vs. 57.06 expected) (79).

According to the Beryllium Case Registry, 421 white males suffering from berylliosis between 1952 and 1975 had excess cases of lung cancer (7 vs. 3.3 expected based upon the United States white male rates) (50). Wagoner et al., in a retrospective cohort study of 3,055 white male workers employed between 1942 and 1948 and followed from 1968 through 1975 in the beryllium refining industry, found an overall statistically significant excess rate at the $p<0.05$ level for lung cancer (47 observed vs. 34.29 expected, based on U.S. white male rates)(142). When looking only at white male workers with 25 years or more after initial exposure, Wagoner et al. found 20 observed and only 10.79 expected ($p<0.01$).

MUSTARD GAS

Respiratory tract cancer has been observed in workers manufacturing mustard gas. Wada et al. determined that 33 deaths from respiratory tract carcinoma had occurred in mustard factory workers since 1952 (138). The 30 historically confirmed neoplasms appeared centrally rather than peripherally and were squamous or undifferentiated in cell type. These findings tend to strengthen the inconclusive results obtained in the 1914-1918 study which show that mustard gas may have been responsible for the lung cancer deaths among those soldiers exposed (10)(17).

FLUORSPAR

Fluorspar, the mineral calcium fluoride, is mined commercially in various parts of the world. However, the only study of health effects associated with miners on fluorspar was that done by de Villiers and Windish in Newfoundland (23). Their results show that, since 1952, two or three deaths from primary lung cancer have occurred each year among males living in a small fluorspar mining community. After comparison of these deaths with a control community of similar size in the same geographical region and with the population of the rest of Newfoundland, the observed death rate from lung cancer was about 29 times more than expected. This confirms the probability of an associated occupational factory. The most likely associated etiological factor was the finding of radon daughter products in concentrations similar to those found in uranium mines. It is of interest that no radioactive ore bodies have been found in the mine.

RADON DAUGHTERS

As early as 1557, fatal lung disease was occurring in miners of uranium-bearing ore in the Erz Mountains of Europe (1). In 1879, this lung disease was later identified as malignant neoplasia (lymphosarcoma) by Harting and Heese (44). By 1913, the miners from the Schneeberg mines were found to be dying of lung cancer at a rate of 40 percent of all deaths (6). In Czechoslovakia, 9 of 17 deaths were observed between 1929-1930, among miners of uranium-bearing ores, which were due to lung cancer (99). Further study by Peller in 1939 indicated that the rate of lung cancer among miners of uranium-bearing ores in the Czechoslovakia mine was 9.77 per 1,000 which was much higher than that reported among nonmining males living in Vienna, Austria (0.34 per 1,000) (96).

In 1950, the Public Health Service began looking at hazards to U.S. uranium miners in 1950. Between 1954 and 1960, 5,370 miners and millers submitted to pulmonary function and chest radiography tests as part of complete physical examinations. Demographic, social and past occupational history data was also collected. In

1964 Wagoner et al. demonstrated that the mean cumulative radiation exposure of the U.S. uranium miners with respiratory cancer was significantly greater than miners with nonrespiratory disease (139). In addition, Wagoner et al. demonstrated a statistically significant excess of respiratory cancer among underground uranium miners which could not be attributed to age, cigarette smoking, heredity, self-selection, diagnostic accuracy, prior hard-rock mining or nonradioactive ore constituents, including silica dust. In another study by Wagoner et al., it was demonstrated that a statistically significant excess of lung cancer did occur in an exposure-response relationship with airborne radiation even after cigarette smoking was excluded as a confounding factor (141). Lundin et al., using data gathered during the U.S. Public Health Service study projected that exposure at 4 working level months (WLM) per year for 30 years could be expected to double the respiratory cancer risk over a 40 year period (74). Epidermoid, small cell undifferentiated, and adenomatous histologic types were all increased among uranium miners, with the small cell undifferentiated type showing the greatest increase (5). With relation to cigarette smoking, in 1976, Lundin et al. hypothesized that if the latent period of radiogluic lung cancer were longer in nonsmokers as compared to smokers (due to the predominance of promoting agent in cigarette smoke) then it is probably too early to expect lung cancers among the nonsmoking uranium miners (74). Both Wagoner et al. (140) and Archer et al. (3) tested the Lundin et al. hypothesis and found that nonsmoking or Indian uranium miners smoking lightly had a mean latent period of 19.1 years as contrasted with 13.7 years for a group of heavy smoking white uranium miners dying of lung cancer. Recently Gottlieb and Husen reported that, among 17 lung cancer cases in Indians diagnosed during 1965 through 1979, 14 were nonsmokers and that 10 had small cell undifferentiated histology as previously shown to be predominant among white underground uranium miners in the United States (39).

Reports from Canada (40); Czechoslovakia (122)(123)(124) and Sweden (7)(51)(104)(126)(127) each have shown an excess of lung cancer associated with radon daughters exposures.

REFERENCES

1. Agricola, A.C.: 1557, "De Re Metallica," Basel. Cited by Hueper, 1942, and as translated by Hoover, H.C. and Hoover, L.C. Dover Publications, New York, 1950.
2. Alwens, W. and Jonas, W.: [Chrome Lung Cancer] ACTA Union Internationale Centre Cancer *3:*103-114, 1938.
3. Archer, V.E., Gillam, J.D., and Wagoner, J.K.: Respiratory disease mortality among uranium miners. N.Y. Acad. Sci. *271:*280-293, 1976.
4. Archer, V.E., Wagoner, J.K., and Lundin, F.E.: Uranium mining and cigarette smoking effects in man. JOM *15:*204-211, 1973.
5. Archer, V.W., Saccomanno, G., and Jones, H.H.: Frequency of different histologic types of bronchogenic carcinoma as related to radiation exposure. Cancer *34:*2056-2060, 1974.
6. Arnstein, A.: Sozialhygienische Untersuchungen uber die Bengleute in den Schneeberger Kobalt-Gruben, insbesodere uber des Vorkommen des sogenannten "Schneeberger Lungenkrebses" Osterreich Sanitatswesen Wien Arbeit., a.d. Geb. I. Soz. Med. Beihefte. *5:*64-83, 1913.
7. Axelson, O. and Sundell, L.: Mining, lung cancer and smoking. Scand. J. Environ. Health *4:*46-52, 1978.
8. Baetjer, A.M.: Pulmonary carcinoma in chromate workers I. A review of the literature and report of cases. Arch. Ind. Hyg. Occup. Med. *2:*485-504, 1950.
9. Baetjer, A.M., Levin, M.L., Lillenfeld, A.: Analysis of mortality experience of Allied Chemical Plant-2000 Rase Street, Baltimore, MD. Unpublished report submitted to Allied Chemical Corporation, Morristown, N.J., July 16, 1974.
10. Beebe, Gilbert W., Ph.D.: Lung cancer in World War I veterans: Possible relation to mustard-gas injury and 1918 influenza epidemic. J. Nat Cancer Inst. *25:*1231-1252, 1960.
11. Berry, G., Newhouse, M.L., and Turok, M.: Combined effect of asbestos ex-

Table VIII-10

EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PRODUCING INDUSTRIES

Study Population	Comparison Population	Respiratory Cancers			Other Cancers			Notes	References
		Site	No.	Estimated Relative Risk	Site	No.	Estimated Relative Risk		
Six chromate plants[a]: -active employees; -4-17 years before 1948; 156 deaths	Cancer mortality in oil-refining company, 1933-1938	Bronchus and lung	32	25	Digestive	13	2	0.01-21.0 mg/m³ (total Cr)	Machle & Gregorius (1948)
Case-control; lung cancer; 290 cases near US chromium plant	Random sample of hospital admissions	Lung	11[b]	*				Levels determined in 1947: 25-6865 μg/m³	Baetjer (1950b)
Cohort study; US chromate-producing plant; workers employed 1 or more years 1931-1949; 33 deaths	Proportionate mortality for county		6	15[c]					Mancuso & Hueper (1951)
Seven US chromium plants; active employees 1940-1950; 5522 person-years	US males white black	Lung	 10 16	 14.3* 80.0	Other sites	6	INS		Gafafer (1953)
Health survey 897 workers	Boston X-ray survey		10	53 (prevalence ratio)					
Three UK factories; 723 men employed 1949-1955	Cancer mortality England and Wales, 1951-1953	Lung	12	3.6*	All other sites	no excess			Bidstrup & Case (1956)

Table VIII-10

EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PRODUCING INDUSTRIES (Continued)

Study Population	Comparison Population	Respiratory Cancers Site	No.	Estimated Relative Risk	Other Cancers Site	No.	Estimated Relative Risk	Notes	References
Three US chromate-producing plants; 1212 males employed 3 or more months between 1937-1940; status to 1960	Cancer mortality US males, 1950, 1953, 1958		71	8.5*	All other sites	32	1.3		Taylor (1966)
Same populations as Taylor (1966); 1941-1960	Cancer mortality US males, 1950, 1953, 1958		69 (2 maxillary sinus)	9.4*	Digestive system	16	1.5NS		Enterline (1974)
Same plant as Mancuso & Hueper (1951); employed 1 or more years 1931-1937; all jobs related to exposure to total and soluble/insoluble chromium; lifetime exposure in months calculated	No independent comparison group	Lung	41	Crude Hoyeau rate: 369.7/ 100,000				[Tables show increased lung cancer risk with increasing total Cr when insoluble level constant and suggest increasing lung cancer with increasing soluble Cr when total constant; exposure into solubility categories may be questioned]	Mancuso (1975)
Same US plant as Bactjer (1959b);	Baltimore City mortality	Lung (162)	59	2*				New sites with better controls;	Hayes *et al.*(1979)

Table VIII-10

EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PRODUCING INDUSTRIES (Continued)

Study Population	Comparison Population	Respiratory Cancers Site	No.	Estimated Relative Risk	Other Cancers Site	No.	Estimated Relative Risk	Notes	References
2101 workers employed 3 or more months 1945-1974; status 1977 (88% complete). Populations working in new and/or old production sites		Cohort 1940-1949	13	3*				2-17 $\mu g/m^3$ Cr in 1973-1975. Significant excess of lung cancer for workers in 'special products' and dichromates (soluble Cr[VI]); case-control	
		Cohort 1950-1959							
		<3 years' work:							
		new	2	0.7					
		old	12	1.8NS					
		>3 years' work:							
		new	3	4NS					
		old	9	3.4*					

[a]One plant, with 37 deaths and 10 respiratory cancers but with no adequate employment records available, has been excluded.
[b]Only 11 cases had been exposed to chromium compounds *versus* none in controls.
[c]Significant if x^2 is applied, but the small number of cancers due to chromate makes use of this procedure questionable.
*—significant
NS—not significant
Others not known or not tested.

Source: IARC (48)

Table VIII-11
EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PIGMENT INDUSTRIES

Study Population	Comparison Population	Respiratory Cancers: Site	No.	Estimated Relative Risk	Other Cancers: Site	No.	Estimated Relative Risk	Notes	References
Norwegian pigment production since 1948; 24 males with over 3 years' employment to 1972	Cancer Registry of Norway	Lung	3	38*	Gastro-intestinal	1		Exposures to Cr in mg/m^3: current, 0.01-1.35; estimated lifetime, 0.5-1.5. Materials; $PbCrO_4$,$ZnCrO_4$, $Na_2Cr_2O_7$	Langard & Norseth (1975)
UK chromate pigment factories: A, lead & zinc chromate; B, lead & zinc chromate; C, lead chromate; followed to 1977	UK mortality rates	Lung High & medium exposure						Lung cancer occurred with latency (25 years); excess disappeared after 25 years	Davies (1978, 1979)
		A(1932-54), 175 workers	18	2.2*					
		B(1948-67), 116 workers	7	5.0*					
		A(1932-54), 175 workers	2	1					
		C(1946-67), all exposures	2	0.7					

*—significant
NS—not significant
Others not known or not tested.

Source: IARC (48)

Table VIII-12

EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN CHROMATE-PLATING INDUSTRIES

Study Population	Comparison Population	Respiratory Cancers			Other Cancers			Notes	References
		Site	No.	Estimated Relative Risk	Site	No.	Estimated Relative Risk		
UK chromium plating workers since 1946	Not stated	Lung	49	1.4*				Incomplete information	Waterhouse (1975)
54 UK chromium plating plants; 1056 male platers; 1099 male controls	Nonexposed workers in plants and in 2 non-plating industries		24	1.8NS	Total Cancer	44	2.0*	Current exposure to 0 0.1 mg/m³ chromium trioxide. Exposure to several metals including Ni.	Royle (1975a,b)
					Gastro-intestinal	8	2.0NS		
					Other Sites	12	2.4NS		
Japanese chromium plating industry; 952 workers with >6 months' exposure	4236 nonexposed workers from same industry		0	<1	Total cancer	5	<1	The very low relative risks suggest incomplete follow-up.	Okeubo & Tsuchiya (1977)

*—significant
NS—not significant
Others not known or not tested.
Source: IARC (48)

Table VIII-13

EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS IN FERROCHROMIUM INDUSTRIES

Study Population	Comparison Population	Respiratory Cancers: Site	No.	Estimated Relative Risk	Other Cancers: Site	No.	Estimated Relative Risk	Notes	References
Soviet workers in 1955-1969 in the ferrochromium alloy industry	City mortality	Lung	not given	(males) 4.4-6.6* by age	Total Cancer Oesophageal	not given not given	(males) 0.5-3.3* 2.0*-11.3*	Exposed to Cr[III], Cr[VI] and benzo [a] pyrene; highest risk with dust exposure; no numbers provided	Pokrovskaya & Shabynina (1973)
Swedish ferrochromium plant; ferroalloys; 1876 workers for 1 year or more 1930-1975; traced by parish lists and cancer registry; 380 deaths	Classification of work areas by exposure to Cr[III] and Cr[VI]; comparison with county or national statistics	Mortality study of all workers	5	1	Prostate (all workers)	23	1.2NS	Asbestos exposure	Axelsson et al. (1980)
		Maintenance workers	4 (2 mesotheliomas)	4.0*					
Norwegian; ferrochromium and ferro silicon; 976 workers employed 1928-1960	General population; internal comparison with nonexposed	Lung (ferrochromium workers)	7	A[a] 2.3NS B[b] 8.5*	Stomach (ferrochromium workers)	5	1.5NS		Langard et al. (1980)
					Prostate (all workers)	20	1.5NS		

*—significant
NS—not significant
Others not known or not tested.
[a]On the basis of national rates.
[b]On the basis of an internal reference population.

Source: IARC (48)

Table VIII-14
EPIDEMIOLOGICAL STUDIES OF CANCER IN WORKERS
IN OTHER INDUSTRIES WITH EXPOSURE TO CHROMIUM COMPOUNDS

Study Population	Comparison Population	Respiratory Cancers: Site	Respiratory Cancers: No.	Respiratory Cancers: Estimated Relative Risk	Other Cancers: Site	Other Cancers: No.	Other Cancers: Estimated Relative Risk	Notes	References
Chemical manufacture; 30,000 employees; cases 1958-1970	Nonexposed workers; used crude incidence		not given		All malignant neoplasms for chromate factory[a]	852/ 10,000	10.1	Exposure to chromium trioxide, iron oxide, nitric acid	Bittersohl (1971)

[a]Numbers calculated by National Institute for Occupational Safety and Health (1975) from a histogram. This study was done in a big chemical manufacture industry, and the numbers of total malignant neoplasms associated with exposure to different compounds are given.

Source: IARC (48)

posure and smoking on mortality from lung cancer in factory workers. Lancet *2:*476, 1972.
12. Bohlig, H., Dabbert, A.F., Palguen, P., Hain, E., and Hinz, I.: Epidemiology of malignant mesothelioma in Hamburg. Environ. Res. *3:*365, 1970.
13. Boucot, K.R., Weiss, W., Seidman, H., et al.: The Philadelphia Pulmonary Neoplasm Research Project: Basic Risk Factors of Lung Cancer in Older Men. Am J. Epidemiol. *95:*4-16, 1972.
14. Bourasset, A. and Galland, G.: Cancer des voies respiratoires et exposition aux sels de nickel. Arch. Malad. Prof. *27:*227-229, 1966.
15. Brinton et al. Morbidity and mortality experience among chromate workers. Public Health Rep. *67:*835-47, 1952.
16. Cancer Statistics. *Ca-A Cancer Journal for Clinicians.* Published by the American Cancer Society. Jan/Feb *31*(1):13-28, 1981.
17. Case, R.A.M. and Lea, A.J.: Mustard gas poisoning, chronic bronchitis, and lung cancer. Brit. J. Prev. Soc. Med. *9:*62-72, 1955.
18. Chief Inspector of Factories: *Annual Report of the Chief Inspector of Factories for the Year* 1932, London, HMSO, p. 103, 1933.
19. Chief, Inspector of Factories: *Annual Report of the Chief Inspector of Factories for the Year* 1950, London, HMSO, p, 145, 1952.
20. Committee of Medical and Biologic Effect of Environmental Pollutants (CMBEFEP). Nickel, Washington, DC., National Academy of Sciences, 1975.
21. Cooper, C.W.: Study of sheet metal workers. Final Contract Report, Contract No. HSM-099-71-55, National Institute for Occupational Safety and Health, 1975.
22. Costa, M. and Mollenhourer, H.H.: Carcinogenic activity of particulate nickel compounds is proportional to their cellular uptake. Science *209:*515-517, 1980.
23. de Villiers, A.J. and Windish, J.P.: Lung cancer in a fluospar mining community I. radiation, dust and mortality experience. Br. J. Ind. Med. *21:*94-109, 1964.
24. Discher, D.P., Breitenstein, B.D., and Schweid, A. I.: Sputum cytology among aluminum potroom workers. Ann. N.Y. Acad. Sci. *271:*239-242, 1976.
25. Doll, R.: The age distribution of cancer: Implications for model of carcinogenesis. J. Roy. Statist. Soc. *A134:*133, 1971.
26. Doll, R.: Cancer of the lung and nose in nickel workers. Br J. Ind. Med. *15:* 217-223, 1958.
27. Doll, R.: Mortality from lung cancer in asbestos workers. Br. J. Ind. Med. *12:*81, 1955.
28. Doll, R., Morgan, L.G., and Speizer, F.E.: Cancers of the lung and nasal sinuses in nickel workers. Br. J. Cancer *24:* 623-632, 1970.
29. Edge, J.R.: Asbestos related disease in Barrow-in-Furness. Environ. Res. *11:*244, 1976.
30. Elmes, P.C. and Simpson, J.C.: Insulation workers in Belfast. 3. Mortality. 1940-66. Br. J. Ind. Med.*28:*226, 1971.
31. Elmes, P.C. and Simpson, M.J.C.: Insulation workers in Belfast. A further study of mortality due to asbestos exposure 1040-75. Br. J. Ind. Med. *34:*174, 1977.
32. Enterline, P.E. and Henderson, V.: Type of asbestos and respiratory cancers in the asbestos industry. Arch. Environ. Health *27:*312, 1973.
33. Fern, V.H.: Arsenic as a teratogenic agent. Environ. Health Persp. *19:*191-196, 1977.
34. Figueroa, W.G., Raszowski, R., and Weiss, W.: Lung cancer in chloromethyl methyl ether workers. New Engl. J. Med *228:* 1096-1097, 1973.
35. Frost, J.V., et al.: Pulmonary cytologic alterations in toxic environmental inhalation. Human Pathology *4:*521-536, 1973.
36. Gafafar, W.M., et al.: Health of workers in chromate producing industry: a study. U.S. Public Health Service, Division of Occupational Health, Publication No. 192, Washington, DC., U.S. Public Health Service.
37. Garcus, J.L., Reese, W.H., Rutter, H.A.: Induction of lung adenomas in newborn mice by bis (chloromethyl) ether. Toxic. Appl. Pharmacol. *15:*92-96, 1969.
38. Gloyne, S.R.: Two cases of squamous carcinoma of the lung occurring in asbes-

tosis. Tubercle *17:*5, 1935.
39. Gottlieb, L.S. and Hussen, L.A.: Lung cancer among Navajo uranium miners. Unpublished, 1980.
40. Ham, J.A.: Report of the Royal Commission on the Health and Safety of Workers in Mines. E. Ministry of the Attorney General, Province of Ontario, Toronto, Canada, 1976.
41. Hammond, E.C. and Selikogg, I. J.: Relation of cigarette smoking to risk of death of asbestos-associated disease among insulation workers in the United States. In: Proceedings of the Conference on Biological Effects of Asbestos. P. Bogovski, J.C. Gilson. V. Trimbrell, and J.C. Wagner, Eds., IARC, Lyon, p. 302.
42. Hammond, E.C., Selikoff, I. J., and Seidman, H.: Asbestos exposure, cigarette smoking and death rates. Ann. N.Y. Acad. Sci. *330:*473, 1979.
43. Harries, P.G.: Experience with asbestos disease and its control in Great Britain's naval dockyards. Environ. Res. *11:*261, 1976.
44. Harting, F.H. and Hesse, W.: Der Lungenkrebs, die Bergkrankheit in den Schneeberger Gruben. Viertelj. F. gerichtl. Med. u. offen. Sanitats. *30:*296-308, *Ibid 31:*102-132, and 313-337, 1879.
45. Hill, A.B. and Faning, E.L: Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. I. Mortality experience in the factory. Br.J. Ind. Med. *5:*1-6, 1948.
46. Hood, R.D., Thacker, G.T. and Patterson, B.L.: Effects in the mouse and rat of prenatal exposure to arsenic. Environ. Health Persp. *19:*219-222, 1977.
47. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 2, Some Inorganic and Organometallic Compounds. Lyon, pp. 100-125, 1973.
48. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Vol. 23, Lyon, pp. 143-204, 1980.
49. IARC Working Group, Nickel and Nickel Compounds, 1975.
50. Infante, P.F., Wagoner, J.K. and Sprince, N.L.: Mortality patterns from lung cancer and non-neoplastic respiratory disease among white males in the Beryllium Case Registry. Environ. Res. *21:*35-43, 1980.
51. Jorgensen, J.S.: A study of mortality from lung cancer among miners in Liruna 1950-1970. Scand. J. Work, Environ. Health *10:*126-133, 1973.
52. Kennaway, E.L. and Kennaway, N.M.: A further study of the incidence of cancer of the lung and larynx. Br J. Cancer *1:*260-298, 1947.
53. Kiviluoto, R.: Pleural calcification as a roentgenologic sign of nonoccupational endemic anthophyllite-asbestos. Acta Radiol. (suppl.) *195:*1, 1960.
54. Kogan, F.M., Guselnikova, N.A., and Gulevskaya, M.R.: The cancer mortality rate among workers in the asbestos industry of the Urals. Gig. Sanit. *37:*29, 1972.
55. Konetzke, G.W.: Berufliche Krebserkrankungen durch arsen and nickel sowei deren Verbindugen. Dtsch. Ges. Wesen. *29:*1334, 1974.
56. Konetzke, G.W.: Die kanzerogene Wirkung von Arsen und Nickel. Arch. Geschulwulstforsch *44:*16-22, 1974.
57. Konstantinov, F.G. and Kuz'minykh, A.I., Tarry substances and 3,4-benzopyrene in the air of electrolytic shops of aluminum works and their carcinogenic significance. Hyg. and Sanit. *36:*368-373, 1971.
58. Kreyberg, L.: Histological lung cancer types. A morphological and biological correlation. Acata Pathologica et Microbiologica Scandinavica, Supplement No. 157, 1962.
59. Kreyberg, L.: Lung cancer in workers in a nickel refinery. Br. J. Ind. Med. *35:* 109-116, 1978.
60. Kuratsune, M., Tokundime, S., Shirakusa, T., Yoshida, M., Tokamitsu, Y., Hayano, T., and Seita, M.: Occupational lung cancer among copper smelters. Int J. Cancer *13:*552-558, 1974.
61. Laskin, S., Drew, R.T., Cappielo, et al.: Inhalation carcinogenicity of alpha haloethers. Presented at the British Occupational Hygiene Society Fourth International Symposium, 1971.
62. Laskin, S., Kuschner, J., Drew, R.T., et al.: Tumors of the respiratory tract in-

duced by inhalation of bis (chloromethyl) ether. Arch, Environ. Health *23:*135-136, 1971.
63. Lee, A.M. and Fraumeni, J.J., Jr.: Arsenic and respiratory cancer in man: an occupational study. J. Natl. Cancer Inst. *42:*1045-52, 1969.
64. Lemen, R.A.: Lung cancer in female asbestos workers. Letter to Vernon Rose, Director, Division of Criteria Documentation and Standards Development, 1976.
65. Lemen, R.A., Johnson, W.M., Wagoner, J.W., Archer, V.E., and Saccomanno, G.: Cytologic observations and cancer incidence following exposure to BCME. Ann. N.Y. Acad. Sci. *271:*71-89, 1976.
66. Lerer, T.J., Redmond, C.K., Breslin, P.P., Salvin, L., and Rush, H.W.: Long-term mortality study of steelworkers VII: Mortality patterns among crane operators. JOM *16:*608-614, 1974.
67. Lessard, R. et al.: Lung cancer in New Caledonia—a nickel smelting island. J. Occup. Med *20:*12, 1978.
68. Liddell, F.D.K., McDonald, J.C., and Thomas, D.C.: Methods of cohort analysis: appraisal by application to asbestos mining. J. Roy. Statist. Soc *A140:*469, 1977.
69. Litvinov, N.W., Goldberg, M.S., and Kimina, S.N.: Morbidity and mortality in man caused by pulmonary cancer and its relation to the pollution of the atmosphere in the areas of aluminum plants. Acta Unionis Internationalis Contra *Cancrum 19:*742-745, 1963.
70. Lloyd, J.W.: Long-term mortality study of steelworkers V. Respiratory cancer in coke plant workers. JOM *13:*53-68, 1971.
71. Lloyd, J.W. and Ciocco, A.: Long-term mortality study of steelworkers: I. Methodology. JOM *11:*299-310, 1969.
72. Lloyd, J.W., Lundin, F.E., Redmond, C.K., and Gieser, P.B.: Long-term mortality study of steelworkers IV. Mortality by work area. JOM *12:*151-157, 1970.
73. Loken, A.C.: Lung cancer in nickel workers. Tidsskr. Norske Laegefor. *70:* 376-378, 1950.
74. Lundin, F.E., Wagoner, J.K., and Archer, V.E.: Radon daughter exposure and respiratory cancer quantitative and temporal aspects. NIOSH-NIEHS Joint Monograph No. 1, Springfield, VA., NTIS, 1971.
75. Lynch, K.M. and Smith, W.A.: Pulmonary asbestosis: Carcinoma of the lung in asbestos-silicosis. AM. J. Cancer *24:*56, 1935.
76. Mabuchi, K., Lillienfeld, A.M., and Snell, L.M.: Cancer and occupational exposure to arsenic: a study of pesticide workers. Preventive Medicine *9:*51-77, 1980.
77. Machle, W. and Gregorius, F.: Cancer of the respiratory system in the United States chromate producing industry. Publ. Health Rep. (Wash.) *63:* 1114-1127, 1948.
78. Mancuso, T.F.: Consideration of chromium as an industrial carcinogen. In: Proceedings of the International Conference on Heavy Metals in the Environment, T.C. Hutchinson, Ed. Toronto, 1975, Toronto, Institute for Environmental Studies, pp. 343-356.
79. Mancuso, T.F.: Mortality study of beryllium industry workers, occupational lung cancer. Environ. Res. *21:*48-55, 1980.
80. Mancuso, T.F.: Occupational lung cancer among beryllium workers. In: *Dusts and Disease.* R.A. Lemen and J.M. Dement, Eds. Pathotox Publishers, Park Forest, Ill, 1979.
81. Mancuso, T.F. and Coulter, E.J.: Methodology in industrial health studies. The cohort approach with special reference to an asbestos company. Arch. Environ. Health *6:*36, 1963.
82. Mastromatteo, E.: Nickel: a review of its occupational health aspects. JOM *9:*127-136, 1967.
83. Mazumdar, S., Lerer, T., and Redmond, C.K.: Long-term mortality study of steelworkers IX: Mortality patterns among sheet and tin mill workers. JOM *17:*751-755, 1975.
84. McDonald, A.D. and McDonald, J.C.: Mesothelioma after crocidolite exposure during gas mask manufacturing. Environ. Res. *17:*340, 1978.
85. McDonald, A.D., Magner, D., and Eyssen, G.: Primary malignant mesothelial tumors in Canada, 1960-1968. A pathologic review by the mesothelioma panel of the Canadian Tumor Reference Cen-

tre. Cancer, *31:*869, 1973.
86. McDonald, J.C., Becklake, M.R., Gibbs, G.W., McDonald, A.D., and Rossiter, C.E.: The health of chrysotile asbestos mine and mill workers of Quebec. Arch Environ. Health *28:*61, 1974.
87. Meurman, L.: Asbestos bodies and pleural plaques in a Finnish series of autopsy cases. Acta. Pathol. Microbiol. Scand. (Suppl.) *181:*1, 1966.
88. Meurman, L., Kiviluoto, R., and Hakama, M.: Mortality and morbidity among the working population of anthophylite asbestos miners in Finland. Br. J. Ind. Med. *31:*105, 1974.
89. Milham, S., Jr.: Cancer mortality patterns associated with exposure to metals. Ann. N.Y. Acad. Sci. *271:*243-249, 1976.
90. Milham, S., Jr. and Strong, T.: Human arsenic exposure in relation to a copper smelter. Environ. Res. *7:*172-182, 1974.
91. Morgan, J.G.: Some observations on the incidence of respiratory cancer in nickel workers. Br. J. Ind Med. *15:*224-234, 1958.
92. Newhouse, M.L. and Thompson, H.: Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. Br. J. Ind. Med *22:*261, 1966.
93. Newman, J., et al.: Histologic types of bronchogenic carcinoma among members of copper-mining and smelting communities. Ann. N.Y. Acad. Sci. *271:*260-268, 1976.
94. Ott, M. G., Holder, B. B., and Gordon, H. L.: Respiratory cancer and occupational exposure to arsenials. Arch. Environ. Health *29:*250-255, 1974.
95. Pederson, L. E., Hogetveit, A. C., and Anderson, A.: Cancer of respiratory organs among workers at a nickel refinery in Norway. Int. J. Cancer *12:*32-41, 1973.
96. Peller, S.: Lung cancer among miner workers in Joachimsthal. Human Biol. *11:*130-143, 1939.
97. Pinto, S. S. and Bennett, B. M.: Effect of arsenic trioxide exposure on mortality. Arch. Environ. Health *7:*583-591, 1963.
98. Pinto, S. S., Henderson, V., and Enterline, P. E.: Mortality experience of arsenic-exposed workers. Arch. Environ. Health *33:*325-332, 1978.
99. Pirchan, A. and Sill, H.: Cancer of the lung in the miners of Jachymov. Am J. Cancer *16:*681-722, 1932.
100. Redmond, C. K.: Comparative cause-specific mortality patterns by work area within the steel industry. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, NIOSH, HEW, Publication No. (NIOSH) 75-157, 1975.
101. Redmond, C. K., Ciocco, A., Lloyd, J. W., and Rush, H. W.: Long-term mortality study of steelworkers VI. Mortality from malignant neoplasms among coke oven workers. JOM *14:*621-629, 1972.
102. Redmond, C. K., Gustin, J., and Kamon, E.: Long-term mortality experience of steelworkers VIII: Mortality patterns of open hearth steelworkers (A preliminary report). JOM *17:*40-43, 1975.
103. Redmond, C. K., Smith, E. M., Lloyd, J. W., and Rush, H. W.: Long-term mortality study of steelworkers: III. Follow-up, JOM *11:*513-521, 1969.
104. Renard, K. G., St. C.: Respiratory cancer mortality in an iron ore mine in northern Sweden. Ambio. *2:*67-69, 1974.
105. Rencher, A. C. and Carter, M. W.: A retrospective epidemiological study of Kennecott's Utah Smelter-Phase II Mortality. Unpublished report submitted to the Kennecott Copper Corporation, New York, NY, April 1971.
106. Robinson, C. F., Lemen, R. A., and Wagoner, J. K.: Mortality patterns, 1940-1975 among workers employed in an asbestos textile friction and packing products manufacturing facilities. In: *Dusts and Disease.* R. A. Lemen and J. M. Dement, Eds. Pathotox Publishers, Park Forest, IL, 1979.
107. Robinson, H.: Long-term mortality study of steelworkers: II. Mortality by level of income in whites and non-whites. JOM *11:*411-416, 1969.
108. Rockette, H. E. and Redmond, C. K.: Long-term mortality of steelworkers X: Mortality patterns among masons. In Press.
109. Rockstroh, H. Von: Sur aetiologie des bronchialkrebses in arsenverarbeitensken. Nickelhitten. Arch. Geschwalstfo.

*14:*151-162, 1958.
110. Roth, F.: Arsenic-liver-tumors (haemangioendothelioma) (Ger). Z. Krebsforsch *61:*468-503, 1975.
111. Roth, F.: Late consequences of chronic arsenicism in Moselle vine-dressers. (Ger) Dtsch. Med. Wochenscher *82:*211-217, 1957.
112. Rubino, G. F., Scanetti, G., Conna, A., and Palestro, G.: Epidemiology of pleural mesothelioma in North-Western Italy (Piedmont). Br. J. Ind. Med. *29:*436, 1972.
113. Saccommano, et al: Histologic types of lung cancer among Uranium miners. Cancer *27*(5):15-523, 1971.
114. Sakabe, H.: Lung cancer due to exposure to bis(chloromethyl)ether. Ind. Health *11:*145, 1973.
115. Saknyn, A. V. and Shabynina, N. K.: Epidemiology of malignant neoplasms at nickel smelters. Gig. Trud. Prof. Zabol. *17:*25-29, 1973.
116. Saknyn, A. V. and Shabynina, N. K.: Some statistical data on carcinogenous hazards for workers engaged in the production of nickel from oxidized ores. Gig. Trud. Prof. Zabol. *14:*10-13, 1970.
117. Selikoff, I. J.: Asbestos disease in the United States 1918-1975. Paper presented at the Conference on Asbestos Disease, Rouen, France, October 27, 1975.
118. Selikoff, I. J.: Partnership for presention — the insulation industry hygiene research program. Ind. Med. *39:*4, 1970.
119. Selikoff, I. J., Churg, J., and Hammond, E. C.: Asbestos exposure and neoplasia. J. Am. Med. Assoc. *188:*22, 1964.
120. Selikoff, I. J., Hammond, C. and Churg, J.: Asbestos exposure, smoking and neoplasia. JAMA *204:*106-112, 1960.
121. Selikoff, I. J., Hammond, E. C., and Seidman, H.: Cancer risk of insulation workers in the United States. In: Proceedings of the Conference of Biological Effects of Asbestos, P. Bogovski, J. C. Gilson, V. Timbrell, and J. C. Wagner, Eds. IARC, Lyon, p. 209, 1973.
122. Sevc, J., Kunz, E., and Placek, V.: Lung cancer in uranium miners and long-term exposure to radon daughter products. Health Phys. *30:*433, 1976.
123. Sevc, J. and Placek, V.: Lung cancer risk in relation to long-term exposure to radon daughters. Second European Congress on Radiation Protection, Budapest, Hungary, 1977.
124. Sevc, J., Placek, V., and Jerubek, J.: Lung cancer risk in relation to long-term radiation exposure in uranium mines. Fourth Conference on Radiation Hygiene, CSSR, 1971.
125. Shuler, P. J., and Bierbaum, P. J.: Environmental surveys of aluminum reduction plants. U.S. Department of Health, Education, and Welfare. NIOSH Publication No. (NIOSH) 74-101, 1974.
126. Snihs, J. O.: The approach to radon problems in non-uranium mines in Sweden. Proceedings of the Third International Congress of the International Radiation Protection Association, September 9-14, 1973.
127. Snihs, J. O.: The approach to radon problems in non-uranium mines in Sweden. In: Proceedings of the Third International Congress of the International Radiation Protection Association, pp. 900-911, 1974.
128. Stellman, S. D. and Stellman, J. M.: *Ca-A Cancer Journal for Clinicians.* Published by the American Cancer Society. Jan/Feb *31*(1):29-43, 1981.
129. Stumphius, J.: Epidemiology of mesothelioma on Waicheren Island. Br. J. Ind. Med. *28:*59, 1971.
130. Sunderman, F. W., Jr.: The current status of nickel carcinogenesis Ann. Clin. Lab. Sci. *3:*156-180, 1973.
131. Tatarskaya, A. A.: Cancer of the respiratory tract in people engaged in nickel industry. Vop. Onkol. *13:*58-60, 1967.
132. Tatarskaya, A. A.: Occupational cancer of upper respiratory passages in the nickel industry. Gig. Trud. Prof. Zabol. *9:* 22-25, 1965.
133. Theiss, A. M., Hay, W., and Zeller, H.: Toxicology of bis(chloromethyl)ether—suspicion carcinogenicity in man. Zentralbl. Arbeismed., *23:*97-102, 1973.
134. Tourine, R. and Ramboud, G.: Les cancers bronchiques primtifs a localisation double unilaterale. J. Fr. Med. Chirurg. Thorac. *22:*757-767, 1968.
135. Tsuchiya, K.: The relation of occupation

to cancer, especially cancer of the lung. Cancer *18:*136-144, 1965.
136. UICC Working Group on Asbestos Cancers. Arch. Environ. Health *11:* 221, 1965.
137. Virtue, J. A.: The relationship between the refining of nickel and cancer of the nasal cavity. Canad. J. Otolaryng. *1:*37-42, 1972.
138. Wada, S., et al.: Mustard gas as a cause of respiratory neoplasia in man. Lancet *1:*1161-1163, 1968.
139. Wagoner, J. K., Archer, V. E., Carroll, B. E., Holaday, D. A., and Lawrence, P. A.: Cancer mortality patterns among U.S. uranium miners and millers, 1950 through 1962. J. Nat. Cancer Inst. *32:*787-801, 1964.
140. Wagoner, J. K., Archer, V. E., and Gillam, J. D.: Mortality of American Indian uranium miners. Proceedings XI International Cancer Congress (Bucalossi, P., Veronesi, U. and Cascinelli, N., Eds.). Vol. 3, pp. 102-107, Excerpta Medica International Congress Services No. 351. Excerpta Medica, Amsterdam, 1975.
141. Wagoner, J. K., Archer, V. E., Lundin, F. E., Jr., Holaday, D. A., and Lloyd, J. W.: Radiation as a cause of lung cancer among uranium miners. New Eng. J. Med *273:*181-188, 1965.
142. Wagoner, J. K., Infante, P. F., and Bayliss, D. L.: Beryllium: An etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease and heart disease among industrially exposed workers. Environ. Res. *21:*15-34, 1980.
143. Wagoner, J. K., Johnson, W. M., and Lemen, R. A.: Malignant and nonmalignant respiratory disease mortality patterns among asbestos production workers. Congressional Record, Senate Proceedings and Debates, 93rd Congress, First Session, U.S. Govt. Printing Office, Vol. 119, Part 6, pp. 7828-7830, 1973.
144. Wedler, H. W.: Asbestose und lungenkrebs. Deut. Med. Wochenschr. *69:*574, 1943.
145. Wedler, H. W.: Asbestose und lungenkrebs bei asbestose. Deut. Arch. Klin. Med. *191:*189, 1943.
146. Weill, H., Hughes, J., and Waggenspack, C.: Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. Am. Rev. Resp. Dis. *120:*345, 1979.
147. Weiss, W.: Mortality of a cohort exposed to chrysotile asbestos. JOM *19:*737, 1977.
148. Wicks, M. J., Archer, V. E., Auerbach, O., and Kuschner, M.: Arsenic exposure in a copper smelter as related to histological type of lung cancer. Am. J. Indus. Med., Vol. 2, pp. 25-31, 1981.
149. Wyers, H.: That legislative measures have proved generally effective in the control of asbestosis. Glasgow, M. E. Thesis University of Glasgow, UK, 1946.
150. Yamada, A.: On late injuries following occupational inhalation of mustard gas with special reference to carcinoma of respiratory tract. Acta. Pathol. Jap. *13:*131-155, 1963.
151. Znamenskii, S. L. W.: Occupational bronchogenic cancers in workers extracting, isolating and reprocessing nickel ore. Vop. Onkol *9:*130, 1963.