CYTOLOGIC OBSERVATIONS AND CANCER INCIDENCE FOLLOWING EXPOSURE TO BCME

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INTRODUCTION

Alkylating agents have been used increasingly in industrial processes as intermediates in organic synthesis, as organic solvents, as bactericides, as fungicides, and as cross-linking agents. During recent years alkylating agents have come under intense scrutiny because of their mutagenic and tumorigenic activities.[1]

One such alkylating agent is bis(chloromethyl)ether (BCME). It is also known as dichlorodimethyl ether and is frequently encountered as a 1–7% contaminant of chloromethyl methyl ether.[2] BCME is a colorless liquid with a suffocating odor and boils at about 102° C.[3, 4]

The carcinogenicity of BCME was first demonstrated in 1968 with skin painting in mice and subcutaneous injection in rats as the bioassay system.[5] 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 injection of BCME in newborn mice.[6]

Because industrial exposure to BCME is more likely to be respiratory than cutaneous, several animal inhalation experiments were undertaken. In 1971, Laskin et al.[7, 8] reported on 30 rats subjected to inhalation of BCME for 101 exposures at a concentration of approximately 0.1 ppm. Five of the 19 rats coming to autopsy revealed squamous cell carcinoma of the lung and five revealed esthesioneuroepithelioma arising from the olfactory epithelium. As a result of these findings, representatives of government, academia, and industry met to address the future research and regulatory actions needed for BCME. Two courses of action were then pursued by the National Institute for Occupational Safety and Health (NIOSH). Firstly, NIOSH initiated a rapid investigation of health and environmental conditions of plants producing anion-exchange resins, a manufacturing process involving BCME as a contaminant. In cooperation with the Health Department of San Mateo County in California, an in-depth hygiene survey was undertaken at a local chemical facility that had developed and used the anion-exchange resin production system involving BCME since about 1955.[9] The health evaluation part of the study involved sputum cytology, since it is a sensitive method for assessing early injury to the bronchial epithelium by a carcinogenic agent, and also shows lung malignancy long before it appears radiographically. Accordingly, a sputum cytology survey in concert with a retrospective cohort study were initiated in the plant cited above to evalu-

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ate the role of BCME in the induction of lung cancer among humans. Secondly, a contract was awarded to New York University for further epidemiological investigations of other anion-exchange facilities.

Results of the study in San Mateo County initially reported by NIOSH in 1973 [10] have been updated and are presented herein with other pertinent new data.

Sputum Cytology Survey

Methods

Cough was induced in each employee of this chemical firm by oropharyngeal exposure to an ultrasonically nebulized solution of about 1% propylene glycol in distilled water. The sputum coughed up by each of the 115 white male current employees was collected separately in a solution of 50% ethanol and 0.8% Carbowax®. Exfoliated cells in the sputum were concentrated by the method of Saccomanno et al.,[11] and smears were made from the sediment with a Papanicolaou stain. Sputum specimens were examined by both cytotechnicians and a pathologist. Each slide was classified as to the type of exfoliated cells seen. Special emphasis was placed on the presence or absence of metaplastic and atypical cells. Atypias were classified as mild, moderate, or marked.[12-14] Sputum that had been obtained during 1969–1972 in connection with studies on uranium miners [15] were available. These samples from uranium miners had been collected, processed, and interpreted in the same manner and by the same personnel as were those from workers in the anion-exchange chemical facility under study. Thus, these uranium-miner sputum data provided a sampling frame from which controls could be selected for each anion-exchange worker who submitted to sputum examination. Uranium miner controls were limited to those individuals who worked above the ground in the uranium industry, since this group was known to experience no unusual lung cancer risk.[16] At the time of sputum collection from the 115 anion-exchange chemical workers, a questionnaire was completed to obtain information on history of tobacco usage. Simultaneously, occupational histories were obtained on all current and past employees.

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,[17] an interval of five years or more of nonsmoking was defined as "former smoking." Cigar and pipe smoking was regarded as "nonsmoking" because of the inherent difficulties involved and because their role in the etiology of lung cancer is very small, as compared to cigarette smoking.

Anion-exchange workers were matched sequentially with use of a random list of surface miners based on similar cigarette usage, ± 6 cigarettes/day, and age at time of sputum collection, ± 5 years.

Evaluation of cases and matched controls was undertaken separately for two groups: (1) male office employees and employees exposed less than five years in the production and maintenance operation; 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,[18, 19] 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. Also, this dichotomization was made after observations derived from the industrial hygiene survey conducted at the facility.

The McNemar Chi-square method [20] for matched pairs was used to evaluate the significance of cytologic distribution for each anion-exchange group and its appropriate control.

Results

TABLE 1 shows the distribution of sputum cytology among those anion-exchange employees with the least or no exposure to BCME. As can be seen, there is no association between type of work and degree of abnormal cytology (17% anion-exchange workers vs. 15% controls).

By contrast, however, TABLE 2 demonstrates that statistically significant association of abnormal cytology associated with exposure to BCME for five or more years. As can be seen, 34% of anion-exchange workers in this group had abnormal cytology, as contrasted with only 11% for uranium surface miners.

RETROSPECTIVE COHORT INVESTIGATION OF LUNG CANCER INCIDENCE

Methods

To evaluate the incidence of lung cancer at this anion-exchange facility, occupational histories were ascertained from company employment files. The study was restricted to the 136 males having achieved five years of employment

TABLE 1

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

* χ^2 = Not significant.

in the plant between January 1, 1955 through March 31, 1972 who were selected for study.

An attempt was made to obtain follow-up of group members from the time of termination of employment to the end of the study period. Vital status was determined through records maintained by federal, state, and local government agencies, including sources such as the Social Security Administration, state vital statistics offices, and state motor vehicle registration files. For those individuals not located through these data sources, others, such as city directories, post office mailing correction services, retail credit bureau searches, voter records, and various local records were used. As a result of this intense follow-up program, no member of the study group was "lost-to-observation." Death certificates were obtained for the known dead and causes of death were interpreted by a qualified nosologist, according to the *Revision of the International Lists of Disease and Causes of Death* in effect at the time of death.

TABLE 2

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 (66%)
	Moderate to Marked Atypia	26	3	29 (34%)
	Total	39 (89%)	5 (11%)	44

χ^2=Significant $p < .025$.

A modified life-table technique was used to obtain person-years at risk of developing lung cancer by five-year age groups and number of years after start of BCME exposure. Comparison was made between the observed risk of developing lung cancer among the study cohort and that expected, with use of age-respiratory cancer-specific incidence rates for white Connecticut males, 1960–1962.

Results

As shown in TABLE 3, during the study period January 1, 1955 through March 31, 1972, nine members of the cohort were identified as being deceased and 127 were known to be alive. Among the total of 136 workers, five of these deaths were due to heart disease, one to lymphosarcoma, and three to bronchogenic cancer. There were two additional persons alive at the cut-off date who had a definite diagnosis of bronchogenic cancer.

TABLE 3

STATUS OF BCME STUDY COHORT AS OF MARCH 31, 1972

Known to be Alive	127
Known to be Deceased	9
Lost-to-Observation	0
Total	136

TABLE 4 shows that whereas only 0.54 cases of lung cancer would have been expected to occur in the plant population, five cases actually 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 5. 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.

Examination of the data in TABLE 6 indicated that the reported cases of bronchogenic cancer were among relatively young persons (mean age 47 years) and that the induction-latency period (mean of 15 years) is consistent with that of other occupational lung cancer. The predominant histologic type of carcinoma found was small cell-undifferentiated, and exposure ranged from seven years, seven months to fourteen years (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 ten years since onset of employment, and indeed only eight percent occurred after 15 years since onset of exposure, a vast majority of these workers have not yet developed sufficient latency for disease manifestation.

TABLE 4

PRODUCTION AND MAINTENANCE WORKERS WITH ≥5 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	.54	5
$SIR = \frac{5}{.54} \times 100 = 924$	$p < 0.01$		

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

TABLE 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	61	11 yr, 3 mos	13	10/days–40 yr	large cell-undifferentiated
2	35	7 yr, 7 mos	8	unknown	small cell-undifferentiated
3	48	9 yr, 5 mos	10	40/days–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 of cig."	small cell-undifferentiated

DISCUSSION

The results of both the sputum cytology investigation and the lung cancer incidence study indicate that the workers of this plant have an unusually high cancer risk.

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.

TABLE 6

BRONCHOGENIC CANCERS AMONG BCME WORKERS *

Case	Age at Cancer (years)	Years of Possible Experience	Induction-Latency Period (years)	Cigarette Usage	Type of Cancer Histologic
1	59	6	8	Smoking histories were 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		

* From Thiess *et al.*[21]

TABLE 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	37	7		none	unknown
2	33	8		20/days–20 yr	small cell-undifferentiated
3	39	8		20/days–20 yr	small cell-undifferentiated
4	47	10		20/days–0 yr	small cell-undifferentiated
5	52	4		20/days–10 yr	small cell-undifferentiated
6	47	3		20/days–21 yr	small cell-undifferentiated
7	43	14		20/days–20 yr	small cell-undifferentiated
8	53	10		40/days–20 yr	small cell-undifferentiated
9	48	5		20/days–33 yr	small cell-undifferentiated
10	50	0–1		20/days–30 yr	epidermal
11	55	12		20/days–40 yr	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

* From Figueroa *et al.*[2]

In the present 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). This appears lower than the number reported in 1973 by Thiess et al.[21] (TABLE 6), who reported eight of fourteen deaths due to respiratory cancer, and twelve of fourteen deaths due to all malignancies (cancer of bladder, testes, respiratory, and stomach). Six of Thiess's cases occurred among 18 experimental technical department workers, a group known to experience very high exposures, contrasted with one in the present study. When looking at only manufacturing workers, Thiess reports two lung cancers among 50, a finding similar to the present study where four occur among 136 manufacturing workers.

As shown in TABLE 7, Figueroa et al.[2] reported that among 125 workers in

TABLE 8

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

* From Sakabe.[28]

a chemical plant participating in a program designed after the Philadelphia Pulmonary Neoplasm Research Project,[22] four cases of lung cancer occurred during the first five-year period of observation. Considering that age, sex, and smoking habits were not significantly different, his observation of 4.54% occurrence among the workers vs. only 0.57% among participants of the Philadelphia Pulmonary Neoplasm Research Project is significant, representing an eightfold excess. After further retrospective observation, ten additional lung cancer cases among individuals working in the plant were identified. However, no population figure or time period was given to determine the incidence.

TABLE 8 shows that in 1973 Sakabe[23] reported five cases of lung cancer among 32 employees exposed to BCME in a dyestuff factory in Japan. 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 by Thiess et al.[21] and Figueroa et al.,[2] the incidence of lung cancer among manufacturing workers, approximately 3–5%, were similar. This is contrasted with more than 12% found in Sakabe's study.[23] His observation probably reflects the nature of the dyestuff plant, where those at risk could be specifically identified. Since 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[24] and with nitrogen mustard,[25] 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, of the men who developed lung cancer had smoked cigarettes. This suggests that cigarette smoke may interact with the primary carcinogen, in a promotional or synergistic fashion, just as it does with asbestos[26] and radiation cancers.[27] The facts 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 provide further evidence that BCME is the primary agent, rather than cigarette smoke.

It has recently been reported that gaseous mixtures of hydrochloric acid and formaldehyde may be present in a large number of biological and chemical laboratories. NIOSH, in cooperation with several manufacturers and numerous medical and scientific personnel, has been investigating the possibility of BCME formation from the reaction of formaldehyde and ionic chloride compounds found in selected work environments. Thus far, NIOSH has found BCME to occur spontaneously in concentrations of parts/billion in the textile industry[29] where both formaldehyde and the chloride ion are present. NIOSH is currently working with this industry to eliminate this formation of BCME. Work is also continuing to determine if the formation of this chemical will occur in other industrial and laboratory settings where formaldehyde and ionic chloride are present, such as particle-board manufacturing, paper manufacturing, insect-rearing laboratories, and various medical environments. Efforts should be made

to ascertain that these two volatile substances are not used in the same setting except under well-controlled conditions.

Summary and Conclusion

The investigative cycle has now advanced full circle. The carcinogenicity of BCME, initially discovered in laboratory-animal experiments, spurred occupational epidemiological sputum cytology and cancer-incidence studies which demonstrated the carcinogenicity of BCME in humans. In turn, these observations spurred laboratory investigations into the spontaneous formation of BCME. Subsequently, this spontaneous formation of BCME was demonstrated to occur in select industrial settings.

These observations on the carcinogenicity of BCME, first in animals and subsequently in man, strongly support the need for animal testing prior to introduction of agents into the environment.

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