HAZARD REVIEW

OF

BIS(CHLOROMETHYL)ETHER (BCME)

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16. Abstract (Limit: 200 words)

The toxic hazards of bis(chloromethyl)ether (BCME) are discussed. The findings of a variety of studies on BCME carcinogenicity in laboratory animals are summarized, including skin painting tests in Swiss-mice, injection tests in rats, subcutaneous injection tests in Swiss-mice, inhalation exposure tests in in mice and Sprague-Dawley-rats. Occurrences of fibrosarcomas, fibromas, and lung adenomas in these animals are discussed. The results of a NIOSH survey of bronchial damage and lung cancer incidence among workers exposed to BCME at an anion exchange resin production factory are reviewed, including an increased incidence of abnormal sputum cytology and of lung cancer, particularly undifferentiated oat cell carcinoma. An increased incidence of lung cancer among workers exposed to chloromethyl-methyl-ether is discussed with respect to the probable concomitant exposure to BCME. Lung cancer deaths are also discussed among 8 of 68 workers from a facility where BCME exposures occurred. The formation of BCME from the reaction of hydrogen-chloride with formaldehyde is described. The author concludes that BCME may be one of the most potentially hazardous carcinogens found in the workplace. The possibility of BCME formation must be considered wherever both hydrogen-chloride and formaldehyde are present. The most stringent measures should be used to prevent any worker exposures to BCME.

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Hazard Review

of

Bis(chloromethyl)ether (BCME)

The first accounting of a carcinogenic potential for bis(chloromethyl)ether (BCME) was made by Van Duuren et al [1] in 1968. In this report Van Duuren et al compared the toxicity of BCME with its monofunctional analog, chloromethyl methyl ether (CMME), and discovered the former to possess much greater potential for inducing skin tumors in mice and rats. He classed BCME with such other biologically active alkylating agents as nitrogen mustards, epoxides, and beta-lactones. In the study, Swiss mice were skin painted with 2.0 mg BCME/0.1 ml benzene three times a week for 325 days. Of 20 mice so treated, 13/20 developed palpillomas of which 12 progressed to squamous cell carcinomas by the termination of the exposure period. The prior application of benzo[a]pyrene as an initiator served only to reduce the latency period for tumor induction, but did not increase tumor yield. No tumors developed in the vehicle control animals.

In a related experiment, 6-week old rats were injected 3 times monthly with 3.0 mg BCME/0.1 ml paraffin oil for 301 days, until severe ulceration at the site of injection precluded further injections. Of the 20 rats [2] so treated, these investigators reported 11 animals with palpable lesions, 2 with fibrosarcomas and one with a fibroma. A later paper by these investigators [2], which

updated these initial findings [1], reported a total of 5/20 animals developed fibrosarcomas and 2 developed fibromas. The BCME used in the study was determined to be greater than 99 percent pure with a trace of a carbonyl-containing impurity, but no detectable quantity of CMME. In the latter study [2] the investigators concluded that, "A single exposure to either CMME or BCME followed by continued low levels of environmental tumor-promoting agents can be tumorigenic."

Gargus et al [3] published a study in 1969 in which newborn Swiss mice were given a single subcutaneous injection of 12.5 µl BCME/kg body weight in 0.05 ml peanut oil. Of the 100 mice so treated (50 male; 50 female), 45/100 developed lung adenomas (45 percent). In vehicle control animals only 7/50 animals developed lung adenomas (14 percent). Commercial grade BCME was used in this study.

In 1971 Leong et al [4] published the results of their investigations involving the induction of lung adenomas in tumor-sensitive mice (Strain A/Heston) exposed to 1 ppm of industrial grade BCME vapor. Analytical determination of the BCME concentration in the animal exposure chambers was not accomplished. Instead, the exposure concentration (1 ppm) was maintained by proportioning the rate of diluent airflow and precision metering of BCME into the airstream. Fifty (50) of the animals were exposed to this concentration of BCME for 6 hours/day, 5 days/week for 82 exposure days in 27 weeks. A total of 37 animals died during the exposure period. Of 47 animals

autopsied, 37 were discovered with lung abnormalities and 26 of the 37 had developed lung tumors (55 percent of the total) with the remaining animals showing pinpoint pulmonary hemorrhages. The mean number of tumors per animal was 2.89. The control group (with a known base frequency of spontaneous lung tumor incidence of 40 percent) recorded 20/49 with lung tumors. The investigators emphasized in the study that, in addition to the carcinogenic potential of BCME, the absence of irritant warning renders this substance extremely hazardous in the occupational setting.

Another inhalation study conducted by Laskin [5], and published in 1971, reported on the extreme hazard associated with exposure to only very small concentrations of BCME. In the study, 30 Sprague-Dawley rats were exposed to 0.1 ppm BCME for 6 hours/day, 5 days/week, for 101 exposures. All 30 of the animals died within 659 days from the initiation of exposure. Histologic examination had been completed on 19 of the 30 animals at the time of the report and squamous cell carcinoma of the lung had been discovered in 5/19. Five (5) other animals revealed esthesioneuroepitheliomas arising from the olfactory epithelium which invaded the sinuses, cranial vault and brain, and one animal had both types of tumors. The pulmonary tumors were observed earlier than the nasal tumors; 332 to 463 days compared to 346 to 488 days, respectively, after initiation of exposure.

In light of the startling incidence of lung carcinomas among rats following chronic inhalation of 0.1 ppm BCME, the National Institute for Occupational Safety and Health undertook a rapid investigation of plants producing anion exchange resins, a manufacturing process involving BCME as a contaminant in the chloromethylation of polystyrene beads. [6]

Selected for study was a chemical facility which developed and used an anion exchange production system since about 1955. An industrial hygiene survey was made of this facility in early 1972. [7] As sputum cytology was considered a sensitive method for assessing early injury to the bronchial epithelium by carcinogenic agents long before lung malignancy appears radiographically, sputum samples were obtained by standard techniques on 115 current employees at this facility.

Survey results (Tables I and II) demonstrated that the prevalence of moderate and marked atypia cytology was significantly higher ($p < 0.025$) among persons exposed to BCME for 5 or more years than among age-sex cigarette matched uranium surface workers not so exposed. No significant difference in cytology was demonstrable, however, for office employees and those individuals employed less than 5 years in areas involving BCME exposure as contrasted with their age-sex cigarette matched controls.

Although no frank malignancies were detected during the course of this sputum survey, the results were consistent with a carcinogenic stimulus of BCME.

Further substantiation of the human carcinogenicity of BCME is provided by provisional results of a NIOSH retrospective cohort study of lung cancer incidence among all former and current employees of this plant (Table III). A significantly increased risk of lung cancer (4 observed vs 0.54 expected, $p<0.01$) was demonstrated within 15 years since onset of exposure among those individuals employed for 5 or more years in production-maintenance operations involving BCME. In addition to the 7 fold increase of lung cancer among this group, a preponderance of undifferential oat cell carcinomas was found. This pattern of risk and histology is similar to that recently reported below by Figueroa et al [8] for another anion exchange facility.

A contemporary epidemiologic study by Figueroa, Raszkowski and Weiss [8] has strongly implicated CMME as a human carcinogen, although concomitant exposure to BCME probably occurred also. The study involved 14 cases of lung cancer in workers exposed to CMME for estimated periods of one to 14 years. All but one of 13 histologically confirmed cases had oat cell carcinoma of the lung. An incidence of 4.54 percent occurred in a prospective five-year study of 125 exposed workers in which the 4 cases observed during this period were in a group of 88 workers 35 to 54 years of age. The incidence of

lung cancer in the Philadelphia Pulmonary Neoplasm Research Project, [9] which was conducted in conjunction with the reported study, was 0.57 percent. The statistical difference between the two indices was highly significant (p 0.0017). One of the cases involved a chemical operator who had been exposed to CMME for 12 years and ". . . stated that 13 of his fellow workers had lung cancer . . ." Working conditions, as described by this employee, had been primitive with open containers of CMME and visible fumes. Furthermore, ". . . The employees considered it a good day if the entire building had to be evacuated only three or four times per eight-hour shift because of noxious fumes."

Retrospective investigation of medical records and smoking histories of all 14 cases revealed that 3 of the 14 had never smoked and that all workers with oat cell carcinoma (12/14) died within 20 months of diagnosis.

The finding that all but one of the 13 histologically confirmed cases involved oat cell carcinoma of the lung, a particularly rare type of lung carcinoma in the general population, [8] further implicated an alkylating agent as the etiologic factor. Wagoner [10] et al emphasized in their epidemiologic study of uranium miners published in 1965 that oat cell carcinoma was the predominant type of lung cancer observed in uranium miners, and also in a Japanese study [11] of workers exposed to mustard gas (an alkylating agent). In a

contemporary paper, Archer, Saccomanno, and Jones [12] presented evidence that the number of cases of oat cell carcinoma of the lung among uranium miners was 24 times greater than that "expected." Alkylating agents are considered to be radiomimetric in their biologic activity.

Figueroa et al [8] stated in their paper that commercial grade CMME contains 1 to 8 percent BCME. On the basis of previous animal investigations which have demonstrated a greater carcinogenic potential for BCME as contrasted to CMME, it must be supposed that the BCME content of the CMME may have been responsible for the observed carcinogenic effects in humans in this study. However, the fact that substantial exposure to CMME (and, it must be presumed, to BCME) did occur in each of the 14 cases demands that a carcinogenic role for this halo ether cannot be eliminated.

In a contemporary paper published by Thiess et al [13] in 1973, it was reported that of 18 individuals employed in a technical research center, 6 died with carcinoma of the lung. In addition, 2 of 50 production facility employees died of lung cancer within the same 6-year exposure period (1956-1962). The average latency period to appearance of lung tumors was 8 to 16 years. Of the 8 total cases observed, 5 were diagnosed as "small-cell carcinoma" ("oat cell carcinoma"). No environmental measurements were made for BCME concentration in the workplace during the exposure period under

consideration (1956-1962), but such concentrations were considered minimal because of the readiness with which BCME is detected at very low concentrations due to its strong irritant action.

It is of interest that the production facility, where 2 of the cases of lung cancer occured, was a "closed unit" equipped with an exhaust apparatus and workers were required to wear fresh air masks.

The investigators concluded that:

> On the basis of information now available, we believe that the lung cancer cases reported by us are, with definite probability, caused by many years of breathing unknown amounts of dichlorodimethyl ether [BCME]. This assertion is supported by animal tests available in the meantime and also by the known observations made in California.

Van Duuren, Laskin, and Nelson [14] summarized the potential hazard associated with exposure to CMME and BCME in a letter to the Editor of Chemical and Engineering News on March 27, 1972:

> Chemical carcinogens can be either direct-acting or indirect-acting. The latter type have to be metabolized in vivo to proximal carcinogens and, hence, these indirect-acting agents are highly organ and species-specific since the metabolic patterns vary by organ and

species. The direct-acting agents, which include alkylating carcinogens such as CMME and BCME, act normally at the site of exposure and they are carcinogenic in several species and organs but usually only at the site of exposure. Since these direct-acting alkylating agents are carcinogenic in several animal species, they must be regarded as potentially carcinogenic in man. The alpha-chloro ethers should, therefore, be regarded as potentially serious occupational hazards in chemical industry and in research laboratories where they may not always be handled with proper precautions.

An announcement [15] recently has been made that hydrogen chloride (HCl) and formaldehyde (HCHO) combine under ordinary ambient conditions, or in aqueous solutions, to form BCME. The importance of this discovery as concerns the ubiquitous availability of BCME is readily apparent. It must not be overlooked in this respect, however, that CMME rapidly decomposes both in air and in aqueous solutions to yield the above reactants [1,13,15]:

$$ClCH_2-O-CH_3 + HOH \rightleftharpoons CH_3OH + HCHO + HCl$$

Hence, pure CMME even under the most rigid experimental conditions is practically impossible to obtain or, once produced, to maintain without the subsequent formation of small amounts of BCME. Therefore,

the practicability of exposure to CMME in the workplace without concomitant exposure to BCME is highly questionable.

It is very possible, based on available animal studies and epidemiologic investigations of exposed workers, that BCME may be one of the most potentially hazardous carcinogens found in the workplace. The fact that under ordinary conditions BCME is formed whenever formaldehyde and hydrogen chloride are present requires continuous surveillance of workplaces where these two compounds may be present simultaneously. The hazard of lung cancer from occupational exposure to BCME requires the most stringent measures be employed to assure employees are not exposed to this substance by any route.

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TABLE I

SPUTUM CYTOLOGY OF
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	Moderate to Marked Atypia	13	2	15 (34%)
	Normal Metaplasia, Mild Atypia	26	3	29 (66%)
	TOTAL	39 (89%)	5 (11%)	44

X^2 - Significant $p < .025$

Archer, VE et al: Carcinogenicity of bis(chloromethyl)ether. Manuscript in preparation. Division of Field Studies and Clinical Investigations, NIOSH

TABLE II

SPUTUM CYTOLOGY OF
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	Moderate to Marked Atypia	11	1	12 (17%)
	Normal Metaplasia, Mild Atypia	49	10	59 (83%)
	TOTAL	60 (85%)	11 (15%)	71

X^2 - Not Significant

Archer, VE et al: Carcinogenicity of bis(chloromethyl)ether. Manuscript in preparation. Division of Field Studies and Clinical Investigations, NIOSH

TABLE III

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

Age	5-9	10-14	15-19	≥ 20	Total	Exp.	Obs.
20-24	5	3			5	.0001	
25-29	56				59	---	
30-34	74	16	1		91	.0028	
35-39	77	28	2		107	.0095	2
40-44	74	59	1		134	.0328	
45-49	45	39	19		103	.0526	1
50-54	22	21	8	5	56	.0518	
55-59	34	13	8		55	.1055	
60-64	20	26	4		50	.1325	1
65-69	8	17	7		32	.1004	
70-74		8	7		15	.0532	
≥75	-	-	-	-	-	-	-
Person Years	415	230	57	5	707	.5413	4
Percent Person Years	58.7%	32.5%	8.8%				

SIR = 4/.5413 x 100 = 733 Confidence limit p<.01 .672

Exp. based on age = respiratory tract cancer specific incidence
white Connecticut males, 1960-1962.

Archer, VE et al: Carcinogenicity
of bis(chloromethyl)ether. Manuscript
in preparation. Division of Field
Studies and Clinical Investigations, NIOSH