HAZARD REVIEW

OF

CHLOROMETHYL METHYL ETHER (CMME)

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Chloromethyl methyl ether (CMME) is used commercially in organic synthesis as a chloromethylating agent, in the manufacture of ion exchange resins, in the treatment of textiles, in the manufacture of polymers, and as a solvent for polymerization reactions. Because of its reactivity, CMME is highly irritating to the skin, eyes, and mucous membranes. [1] With the exception of one less -Cl atom, CMME is structurally identical to its highly carcinogenic bifunctional analog, bis(chloromethyl)ether (BCME). It is, therefore, of utmost importance in any consideration of the health consequences of occupational exposure to CMME that cognizance be given to concomitant exposure to BCME, which is normally present in commercial grade CMME in quantities of 1 to 7 percent. [2,3] Likewise, in evaluating experimental evidence implicating CMME as a carcinogen, it is important also to know the BCME content of the CMME.

Van Duuren et al [1] presented the first evidence for the carcinogenicity of the alpha-haloethers in 1968 and classified them with other such biologically active alkylating agents as nitrogen mustards, epoxides and beta-lactones. The study, which involved skin application of BCME or CMME of mice (2.0 mg/0.1 ml benzene 3 times weekly for 47 weeks) provided no evidence for CMME of "complete" carcinogenicity, although a slight irritating activity was elicited in mice when croton resin (0.025 mg/0.1 ml acetone) was used as a

promoting agent. Of 20 rats injected subcutaneously with CMME (1 to 3 mg/injection 3 to 4 times monthly) 13 developed sizable palpable lesions in the treatment area. The purity of the CMME used in the study was verified by I.R. and GLC analysis, with no BCME detected.

A study by Gargus et al [4] published in 1969 in which newborn Swiss mice were given a single subcutaneous injection of CMME (125 ul/kg body weight) revealed no significant difference between experimental and control animals. Unlike the purity of the CMME used by Van Duuren, [1] the two samples used by Gargus contained 0.3 and 2.6 percent of BCME, respectively.

In a later report [5] of the results of the study by Van Duuren et al published earlier, [1] CMME proved to possess activity only as an initiating agent in skin application, with phorbol ester as the promoting agent. Under these conditions, 1000 and 100 ug of CMME induced papillomata in 5/20 and 7/20 mice, respectively, and squamous cell carcinomata in 1/20 and 4/20, respectively. One of 20 rats injected with 3 mg CMME/0.1 Nujol developed a malignant injection site fibrosarcoma. These investigators concluded that: "A single exposure to either CMME or BCME followed by continued low levels of environmental tumor-promoting agents can be tumorigenic."

In 1971 Leong et al [6] published the results of their investigations involving the induction of lung adenomas in tumor sensitive mice (strain A/Heston) exposed to 2 ppm of CMME vapor. The

CMME used for the animal exposures contained 0.5 to 2.6 percent BCME. Analytical determination of the CMME concentration in the animal exposure chambers was not accomplished. Instead, the exposure concentration (2 ppm) was maintained by proportioning the rate of diluent airflow and precision metering of CMME into the airstream. Fifty (50) of the mice were exposed to this concentration of CMME for 6 hours/day, 5 days/week for 101 exposure days in 21 weeks. Lung abnormalities occured in 37/50 animals and of these 37, 25 (50 percent) developed lung tumors. The mean number of tumors for this group was 1.53/animal compared to 0.87/animal in an unexposed control group of 50 animals. The control group (with a known base frequency of spontaneous lung tumor incidence of 40 percent) recorded 20/49 with lung tumors. The investigators concluded in this study that the carcinogenicity of CMME could not be established because of the small contamination of the CMME by BCME.

Van Duuren et al [7] used CMME as a positive control compound in a series of experiments published in 1971. Of 30 mice, injected subcutaneously with CMME once a week with 300 ug/0.1 ml Nujol for 26 weeks, 10 developed malignant sarcomas at the site of injection including 5 lymphoblastic lymphosarcomas and 5 spindle cell sarcomas. The CMME used in the experiment was purified as reported earlier [1] by these investigators in which no BCME contamination was discovered.

A contemporary epidemiologic study by Figueroa, Raszkowski and Weiss [2] 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 CME for estimated periods of one to 14 years. Regarding exact exposure durations the investigators stated that:

> Estimates on duration of exposure to CME were obtained from Case 14 since company management was unable to provide this information. Because they depend on one man's memory, these estimates are only approximate, and the exact chronologic relation between exposure to CME and diagnosis of the cancer is uncertain.

All but one of 13 histologically confirmed cases had oat cell carcinoma of the lung. An incidence of 4.54 percent occured 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, [8]. 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 CME 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 CME 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 (12/14) with oat cell carcinoma 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 [9] 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 of workers exposed to mustard gas (an alkylating agent). In a contemporary paper, Archer, Saccomanno, and Jones [10] 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 radiometric in their biologic activity.

Figueroa et al [2] stated in their paper that commercial grade CME contains 1 to 7 percent BCME. On the basis of previous animal investigations which have demonstrated a greater carcinogenic potential for BCME as contrasted to CME, 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.

A field survey conducted by NIOSH personnel in 1972 [11] revealed 6 cases of lung cancer in a West Coast facility which formed both BCME and CMME in the manufacture of ion exchange resins and employed approximately 75 "blue-collar" workers. At least 4 of the 6 employees with lung cancer had worked in operations involving exposure to BCME and CMME. It was concluded from the field survey that an excess lung cancer risk was suspect in the worker population, and the results of a recent sputum cytologic survey among workers has demonstrated a greater than normal proportion with atypical sputum cells. Although BCME was suspected as the etiologic agent in this survey, the contributory influence of CMME was unknown.

An announcement [12] 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 [1,3]:

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

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.

Aside from the work of Van Duuren et al which demonstrated an initiating role for CMME in one study [1,5] and injection site sarcomata in another, [7] other animal studies, [4,6] and several epidemiologic studies, [2,11] which have demonstrated a carcinogenic potential for CMME have also included some contaminating exposure to BCME as well. Nevertheless, Van Duuren et al [3] considered occupational exposure to CMME to present a real hazard:

> 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.

Although contaminating exposures to BCME have precluded a definitive role for CMME, the industrial experience with this halo ether is sufficient reason to consider CMME as a carcinogen.

Bibliography for Chloromethyl Methyl Ether (CMME)

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