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REVIEW

Comparison of Potency of Human Carcinogens: Vinyl Chloride, Chloromethylmethyl Ether and Bis(chloromethyl)ether

BENJAMIN L. VAN DUUREN

Laboratory of Organic Chemistry and Carcinogenesis, Institute of Environmental Medicine, New York University Medical Center, New York, New York 10016

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The α-chloroether carcinogen chloromethylmethyl ether (CME) and its impurity bis(chloromethyl)ether (BCME) are direct-acting alkylating agents. Vinyl chloride (VC) is an indirect-acting carcinogen but its accepted carcinogenic intermediate, chloroethylene oxide, is also an α-chloroether. Both CME–BCME and VC have been in industrial use since about 1950. Hence, they were selected for comparison of potency as human carcinogens using numerous epidemiologic reports. There were 115 deaths due to angiosarcoma of the liver among several hundred thousand VC-exposed workers on the basis of reports from 10 countries during 1955 and 1984 Reports from five countries cited a total of 87 respiratory cancer deaths among only 3024 CME–BCME-exposed workers. If a recent court settlement in the United States is taken into account, the number of respiratory cancer deaths due to CME–BCME rises to 117. On the basis of these numbers of cancer deaths, and the levels and durations of exposure, it is concluded that VC is a weak human carcinogen compared to CME–BCME.

INTRODUCTION

Thirty-six chemicals or mixtures of chemicals are now classed as materials for which there is sufficient evidence of human carcinogenicity (IARC, 1987). They are referred to as Group 1 human carcinogens by the IARC. In most instances sufficient animal carcinogenicity data are also available for these 36 materials. Included in this group are chloromethylmethyl ether (CME), bis(chloromethyl)ether (BCME), and vinyl chloride (VC). The purpose of the present report is to compare the potency of these carcinogens to humans based on animal bioassay data and epidemiologic studies.

These chemicals came into use in chemical industry at about the same time, 1950, although VC was used on a small scale prior to 1950. The animal and human carcinogenicity data on these chemicals first became known during the years 1968–1973. Since then, extensive studies on their animal carcinogenicity and epidemiologic studies on occupational exposure to them have been carried out. Thus, they provide a valuable series in which to compare potency as human carcinogens.

The animal carcinogenicity results on CME, BCME, and VC preceded publication of the first case reports and epidemiologic studies by several years. Thus, these human carcinogens are unusual in that the historical sequence of events for

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most human carcinogens is the reverse. For most of the 36 chemicals on the current list of Group 1 human carcinogens, epidemiologic studies provided the stimulus for subsequent laboratory animal carcinogenesis bioassays and related biochemical studies, as was pointed out in the preamble of the most recent compilation (IARC, 1987).

INDUSTRIAL PRODUCTION

CME is used on a small scale in chemical industry as an intermediate in the manufacture of anion-exchange resins from polystyrene and related polymers (Van Duuren *et al.*, 1968).

The resin made from polystyrene, CME, and trimethylamine, named Amberlite IRA-400, is used in the purification of household water and on a larger scale for deionization of water used by the electric power and pharmaceutical industries.

CME is synthesized from methyl alcohol, hydrochloric acid (HCl), and formaldehyde (CH_2O). The latter two reagents lead to the formation of BCME. Thus, CME as manufactured and used contains varying amounts of BCME, ranging from 1 to 10%, depending upon the exact conditions of manufacture (Van Duuren 1980). BCME was manufactured on a pilot-plant scale when CME first came into full-scale production, but it is not used in chemical industry because of its acute toxicity. Because CME as manufactured and used contains BCME, these two chemicals are referred to as CME–BCME in the discussion on occupational exposure that follows.

VC was used in industry from about 1930 but did not come into large-scale use until about 1950 for the manufacture of its polymer (PVC) and copolymers, e.g., with vinylidine chloride (Wessling and Edwards, 1971).

Production figures for CME–BCME or the anion-exchange resins for which it is used were not given in any of the published epidemiologic studies and could not be ascertained from industry sources. VC on the other hand, is No. 8 on the list of the top 10 organic chemicals manufactured in the United States (Anonymous *Chem. Eng. News*, 1988). In 1987, 8.23 billion pounds of VC was manufactured in the United States alone. It was estimated that in the same year 7.6 billion pounds of PVC was manufactured in the United States (Anonymous *Chem. Eng. News*, 1987). Because of the relatively limited use of anion-exchange resins compared to PVC, it can be safely concluded that the amount of CME–BCME manufactured worldwide is minuscule by comparison to the amount of VC produced. It should be noted that both CME and BCME are used in laboratory syntheses as alkylating agents in reaction with nucleophiles such as amines, as well as in displacement and addition reactions (Summers, 1955).

ANIMAL BIOASSAYS

Laboratory-purified CME is a weak carcinogen and an initiating agent in two-stage carcinogenesis on mouse skin. It also causes induction of fibrosarcomas by subcutaneous injection in rats. BCME is a mouse skin initiating agent and carcinogen and causes fibrosarcoma by subcutaneous injection in rats. In all three bioassays BCME was notably more potent than CME (Van Duuren *et al.*, 1968, 1969). In further studies subcutaneous injection of CME and BCME in newborn mice resulted in increased induction of lung adenomas in animals exposed to

BCME but not in those exposed to CME (Gargus *et al.*, 1969). In several subsequent studies the inhalation exposure of rats to CME and to BCME was studied. BCME proved to be a potent carcinogen for rats by this route at 0.1 ppm resulting in lung cancer and esthesioneuroepithelioma (Kuschner *et al.*, 1975). In other inhalation experiments in rats at various doses, induction of lung cancer was not observed but nasal tumors were induced (Leong *et al.*, 1981). These bioassays were recently reviewed (Van Duuren and Van Duuren, 1988).

On the basis of inhalation bioassays in which rats were exposed to mixtures of hydrochloric acid and formaldehyde (Sellakumar *et al.*, 1985) and hence to BCME it was subsequently concluded that BCME is markedly carcinogenic to rats in the dose range of only 0.1 to 0.4 parts per billion (Van Duuren and Van Duuren, 1988).

VC was first shown to be carcinogenic by inhalation exposure using Wistar rats at a dose level of 30,000 ppm (Viola *et al.*, 1971). Zymbal gland tumors were observed together with metastases to the skin, lung, and bone. Subsequently, a series of large-scale bioassays was undertaken using inhalation exposure of Wistar and Sprague–Dawley rats, Swiss mice, and golden hamsters (Maltoni *et al.*, 1984). Extensive dose–response studies were performed in these bioassays. Lung adenomas, angiosarcoma of the liver (ASL), and adenocarcinoma of the mammary gland in mice were observed. The same type of exposure in rats in the 50- to 10,000-ppm range led to induction of ASL, nephroblastoma, neuroblastoma, Zymbal gland tumors, and miscellaneous tumors at other sites.

From the above bioassays it is clear that BCME is a much more potent carcinogen by several orders of magnitude than VC in rat inhalation experiments, on the basis of numbers of animals with malignant tumors and doses used in the inhalation experiments. CME must be classed as a weak carcinogen and its carcinogenicity can be ascribed in part to the presence of BCME in industrial grade CME and to the formation of BCME from the hydrolysis products of CME.

Both CME and BCME are highly reactive direct-acting alkylating agents which do not need to be metabolized *in vivo* in order to exert their biological activity. Like other direct-acting carcinogens such as epoxides and β-lactones, they are expected to exert carcinogenic action at the site of contact in animal tests (Van Duuren, 1980). This is indeed the case, as shown by induction of nasal and lung tumors by inhalation exposure in rats, skin cancer by topical application in mice, and lung cancer by occupational exposure in humans.

Unlike CME and BCME, VC is an indirect-acting carcinogen which is activated *in vivo* to chloroethylene oxide, a highly reactive and unstable epoxide. Extensive studies on metabolism of VC *in vitro* and *in vivo* and bioassays of the metabolites point to this epoxide as the activated carcinogenic intermediate of VC, as originally suggested on the basis of structure–activity considerations (Van Duuren, 1975). This subject has been reviewed (Singer and Grunberger, 1983). Because of its accepted mode of action, VC is expected to be a multipotential carcinogen in animals and humans. This is borne out by the animal carcinogenicity data and epidemiologic studies in workers exposed to VC.

OCCUPATIONAL EXPOSURE: CME–BCME

Three reports appeared in 1973 describing the occurrence of lung cancer, most frequently oat cell carcinoma, in workers exposed to CME–BCME (Figueroa *et*

respiratory cancer (Krimsky, 1987). It is notable that the number of workers compensated for this one manufacturing facility, 62, is almost double that given in the recent epidemiologic reports (Collingwood *et al.*, 1987, Maher and DeFonso, 1987).

It has been pointed out in some of these reports that (1) the respiratory cancers were mostly oat cell carcinoma of the lung and, (2) in a number of cases there was a remarkably short latent period between beginning of exposure and diagnosis of lung cancer and hence an unusually high incidence of this cancer among younger workers.

Smoking histories were examined in some of the studies summarized in Table 1 but were not considered in calculations of cancer risk, on the basis of the conclusion that this confounding factor is difficult to assess quantitatively (Doll, 1984).

The levels of exposure to CME–BCME were in earlier years, i.e., up to the early 1970s, rough estimates at best, and moreover, varied not only from one facility to the next, but also frequently within the same facility. It was only after these chemicals were known to be carcinogenic to animals and humans that exposure to them became monitored, regulated, and reduced. Before 1970 exposure to CME–BCME at certain stages of use in the manufacture of anion-exchange resins was so high that buildings had to be routinely evacuated three or four times during one 8-hr shift (Figueroa *et al.*, 1973).

During the process of manufacture of anion-exchange resin, excess CME was destroyed by addition of water to the reaction vessels. This step, referred to as quenching, is a highly exothermic reaction, which results in the release of HCl, CH_2O, methyl alcohol, and undoubtedly unreacted CME–BCME, all within the building where the resin was being manufactured, at times with inadequate ventilation.

Attempts were made in some of these studies to divide worker exposure into low-, medium-, and high-risk levels (Maher and DeFonso, 1987; McCallum *et al.*, 1983). This type of classification is difficult to evaluate because exposure levels are not available for at least the first 20 years that these chemicals have been in use. Moreover, the manufacture of CME is by its nature a batch-type operation. The number of batches and the quantities produced and used for any given length of time did not emerge from any of the studies reviewed here. It was also impossible to obtain with any degree of certainty the temporal exposure levels for the critical 20-year period, i.e., intense exposure for brief periods of time compared to long-term exposure to low levels of CME–BCME.

OCCUPATIONAL EXPOSURE: VC

The first full report dealing with the occurrence of angiosarcoma of the liver (ASL) in VC–PVC workers (Creech and Johnson, 1974), appeared 3 years after the initial animal carcinogenicity bioassays were described (Viola *et al.*, 1971). Since then numerous papers have dealt with ASL and cancers in other organs and systems in workers in the VC–PVC industry (IARC, 1987).

The most recent compilation of worker deaths ascribed to ASL as a result of exposure to VC was reported by the Association of Plastics Manufacturers in

Europe (APME) for the years 1955 through 1984. (Forman *et al.*, 1985). A total of 115 deaths from ASL were counted for Europe, North America, and Japan. Thirty-five of these cases were from 10 manufacturing facilities in the United States. The largest proportion of ASL cases occurred between 20 and 29 years from the beginning of exposure. The median latent period was given as 22.6 years. The authors concluded that additional cases may be expected after more than 30 years. Close to 77% of the ASL deaths occurred in autoclave cleaners and production operators where the highest levels of exposure to VC were encountered. The total number of workers exposed to VC was not given in this compilation.

During two-and-a-half decades, 1950–1975, i.e., before human carcinogenicity was established (IARC, 1979a), the major concerns in manufacturing industries were the narcotic properties of VC and the fact that at sufficiently high levels, 4% by volume (Weast and Astle, 1981), it becomes a fire and explosion hazard. As a result of these concerns some information is available on VC concentrations in components of some manufacturing facilities prior to the early 1970s. The highest concentration of VC was found in the polymerization reaction vessels after completion of the process. This has been reported to reach 3000 to 4000 ppm. Other areas in the facility gave measurements ranging from 1 to 1000 ppm (Barnes, 1976). These levels decreased markedly after the early 1970s (IARC, 1979b; Barnes, 1976; Purchase *et al.*, 1987).

Several recent reports present additional epidemiologic findings on cancer incidences in VC–PVC workers (Laplanche *et al.*, 1987; Heldaas *et al.*, 1984; Smulevich *et al.*, 1988). They present data on ASL, lung, stomach, skin, hematopoietic and lymphatic systems. Some of these cancers of organs and systems other than the liver were mentioned in earlier reports and reviews (IARC, 1987). Further studies in some of these areas are indicated because of marginal significances in some instances, e.g., malignant melanoma as pointed out by the authors (Heldaas *et al.*, 1984). There are indications that ASL may occur only at high levels of and/or prolonged exposure to VC (Forman *et al.*, 1985; Smulevich *et al.*, 1988). In one study increased deaths in VC-exposed workers were reported from cancers of the lymphatic, hematopoietic, digestive, respiratory systems, including bone, brain, and skin, but no ASL's were observed (Smulevich *et al.*, 1988).

CONCLUSIONS

The number of workers exposed to VC during the years 1948–1981 is probably two orders of magnitude higher than the number of those exposed to CME–BCME during the same period. In the latter case, and if the legal settlement reached for one manufacturing facility is taken into account, there were 117 respiratory cancer deaths reported from five countries from 1948–1981 among 3024 workers. By comparison there were 115 ASL deaths among several hundreds of thousands of VC workers from 1955–1984 in the APME compilation. The latter is undoubtedly much more complete than that given in Table 1 for CME–BCME respiratory cancer deaths.

Exposure levels to VC range from one to 4000 ppm with roughly 77% of ASL deaths occurring in workers exposed to a 3000- to 4000-ppm level. VC is a narcotic gas with a pleasant odor which leads to euphoria, unconsciousness, and sleep. On

the other hand CME–BCME is highly irritating and noxious in vapor form. Moreover, in air even at low levels of humidity, CME–BCME releases highly noxious fumes of HCl and CH_2O. CH_2O causes eye and mucous membrane irritation at 0.01 ppm to 2.0 ppm (NRC–NAS, 1981). The odor threshold concentration for HCl is about 0.1 ppm and irritancy becomes pronounced in the range of 5–20 ppm (NRC-NAS, 1976). Thus, unlike VC exposure, CME–BCME exposure forces a warning on workers to such an extent that they evacuate work areas when unbearable levels of these chemicals and their hydrolysis products appear. It is therefore reasonable to conclude that levels of exposure to CME–BCME were lower than those to VC by several orders of magnitude.

There is another factor which should be borne in mind. The Group 1 occupational carcinogens (IARC, 1987) are indirect-acting agents with the exception of CME–BCME, melphalan, and sulfur mustard. It is expected that the markedly higher human and animal carcinogenicity of CME–BCME compared to VC is ascribable to their high order of direct-acting alkylating reactivity; i.e., metabolic activation is not required for CME–BCME. In the case of the indirect-acting carcinogen VC, the delivered level of activated carcinogenic intermediate is undoubtedly substantially lower than the amounts of VC inhaled. A part of the VC inhaled is metabolized to innocuous products and the activated carcinogenic intermediate will also be partially removed by irrelevant reactions with glutathione, proteins, and other tissue constituents (Van Duuren and Van Duuren, 1988).

It is possible that additional information will be forthcoming concerning such matters as total number of workers exposed to VC or quantities of CME–BCME manufactured, in order to place the above observations and conclusions on a more solid foundation.

From the animal bioassays and epidemiologic studies summarized in this report it is clear that CME–BCME represents a much more potent animal and human carcinogen than VC.

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