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EVALUATION OF THE POTENTIAL CARCINOGENICITY OF BIS(CHLOROMETHYL)ETHER (542-88-1)

IN SUPPORT OF REPORTABLE QUANTITY ADJUSTMENTS PURSUANT TO CERCLA SECTION 102

PREPARED FOR

OFFICE OF EMERGENCY AND REMEDIAL RESPONSE

OFFICE OF SOLID WASTE AND EMERGENCY RESPONSE

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DISCLAIMER

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PREFACE

This report summarizes and evaluates information on the potential carcinogenicity of a substance designated as hazardous under Section 101 (14) of the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA). Pertinent epidemiologic and toxicologic data were obtained through on-line searches and from hard-copy sources. On-line searches were extended as far back as the data bases would allow. Retrieval of historical data was accomplished through searches of hard-copy sources and bibliographies of relevant publications. Every attempt has been made to rely upon primary publications as opposed to data summaries or abstracts contained in secondary sources such as monographs, surveys, review articles, criteria documents, etc. The on-line data bases that were searched included CHEMLINE (National Library of Medicine [NLM]), RTECS (NLM), Toxicology Data Bank (NLM), TOXLINE (NLM), CANCERLINE (NLM), and Chemical Abstracts (DIALOG Information Services). Unpublished data were not used in this evaluation.

The Agency's Methodology for obtaining, evaluating, and ranking CERCLA potential carcinogens is described in the Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, Volume 3, April 26, 1988 (EPA/600/8-89/053). This document revises the previous methodology document of 1986 according to the public comments received on the March 16, 1987 Notice of Proposed Rulemaking (52 FR 8140). The Methodology for Adjusting reportable quantities is described in the Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, Volume 1, March, 1985, and is also summarized in Volume 2, August, 1986, and Volume 3, December, 1986. The EPA's Office of Emergency and Remedial Response (OERR) has considered this evaluation in adjusting reportable quantities pursuant to CERCLA Section 102. This report is consistent with the revised methodology. It draws largely on information supplied by the Syracuse Research Corporation in 1984 under EPA Contract No. 68-03-3112. Due to the amount of time elapsed between the original work performed by Syracuse Research Corporation and the present

effort to produce this document, Environmental Monitoring & Services, Inc., under EPA Contract No. 68-03-3182, has been involved in an extensive review of all the Syracuse documents. In some cases, this review involved updating the information provided but it was primarily a quality assurance effort. The present document is a result of this effort.

ABSTRACT

Bis(chloromethyl)ether is a human carcinogen, classified as weight-of-evidence Group A under the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a). Evidence on potential carcinogenicity from animal studies is "Sufficient," and the evidence from human studies is "Sufficient."

The potency factor (F) for bis(chloromethyl)ether is estimated to be 10,377 $(mg/kg/day)^{-1}$, placing it in potency group 1 according to the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b).

Combining the weight-of-evidence group and the potency group, bis(chloromethyl)ether is assigned a "HIGH" hazard ranking for the purposes of RQ adjustment.

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1.0 WEIGHT OF EVIDENCE

1.1 ANIMAL STUDIES

The effect of bis(chloromethyl)ether administered by inhalation has been investigated in rats (Laskin et al., 1971; Kuschner et al., 1975; Leong et al., 1981) and mice (Leong et al., 1971, 1981). Laskin et al. (1971) reported in a preliminary study that 10 of 19 rats (Sprague-Dawley) exposed to 0.1 ppm bis(chloromethyl)ether for 6 hours/day, 5 days/week (total of 101 exposures) developed respiratory tumors (5 squamous-cell carcinomas of the lung; 5 aesthesioneuroepitheliomas of the nasal cavity). This study also indicates the occurrence of lung and nasal cavity tumors in rats exposed for shorter periods, but specific data are not reported. In a subsequent report, Kuschner et al. (1975) reported a duration-response in rats exposed to 0.1 ppm bis(chloromethyl)ether for 6 hours/day, 5 days/week for 2, 4, 8, 12, 16, and 20 weeks (10, 40, 60, 80, and 100 exposure days, respectively). In groups of rats exposed by inhalation for 80 or 100 exposure days, high incidences of nasal cavity (12/50 and 5/30, respectively) and lung cancers (3/50 and 8/30, respectively) were reported. A decreasing number of cancers was seen in groups exposed for shorter periods. No tumors were reported in 240 control animals.

Leong et al. (1981) exposed rats by inhalation to several dose levels of bis(chloromethyl)ether (1, 10, and 100 ppb) for 6 months (6 hours/day, 5 days/week) and observations were made for the lifespan of the animals. A significant increase in the incidence of tumors was seen only in the group exposed to 100 ppb bis(chloromethyl)ether. Tumors were detected in the nasal cavity (96/111, $P<0.05$), and lung (4/111, $P=0.059$), and metastases were detected in the lymphoreticular tissues (5/111). No similar tumors were reported in rats exposed to lower concentrations of bis(chloromethyl)ether or in controls (0/112).

The effect of inhalation of bis(chloromethyl)ether at 1, 10, or 100 ppb was also tested in mice (Ha/ICR) by Leong et al. (1981). Even though gross, histological, and hematological examinations were conducted, no significant

increase in tumors was reported for any treated group when compared with controls. In an earlier study, Leong et al. (1971) administered 1 ppm bis(chloromethyl)ether to mice (A/He) and reported a slight but insignificant increase in the incidence of lung tumors (26/47 versus 20/49). It is noted that it may be inappropriate to use these strains of mice (Strain A hybrid) for pulmonary tumorigenesis testing.

A dose-response relationship was demonstrated for the progressive development of hyperplasia and metaplasia in rats and hamsters (Drew et al., 1975). This study also reported an ulcerating squamous-cell carcinoma in a rat following 3 exposures (6 hours each) to 1 ppm bis(chloromethyl)ether, and a malignant nasal tumor in a hamster treated for a single 6-hour exposure to 1 ppm bis(chloromethyl)ether.

Dermal application of bis(chloromethyl)ether (2 mg/0.1 ml benzene, 3 times/week) resulted in a high incidence of skin papillomas (13/20) and squamous-cell carcinomas (12/20) in female mice (ICR/Ha Swiss). The control group, treated with benzene (0.1 ml, 3 times/week) alone, developed no similar tumors (0/20) (Van Duuren et al., 1969). A progression from papillomas to carcinomas was reported. The first papilloma was seen at 161 days and the first carcinoma was apparent at 231 days.

Gargus et al. (1969) treated neonatal (24-72 hrs) ICR-Swiss mice with a single subcutaneous injection of bis(chloromethyl)ether (12.5 ul of 0.05% solution/kg). The incidence of lung adenomas after 6 months was 45/100 in treated animals and 7/50 in vehicle controls. Injection site tumors have been reported following the subcutaneous injection of bis(chloromethyl)ether in mice (Gargus et al., 1969) and rats (Van Duuren et al., 1969), while similarly treated controls showed no injection site tumors.

1.2 HUMAN STUDIES

There are six studies of workers exposed to bis(chloromethyl)ether (BCME). In three studies, workers were primarily exposed to CMME (technical-grade chloromethyl methyl ether) with 1% to 8% BCME as a contaminant.

Thiess et al. (1973) reported that 6/18 testing laboratory workers exposed to bis(chloromethyl)ether for 6-9 years developed lung cancer. Two additional lung cancer deaths were reported in a group of 50 production workers. Predominantly, oat-cell carcinomas developed with a latent period of 8-16 years.

Sakabe (1973) reported five cases of lung cancer among 32 dyestuff employees exposed to bis(chloromethyl)ether. Workers exposed to bis(chloromethyl)ether in the chemical manufacture of anion-exchange resin were studied by Lemen et al. (1976). This follow-up study revealed 5 cases of bronchogenic cancer in 136 exposed workers. Based on mortality statistics of white males in Connecticut, only 0.54 deaths would be expected ($P<0.01$). Small-cell, undifferentiated (oat-cell) carcinoma was the predominant malignancy.

In a chemical plant where workers were exposed to chloromethyl ether and bis(chloromethyl)ether as a contaminant, Figueroa et al. (1973) reported 14 lung cancer cases. Four cases of lung cancer occurred in 88 men aged 35-54 years while only about 0.50 cases would be expected from the reference group (2804 men 45-54 years of age from Pulmonary Neoplasm Research Project study).

Epidemiological studies to evaluate workers exposed to chloromethyl ether and bis(chloromethyl)ether in six of the major chemical companies that use these chemicals have been conducted by Albert et al. (1975) and Pasternack et al. (1977). Albert et al. (1975) reported on 1794 exposed workers and emphasized 700 who were employed by one chemical firm. Of these 700 workers, 19 developed respiratory tract cancer while 8 cases would be expected from the control group. Subsequently, Pasternack et al. (1977) reported 26/1827 respiratory cancers in the same six chemical industries, and only 9.3 would be expected ($P<0.05$). The single chemical firm now posted 23/721 deaths due to respiratory cancer. The number of expected cases was reported as 4.5 ($P<0.05$). Once again it was noted that predominantly oat-cell carcinomas were seen in these workers exposed to bis(chloromethyl)ether and chloromethyl ether.

Despite a lack of information on adjustment of confounders, latency analysis, the consistent finding of a high incidence of oat-cell carcinoma of the lung, in similar age groups after an appropriate latency period in all studies, provides sufficient causal evidence of the carcinogenicity of BCME in humans.

1.3 WEIGHT-OF-EVIDENCE ASSESSMENT

Bis(chloromethyl)ether is carcinogenic in rats when administered by inhalation or subcutaneous injection. It is carcinogenic in mice following inhalation and skin application, and tumors develop in neonatal mice given a single subcutaneous injection of bis(chloromethyl)ether.

Several studies in addition to those reviewed by IARC (1974) indicate that exposure to bis(chloromethyl)ether and mixtures of bis(chloromethyl)ether and chloromethyl ether results in a high incidence of respiratory cancers. Predominantly oat-cell carcinomas of the lung are seen. Thus, using the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a) for evaluating the overall weight of evidence to humans, bis(chloromethyl)ether is most appropriately classified as a Group A chemical. The appendix contains summaries of the significant human and/or animal studies cited in this review.

2.0 POTENCY

The potency factor (F) for bis(chloromethyl)ether is estimated to be 10,377 $(mg/kg/day)^{-1}$, placing it in potency group 1 under the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b). Table 2-1 contains data from the selected study used to derive the potency factor (F) for bis(chloromethyl)ether.

Table 2-1. Derivation of Potency Factor(F) Agent: **Bis(chloromethyl) ether**

REFERENCE:	Kuschner et al., 1975						
EXPOSURE ROUTE:	inhalation						
SPECIES:	rat						
STRAIN:	Sprague-Dawley						
SEX:	M						
VEHICLE OR PHYSICAL STATE:	air						
BODY WEIGHT:[a]	0.35 kg						
DURATION OF TREATMENT:	0 hours	60 hours	120 hours	240 hours	360 hours	480 hours	600 hours
DURATION OF STUDY:[b]	462 days	483 days	483 days	497 days	427 days	301 days	350 days
LIFESPAN OF ANIMAL:[a]	728 days						
TARGET ORGAN:	lung/nasal						
TUMOR TYPE:	carcinoma						
EXPERIMENTAL DOSES:[c]	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm
NO. OF EXPOSURES:	0	10	20	40	60	80	100
TRANSFORMED DOSES:[d] (mg/kg/day)	0	0.001	0.002	0.004	0.006	0.008	0.010
TUMOR INCIDENCE:	0/240	1/41	3/46	4/18	4/18	15/34	12/20
ANIMAL POTENCY: $(mg/kg/day)^{-1}$	363.1						
HUMAN POTENCY:[e] $(mg/kg/day)^{-1}$	10,377						

[a] Estimated

[b] The duration of study data is based on the median lifespan at each dosage level as given in the study.

[c] 0.1 ppm for 6 hours/exposure

[d] To derive the transformed dose from the experimental dose data: concentration (mg/m^3) x breathing rate of rat (0.22 m^3/day)/animal weight (0.35 kg)/24 (hours/day) x total number of exposure hours/lifespan of animal (728 days).

[e] Human potency = animal potency x $(70 \text{ kg}/0.35 \text{ kg})^{1/3}$ x $(728 \text{ days}/429 \text{ days})^3$ to adjust for the short study duration. The duration of study value used in this calculation (429 days) was the average of the seven durations of study values given for the groups.

3.0 HAZARD RANKING

Based on the weight-of-evidence **Group A** for bis(chloromethyl)ether, and the potency factor (F) of 10,377 $(mg/kg/day)^{-1}$, bis(chloromethyl)ether receives a hazard ranking of "HIGH."

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APPENDIX

SUMMARY OF SIGNIFICANT HUMAN AND/OR ANIMAL STUDIES

Table A. An

Agent: Bis(chloromethyl)ether

Reference: Gargus et al., 1969

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
sc	mouse[a]/ ICR-Swiss	M,F	12.5 ug/kg	single injection	6 months	industrial grade	peanut oil (0.05% solution)	lung	adenoma	45/100
sc	mouse/ ICR-Swiss	M,F	0.0 ml/kg	single injection	6 months	NA	0.5 mg peanut oil only	lung	adenoma	7/50

QUALITY OF EVIDENCE

Strengths of Study: Appropriate vehicle control animals were used. Bis(chloromethyl)ether was tested near the maximum tolerated dose.

Weaknesses of Study: The duration of study was short. Neonatal mice were given a single subcutaneous dose.

Overall Adequacy: Adequate

Comments: Due to the sensitivity of neonatal animals, the induction of tumors is circumspectly viewed.

[a] Newborn (24-72 hours) mice were injected.
NA = Not applicable

Table A. A

Agent: Bis(chloromethyl)ether

Reference: Kuschner et al., 1975

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study[a]	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
i	rat/ Sprague-Dawley	M	0.1 ppm, 6 hrs/day, 5 days/week	20 weeks (100 exposures)	50 weeks	NR	air	nasal cavity	various[b]	5/30
								lung	various[c]	8/30
i	rat/ Sprague-Dawley	M	0.1 ppm, 6 hrs/day, 5 days/week	16 weeks (80 exposures)	43 weeks	NR	air	nasal cavity	various[b]	12/30
								lung	various[c]	3/30
i	rat/ Sprague-Dawley	M	0.1 ppm, 6 hrs/day, 5 days/week	12 weeks (60 exposures)	61 weeks	NR	air	nasal cavity	various[b]	2/20
								lung	various[c]	2/20
i	rat/ Sprague-Dawley	M	0.1 ppm, 6 hrs/day, 5 days/week	8 weeks (40 exposures)	71 weeks	NR	air	nasal cavity	various[b]	3/20
								lung	various[c]	1/20
i	rat/ Sprague-Dawley	M	0.1 ppm, 6 hrs/day, 5 days/week	4 weeks (20 exposures)	69 weeks	NR	air	nasal cavity	various[b]	3/50
								lung	various[c]	0/50
i	rat/ Sprague-Dawley	M	0.1 ppm, 6 hrs/day, 5 days/week	2 weeks (10 exposures)	69 weeks	NR	air	nasal cavity	various[b]	1/50
								lung	various[c]	0/50
NA	rat/ Sprague-Dawley	M	0.0 ppm	NA	66 weeks	NA	control	nasal cavity	various	0/240[d]
								lung	various	0/240[d]

Table A. Ar[redacted]

Reference: Kuschner et al., 1975 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study[a]	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)

QUALITY OF EVIDENCE

Strengths of Study: Several different exposure levels were used to show a dose response. Animals were observed for their lifespan. A large number of animals were used in each group. Microscopic examination of tumors was performed.

Weaknesses of Study: Purity of the compound is not stated.

Overall Adequacy: Adequate

Comments: No tumors for the control group are reported but it is not specifically stated that there were none.

[a] Median lifespan
[b] Esthesioneuroepitheliomas, unclassified malignant olfactory tumor, ganglioneuroepithelioma, squamous cell carcinoma, poorly differentiated epithelial tumor, adenocarcinoma
[c] Squamous cell carcinoma, adenocarcinoma
[d] No tumors were reported in the control group.
NA = Not applicable; NR = Not reported

Table A.

Agent: Bis(chloromethyl)ether

Reference: Laskin et al., 1971

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
i	rat/ Sprague-Dawley	M	0.1 ppm, 6 hrs/day, 5 days/week	20 weeks	659 days[a]	NR	air	lung	squamous cell carcinoma	5/19
								olfactory epithelium	esthesioneuro-epitheliomas	5/19

QUALITY OF EVIDENCE

Strengths of Study: Low dose levels were tested by inhalation. Microscopic examination of animals was conducted.

Weaknesses of Study: Tumor incidences in an untreated group are not reported. The purity of compound is not reported.

Overall Adequacy: Limited

Comments: This is a preliminary report on rats exposed to the highest dose level tested. Tumors in rats exposed for shorter periods are noted.

[a] Lifespan of oldest animal

NR = Not reported

Table A. A

Agent: Bis(chloromethyl)ether

Reference: Leong et al., 1971

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
i	mouse/ A/Heston	M	0.005 mg/l (1 ppm), 6 hrs/day, 5 days/week	82 days	189 days	industrial grade	air	lung	pulmonary tumors	26/47[a]
i	mouse/ A/Heston	M	0 mg/l	130 days	196 days	NA	air	lung	pulmonary tumors	20/49[b]

QUALITY OF EVIDENCE

Strengths of Study: Biological study on chronic and acute inhalation conducted.

Weaknesses of Study: Only males used; only one dose level administered. Short study duration.

Overall Adequacy: Limited

[a] .2 tumors per tumor-bearing animal, average; 55% incidence of lung tumors.
[b] 2.2 tumors per tumor-bearing animal, average; 41% incidence of lung tumors.
NA = Not applicable

Table A. A[redacted]

Agent: Bis(chloromethyl)ether

Reference: Leong et al., 1981

Exposure Route	Species/ Strain	Sex	Dose or Exposure[a]	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
i	rat/ Sprague-Dawley, Spartan substrain	M	100 ppb	6 months	lifetime	NR	air	respiratory system	neoplasm of olfactory neuroepithelioma	96/111 (P<0.05)
			10 ppb	6 months	lifetime	NR	air	respiratory system		0/111
			1 ppb	6 months	lifetime	NR	air	respiratory system	esthesioneuro-epithelioma	0/113
			0 ppb	NA	lifetime	NA	air	respiratory system		0/112
i	rat/ Sprague-Dawley, Spartan substrain	M	100 ppb	6 months	lifetime	NR	air	respiratory system	pulmonary adenoma	4/111 (P=0.059)
			10 ppb	6 months	lifetime	NR	air	respiratory system	pulmonary adenoma	0/111
			1 ppb	6 months	lifetime	NR	air	respiratory system	pulmonary adenoma	0/113
			0 ppb	NA	lifetime	NA	air	respiratory system	pulmonary adenoma	0/112
i	rat/ Sprague-Dawley, Spartan substrain	M	100 ppb	6 months	lifetime	NR	air	lymphor-eticular	metastasis of esthesioneuro-epithelioma of regional lymph nodes	5/111 (P<0.05)
			10 ppb	6 months	lifetime	NR				0/111
			1 ppb	6 months	lifetime	NR				0/113
			0 ppb	NA	lifetime	NA				0/112

QUALITY OF EVIDENCE

Strengths of Study: Complete histological, hematological, and other examinations were conducted. The number of animals in each group was significant. The animals were exposed to a variety of dose levels.

Weaknesses of Study: Exposure was limited to only one quarter of the animals' lifespan. Only male rats were studied.

Overall Adequacy: Adequate

[a] Exposure is for 6 hours/day, 5 days/week for 6 months.

NR = Not reported; NA = Not applicable

Table A. [redacted]

Agent: Bis(chloromethyl)ether

Reference: Leong et al., 1981

Exposure Route	Species/ Strain	Sex	Dose or Exposure[a]	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
i	mouse/ Ha/ICR	M	100 ppb	6 months	lifetime	NR	air	respiratory system	pulmonary adenoma	7/144
			10 ppb							2/143
			1 ppb							4/138
			0 ppb							6/157
i	mouse/ Ha/ICR	M	100 ppb	6 months	lifetime	NR	air	respiratory system	pulmonary adeno-carcinoma	8/144
			10 ppb							1/143
			1 ppb							3/138
			0 ppb							4/157
i	mouse/ Ha/ICR	M	100 ppb	6 months	lifetime	NR	air	liver	hepatocellular carcinoma	0/144
			10 ppb							0/143
			1 ppb							1/138
			0 ppb							3/157
i	mouse/ Ha/ICR	M	100 ppb	6 months	lifetime	NR	air	liver	angioma	0/144
			10 ppb							0/143
			1 ppb							0/138
			0 ppb							1/157

QUALITY OF EVIDENCE

Strengths of Study: Complete histological, hematological, and other examinations were conducted. The number of animals in each group was significant. The animals were exposed to a variety of dose levels.

Weaknesses of Study: The exposure was limited to only one quarter of the animals' lifespan. Only male mice were studied.

Overall Adequacy: Adequate

[a] Exposure is 6 hours/day, 5 days/week for 6 months.

NR = Not reported

Table A. [redacted]

Agent: Bis(chloromethyl)ether

Reference: Van Duuren et al., 1969

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
d	mouse/ ICR/Ha Swiss	F	2 mg/0.1 ml 3 times/week	311 days	325 days	NR	benzene	skin	papilloma	13/20[b]
									squamous carcinoma	12/20
			0 mg/0.1 ml 3 times/week	526 days	540 days	NA	benzene	skin	NA	0/20
sc	rat/ Sprague-Dawley	F	3 mg/0.1 ml[a] once/week	300 days	515 days	NR	nujol	injection site	fibrosarcoma	5/20[c]
								connective tissue	fibroma	2/20
			0 mg/0.1 ml once/week	515 days	515 days	NA	nujol	injection site	NA	0/20

QUALITY OF EVIDENCE

Strengths of Study: Two species of animals were considered.

Weaknesses of Study: Only females were studied. One dose level was given to the animals.

Overall Adequacy: Limited

[a] 3 mg/0.1 ml dose reduced after 114 weeks to 1 mg/0.1 ml and subsequent injections reduced to 3 times/month.
[b] First papilloma was seen at 161 days; median survival was 313 days.
[c] Confirmed in animals that died at 245 days
NA = Not applicable; NR = Not reported

Table B. Hu

Agent: Bis(chloromethyl)ether

Reference: Albert et al., 1975

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (P Value)
d+i+o	700	1819	NR	heavy[a]	≥5 years	respiratory tract	cancer	19	8[b]	NR

QUALITY OF EVIDENCE

Strengths of Study: A large population of exposed chemical workers was studied. The reference group was workers of the same factories not exposed to chemicals. Analyses were conducted based on exposure level and duration of exposure.

Weaknesses of Study: Exposure to many other chemicals is likely in a chemical plant. Exposure to bis(chloromethyl)ether and chloromethyl methyl ether is reported.

Overall Adequacy: Adequate

Comments: A dose-response relationship is reported by the authors.

[a] Exposure was to bis(chloromethyl)ether (2-8%) and chloromethyl methyl ether.
[b] Estimated, based on 21/1819 respiratory cancers in the control group.
NR = Not reported

Table B. Hu[redacted]

Agent: Bis(chloromethyl)ether

Reference: Figueroa et al., 1973

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (P Value)
d+i+o	111	2804	M	NR[a]	3-14 years	lung	oat-cell carcinoma[b]	4	0.63	P<0.002

QUALITY OF EVIDENCE

Strengths of Study: This study was based on the Philadelphia Pulmonary Research Project and used 2804 men, 45-54 years of age, as a reference group. Cigarette smoking in both groups was similar.

Weaknesses of Study: Exposure was to several chemicals within the factory.

Overall Adequacy: Adequate

[a] Exposure was reported for chloromethyl ether and bis(chloromethyl)ether.
[b] Predominant type of tumor
NR = Not reported

Table B. H

Agent: Bis(chloromethyl)ether

Reference: Lemen et al., 1976

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (P Value)
d+i+o	136	Connecticut white males	M	NR	10.5 years	respiratory tract	bronchogenic cancer[a]	5	0.54	P<0.01

QUALITY OF EVIDENCE

Strengths of Study: A follow-up study of workers exposed to BCME in a chemical factory producing anion-exchanging resin. The incidence of lung cancer was compered to mortality statistics for white males of Connecticut. The duration of exposure of all cancer cases is reported.

Weaknesses of Study: The level of exposure to BCME was not reported. The number of cases observed is small.

Overall Adequacy: Adequate

Comments: Exposure was thought to be predominantly by inhalation.

[a] Large or small-cell, undifferentiated carcinomas

NR = Not reported

Table B. H

Agent: Bis(chloromethyl)ether

Reference: Pasternack et al., 1977

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (P Value)
d+i+o	1827	8870	NR	various[a]	<20 years	respiratory tract	cancer	26	9.3	P<0.05
d+i+o	721	1815	NR	all levels[b]	<20 years	respiratory tract	cancer	26	4.5	P<0.05

QUALITY OF EVIDENCE

Strengths of Study: Analyses were conducted on a large population of exposed chemical workers. Statistics of observed versus expected incidences of cancers are reported.

Weaknesses of Study: Increased cancers cannot be absolutely attributed to bis(chloromethyl)ether since exposure to many chemicals is likely in a chemical plant.

Overall Adequacy: Adequate

[a] Exposure was generally not reported, but, where possible, estimates were made depending on job area, exposure to bis(chloromethyl)ether and exposure to chloromethyl methyl ether.

[b] Exposure levels were denoted into four groups based on duration of exposure; exposure was to bis(chloromethyl)ether and chloromethyl methyl ether.

[c] Predominantly oat-cell carcinoma

NR = Not reported