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RESEARCH AND DEVELOPMENT

EVALUATION OF THE POTENTIAL CARCINOGENICITY OF ETHYLENE OXIDE (75-21-8)

IN SUPPORT OF REPORTABLE QUANTITY ADJUSTMENTS PURSUANT TO CERCLA SECTION 102

PREPARED FOR

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DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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 Unpublished data were not used in this evaluation.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

Ethylene oxide is a probable human carcinogen, classified as weight-of-evidence **Group B1** 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 **"Limited."**

The potency factor for ethylene oxide is estimated to be **1.34 (mg/kg/day)$^{-1}$**, placing it in potency group 2 according to the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b).

Combining the weight-of-evidence group and the potency group, ethylene oxide is assigned a **"MEDIUM"** hazard ranking for the purposes of RQ adjustment. (When the weight-of-evidence is expressed as a range, i.e., B1, the hazard ranking is based on the higher weight-of-evidence group).

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1.0 WEIGHT OF EVIDENCE

1.1 ANIMAL STUDIES

Weekly subcutaneous injections of 0.1-1.0 mg ethylene oxide for 95 weeks induced dose-related local sarcomas in female NMRI mice (Dunkelberg, 1979, 1981), but the incidence of tumors at distant sites was not significantly greater in the treated mice than in controls. Walpole (1958) reported that subcutaneous injections of ethylene oxide over a period of 94 days did not induce local sarcomas in 12 rats (species not stated). The maximum total dose (MTD) was 1 g/kg and the animals were observed for their lifetimes, but the dosing schedule was not specified. Thrice weekly dermal applications of ethylene oxide for life (approximately 10 mg per application) did not cause skin papillomas or carcinomas in Swiss-Millerton mice (Van Duuren et al., 1965).

Reyniers et al. (1964) observed that tumors developed at various sites (e.g., ovaries, lymphatic system, lungs) in 63 of 86 female germ-free Swiss-Webster mice that were accidentally exposed to ethylene oxide- treated ground-corncob bedding for their lifespan (maximal, 900 days). No tumors were reported in 83 female mice (100-600 days old) that were not exposed to treated bedding. It should be emphasized that this study was not designed to test the carcinogenicity of ethylene oxide, and that the causative agent was not identified since chemical analysis of the bedding was not performed.

A chronic inhalation study was performed by the Bushy Run Research Center (Snellings et al., 1984). Fischer 344 rats were exposed to 100, 33 and 10 ppm ethylene oxide vapor for 6 hours/day, 5 days/week for 24.5 months (females) or 25 months (males). Two untreated air groups were exposed under similar conditions. Initially, 120 rats/sex/group were exposed, but interim sacrifices were conducted at 6, 12, and 18 months (10, 10 and 20 rats, respectively). At terminal sacrifice, histopathologic examinations were performed on approximately 15 major organs and tissues of rats in the 100 ppm and both control groups, and on potential target tissues, selected tissues, and tissues

with gross lesions in the 10 and 33 ppm groups. The results showed that there was a dose-related increase in the incidence of mononuclear cell leukemia in the female rats at terminal sacrifice (15/26, 14/48, 11/54 and 11/115 in the 100, 33, 10 ppm and combined controls, respectively). In male rats, statistically significant increases in subcutis fibroma at 100 ppm (15/58 vs. 4/137 in combined controls) and pancreas islet cell adenoma at 100 ppm (10/59 vs. 10/129 in combined controls) were found. The exposure of both the male and female rats was temporarily terminated during exposure weeks 65 and 66, due to a Sialodacryoadenitis virus infection, but no evidence was presented that the infection increased tumor incidence.

The chronic inhalation toxicity and carcinogenicity of ethylene oxide was evaluated in a 2-year inhalation bioassay (Lynch et al., 1984). Five groups of male weanling Fischer 344 rats, 80 per group, were exposed at 0 ppm (paired control; filtered air), 50 ppm, or 100 ppm (7 hr/day, 5 days/week) for 104 weeks. statistically significant increase in mortality was observed in all groups of exposed rats compared to controls. Statistically significant associations between ethylene oxide exposure and an increased incidence of the following rat neoplasms were observed: peritoneal mesothelioma, and mixed cell brain glioma. A statistically significant increase in mononuclear cell leukemias was seen at the low dose (50 ppm) but not at the high dose (100 ppm).

In the Garman et al. (1985) study, groups of F344 rats of each sex were exposed to either ethylene oxide vapor (concentrations of 100, 33 or 10 ppm) or to room air for 6 hours daily, 5 days/week, for up to 2 years. Three representative sections of the brain from each rat were evaluated. Twenty-three primary brain tumors were found, two of which were in control animals. Increased numbers of brain tumors were seen in 100 ppm and 33 ppm ethylene oxide exposed male and female rats. Significant trend analyses were found for both males and females, indicating that, under the conditions of this study, ethylene oxide exposure above 10 ppm was related to the development of these brain tumors.

The National Toxicology Program conducted toxicological and carcinogenesis studies of ethylene oxide by exposing groups of 50 B6C3F1 mice of each sex to air containing 0, 50 or 100 ppm ethylene oxide for 6 hours/ day, 5 days/week

for 102 weeks (NTP, 1986). This study has been peer-reviewed and the data is reproduced in Appendix A, and sumarized below.

In male B6C3F1 mice, alveolar/bronchial adenomas or carcinomas and harderian gland cystadenomas were produced with a positive trend. Both the life table and the incidental tumor tests showed a significant difference between controls and experimentals exposed at 100 ppm. At 50 ppm, the above two tests were also significant for harderian gland tumors but not for alveolar/bronchial adenomas or carcinomas.

In female B6C3F1 mice, alveolar/bronchial adenomas or carcinomas and harderian gland cystadenomas, malignant lymphomas and uterine adenocarcinomas occurred with positive trends. Both life table and incidental tumor tests showed a significant difference between controls and experimentals exposed at 100 ppm for lung tumors, harderian gland tumors and malignant lymphomas, but not for uterine adenocarcinomas.

The NTP staff and peer review group concluded that there was "clear evidence of carcinogenic activity for B6C3F1 mice" as indicated by dose-response increases in the incidence of benign and malignant neoplasms of the lung and benign neoplasms of the harderian gland in both male and female mice. The NTP also concluded that "in female mice, ethylene oxide caused additional malignant neoplasms of the uterus, mammary gland and hemopoietic system (lymphoma)," but of these tumors, only lymphomas were significantly different from concurrent controls. The incidence of lymphomas in these ethylene oxide exposed mice was not significantly different from historical controls for this strain of mice (NTP, 1986).

1.2 HUMAN STUDIES

Three studies conducted in Sweden reported an increased risk of leukemia following occupational exposure to ethylene oxide. In the first study (Hogstedt et al., 1979a), which also showed increased rates of gastric cancer, a small number of Swedish ethylene oxide production workers were also

concurrently exposed to chemicals other than ethylene oxide and the increased rates cannot confidently be attributed to ethylene oxide alone.

In the second study (Hogstedt et al., 1979b), three cases of leukemia occurred in a small group (230) of Swedish workers who were exposed to fugitive ethylene oxide emissions that originated from sterilized hospital equipment. The exposure to ethylene oxide in this study (20 ± 10 ppm) was fairly well characterized. In 1984, Hogstedt et al. reported the first follow-up on their original studies reported in 1979. In this report, the reported cases of leukemia increased from three cases to five cases. These were in women who had been exposed to from two to 70 ppm ethylene oxide (8 hr/day, time-weighted average calculated to be 20 ± 10 ppm).

Hogstedt et al. (1986) reported eight cases of leukemia and six cases of stomach cancer in workers exposed to ethylene oxide as compared to 0.8 and 0.65 cases expected as indicated in a similar industrial cohort. This study was a follow-up on their investigations reported previously in 1979 and 1984.

In another mortality study (Morgan et al., 1981), no significant excess of deaths from leukemia or other malignant neoplasms was reported in a group of 767 males who were potentially exposed to ethylene oxide for 5 to 18 years at a U.S. production facility. Although the size of the cohort was small and the workers appeared to have only minimal exposure (<10 ppm), exposure was associated with increased incidences of pancreatic cancer and Hodgkin's disease (U.S. EPA, 1985).

1.3 WEIGHT-OF-EVIDENCE ASSESSMENT

There are sufficient data to indicate that ethylene oxide is a carcinogen in rats and mice when administered via inhalation. Weekly subcutaneous injections of ethylene oxide for 95 weeks produced a dose-related increase in the incidence of local tumors in mice. The results of an inadequately reported subcutaneous injection study with rats were negative, and the results of a lifetime skin application bioassay with mice were also negative. An increased incidence of tumors was observed in a group of mice that were accidentally

exposed to ethylene oxide-treated bedding, but the exposure was not characterized and this observation does not allow an evaluation of carcinogenicity.

In a two-year inhalation study, a dose-related increased incidence of mononuclear cell leukemia was found in female rats. Significantly increased incidences of subcutis fibromas and pancreatic adenomas were found in males. Gliomas were also significantly increased in both males and females.
Thus in B6C3F1 mice, there was clear evidence of carcinogenic activity as indicated by a dose-related increased incidence of benign and malignant neoplasms of the lung as well as benign neoplasms of the harderian gland. The incidences were significantly elevated above control animals in both sexes.

The evidence indicating a carcinogenic effect in humans due to ethylene oxide exposure is limited because human exposure has been difficult to quantitate. Three studies of human populations exposed occupationally to ethylene oxide have shown increased rates of stomach cancer and leukemia, but the exposure associated with these increases in cancer has been difficult to quantitate, making human potency estimates tenuous. The results of a fourth mortality study did not report increased leukemia or stomach cancer, but significant increases in pancreatic cancer and Hodgkin's disease were noted.

The findings of leukemia in rats exposed to ethylene oxide via chronic inhalation, however, were consistent with the epidemiologic data. Thus, using the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a) for evaluating the overall weight of evidence to humans, ethylene oxide is most appropriately classified as a Group B1 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 ethylene oxide is estimated to be 1.34 (mg/kg/day)-1, placing it in potency group 2 under the CAG's 2-1 contains data from the selected study used to derive the potency factor (F) for ethylene oxide.

Table 2-1. Derivation of Potency Factor(F) Agent: Ethylene oxide

REFERENCE:	NTP, 1986		
EXPOSURE ROUTE:	inhalation		
SPECIES:	mice		
STRAIN:	B6C3F1		
SEX:	M		
VEHICLE OR PHYSICAL STATE:	inhalation		
BODY WEIGHT:	0.035 kg		
DURATION OF TREATMENT:	730 days (6 hrs/day, 5 days/week)		
DURATION OF STUDY:	730 days		
LIFESPAN OF ANIMAL:	730 days		
TARGET ORGAN(S):	lung		
TUMOR TYPE:	adenomas and carcinomas		
EXPERIMENTAL DOSES/EXPOSURE:[a]	100 ppm	50 ppm	0 ppm
TRANSFORMED DOSES:[b] (mg/kg/day)	39.90	19.95	0
TUMOR INCIDENCE:[c]	26/50[d]	19/50[e]	11/50
ANIMAL POTENCY: $(mg/kg/day)^{-1}$	0.106		
HUMAN POTENCY:[f] $(mg/kg/day)^{-1}$	1.34		

[a] Exposure was via inhalation for 6 hours/day, 5 days/week, for approximately 2 years.

[b] To derive the transformed dose from the experimental dose data: experimental dose (ppm) x 0.041 x M.W. of ethylene oxide (44.05 g/mol) x 0.0432 mg/day (rat's breathing rate)/ 0.035 kg (animal weight) x 5 (treatment days/week)/7 (days/week) x 6 (treatment hours/day)/24 (hours/day).

[c] Total tumor count ratios based on number of rats alive at 24 months.

[d] One animal developed both an adenoma and a carcinoma.

[e] Two animals developed both an adenoma and a carcinoma.

[f] Human potency = animal potency x $(70 \text{ kg}/0.035 \text{ kg})^{1/3}$

3.0 HAZARD RANKING

Based on the weight-of-evidence **Group B1** for ethylene oxide, and the potency factor (F) of 1.34 $(mg/kg/day)^{-1}$, ethylene oxide receives a hazard ranking of "MEDIUM."

4.0 REFERENCES

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U.S. EPA (Environmental Protection Agency), 1986a. Guidelines for Carcinogen Risk Assessment, 51 FR 33992-34003, September 24, 1986.

U.S. EPA (Environmental Protection Agency), 1986b. Methodology for Evaluating Potential Carcinogenicity in Support of Reportable Quantity Adjustments Pursuant to CERCLA Section 102, OHEA-C-073, December 1986. Available from CERCLA Docket 102RQ-273C. The public document for RQ rulemaking is located in room M2427, U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460. It is available for inspection Monday through Friday excluding Federal holidays, between the hours of 9:00 a.m. and 4:00 p.m.

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Van Duuren, B., L. Orris and N. Nelson, 1965. Carcinogenicity of Epoxides, Lactones, and Peroxy Compounds. II. J. Natl. Cancer Inst. 35: 707-717.

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APPENDIX

SUMMARY OF SIGNIFICANT HUMAN AND/OR ANIMAL STUDIES

Table A. Animal
Agent: Ethylene Oxide
Reference: Dunkelberg, 1979; 1981

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)
subcutaneous	mice/NMRI	F	1.0 mg/injection/wk	95 weeks	91 weeks	NR[b]	tricaprylin	injection site (interscapular)	total tumors sarcoma[c] lymphoma granuloma	15/100 11/100 2/100 2/100
subcutaneous	mice/NMRI	F	0.3 mg/injection/wk	95 weeks	91 weeks	NR[b]	tricaprylin	injection site (interscapular)	total tumors sarcoma[c] lymphoma basal cell carcinoma	12/100 8/100 2/100 2/100
subcutaneous	mice/NMRI	F	0.1 mg/injection/wk	95 weeks	91 weeks	NR[b]	tricaprylin	injection site (interscapular)	total tumors sarcoma[c] lymphoma	7/100 5/100 2/100
subcutaneous	mice/NMRI	F	0.0 mg/injection/wk	NA	91 weeks	NA	tricaprylin	injection site (interscapular)	total tumors sarcoma[c] lymphoma	5/100 4/100 1/100

QUALITY OF EVIDENCE

Strengths of Study: Multiple dose levels of the compound were administered over a significant portion of the lifespan.

Weaknesses of Study: A non-natural route of administration was employed.

Overall Adequacy: Limited.

Comments: The number of tumors at distant sites was not significantly greater in treated mice compared with vehicle controls.

[a] Preliminary results up to 91st week of treatment.
[b] Purity not reported, but impurities checked for by IR, GC, and Fluoresence methods.
[c] Predominately fibrosarcomas.
NA = Not applicable; NR = Not reported

Table A. Animal

Agent: Ethylene Oxide

Reference: Lynch et al., 1984

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)
inhal- ation	rats/ Fischer 344	M	100 ppm	104 weeks	104 weeks	99.7% pure	filtered air	adrenal	pheochromocytoma	13/78 (NS)
								brain	glioma (mixed cell)	5/79 (P<0.05)
								body cavity	peritoneal mesotheliomas	21/79 (P<0.01)
								pancreas	islet cell adenoma	15/73 (NS)
								pituitary	adenoma	21/67 (P<0.05)
								spleen	mononuclear cell leukemia	30/76 (NS)
inhal- ation	rats/ Fischer 344	M	50 ppm	104 weeks	104 weeks	99.7% pure	filtered air	adrenal	pheochromocytoma	14/77 (NS)
							brain	glioma (mixed cell)		2/77 (NS)
								body cavity	peritoneal mesotheliomas	9/79 (NS)
								pancreas	islet cell adenoma	16/73 (NS)
								pituitary	adenoma	20/66 (P<0.05)
								spleen	mononuclear cell leukemia	38/79 (P<0.05)

Table A. Animal

Agent: Ethylene Oxide

Reference: Lynch et al., 1984 (Page 2)

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)
inhal-ation	rats/ Fischer 344	M	0 ppm	104 weeks	104 weeks	99.7% pure	filtered air	adrenal	pheochromocytoma	8/78
								brain	glioma (mixed cell)	0/76
								body cavity	peritoneal mesotheliomas	3/78
								pancreas	islet cell adenoma	23/77
								pituitary	adenoma	44/73
								spleen	mononuclear cell leukemia	24/77

QUALITY OF EVIDENCE

Strengths of Study: 2-year study duration

Weaknesses of Study: Only one species and strain used

Overall Adequacy: Adequate

Comments: Other response data was given, but is not recorded in this table.

Table A. Animal

Agent: Ethylene Oxide

Reference: NTP, 1986-Draft (Page 1)

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)
inhal- ation	mice/ B6C3F1	M	0 ppm	102 weeks	104 weeks	>99% pure	air	lung	alveolar/ bronchiolar adenoma	5/10
								lung	alveolar/ bronchiolar carcinoma	6/50
inhal- ation	mice/ B6C3F1	M	50 ppm	102 weeks	104 weeks	>99% pure	air	lung	alveolar/ bronchiolar adenoma	11/50 (P=0.095)
								lung	alveolar/ bronchiolar carcinoma	10/50 (P=0.230)
inhal- ation	mice/ B6C3F1	M	100 ppm	102 weeks	104 weeks	>99% pure	air	lung	alveolar/ bronchiolar adenoma	11/50 (P=0.127)
								lung	alveolar/ bronchiolar carcinoma	16/50 (P=0.019)

Table A. Animal

Agent: Ethylene Oxide

Reference: NTP, 1986-Draft (Page 2)

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)
inhal-ation	mice/ B6C3F1	F	0 ppm	102 weeks	104 weeks	>99% pure	air	lung	alveolar/ bronchiolar adenoma	2/49
								lung	alveolar/ bronchiolar carcinoma	0/49
								lymph gland	malignant lymphoma	9/49
inhal-ation	mice/ B6C3F1	F	50 ppm	102 weeks	104 weeks	>99% pure	air	lung	alveolar/ bronchiolar adenoma	4/48 (P=0.277)
								lung	alveolar/ bronchiolar carcinoma	1/48 (P=0.492)
								lymph gland	malignant lymphoma	6/48 (P=0.334N)
inhal-ation	mice/ B6C3F1	F	100 ppm	102 weeks	104 weeks	>99% pure	air	lung	alveolar/ bronchiolar adenoma	17/49 (P<0.001)
								lung	alveolar/ bronchiolar carcinoma	7/49 (P=0.017)
								lymph gland	malignant lymphoma	22/49 (P=0.005)

Table A. Animal

Agent: Ethylene Oxide

Reference: NTP, 1986-Draft (Page 3)

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)
inhala- ation	mice/ B6C3F1	F	50 ppm	102 weeks	104 weeks	>99% pure	air	uterus	uterine adenocarcinoma	1/47 (P=0.383)
								mammary gland	mammary gland adenocarcinoma or adenosquamous carcinoma	8/48 (P=0.012)
			100 ppm					uterus	uterine adenocarcinoma	5/49 (P=0.051)
								mammary gland	mammary gland adenocarcinoma or adenosquamous carcinoma	6/49 (P=0.087)

QUALITY OF EVIDENCE

Strengths of Study: Used two sexes; 2-year study duration; statistical information given.

Weaknesses of Study: Only one species and strain of animal used.

Overall Adequacy: Adequate

Comments: Authors report benign neoplasms of the Harderian gland (not included in this table).

Table A. Animal

Agent: Ethylene Oxide

Reference: Snelling et al., 1981

Exposure Route	Species/ Strain	Sex	Dose or Exposure[a]	Duration of Treatment[b]	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[c] (P value)
inhal-ation	rat/F344	M	100 ppm	98 weeks	100 weeks	NR	vapor	subcutis	fibroma	10/28[e] (P<0.001)
										15/78[e] (P<0.001)
								pancreas	adenoma	5/30 (NS)
										11/80 (P<0.05)
								pituitary	adenoma	12/29 (NS)
										11/80 (P<0.05)
								peritoneum	mesothelioma	4/30 (NS)
										21/80 (P<0.001)
								spleen	leukemia[d]	8/30 (NS)
										25/80 (NS)

Table A. Animal

Reference: Snelling et al., 1981 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure[a]	Duration of Treatment[b]	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[c] (P value)
inhal-ation	rat/F344	M	33 ppm	98 weeks	100 weeks	NR	vapor	subcutis	fibroma	1/34[e] (NS)
										3/75[e] (NS)
								pancreas	adenoma	1/2[f]
										1/43[f]
								pituitary	adenoma	13/39 (NS)
										16/79 (NS)
								peritoneum	mesothelioma	4/39 (NS)
										6/80 (P<0.05)
								spleen	leukemia[d]	10/39 (NS)
										23/80 (NS)
inhal-ation	rat/F344	M	10 ppm	98 weeks	100 weeks	NR	vapor	subcutis	fibroma	8/48[e] (P<0.01)
										10/77[e] (P<0.001)
								pancreas	adenoma	2/30
										2/32[f]
								pituitary	adenoma	15/51 (NS)
										26/79 (NS)
								peritoneum	mesothelioma	2/51 (NS)
										3/80 (NS)
								spleen	leukemia[d]	9/51 (NS)
										21/80 (NS)

Table A. Animal

Reference: Snelling et al., 1981 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure[a]	Duration of Treatment[b]	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[c] (P value)
inhal-ation	rat/F344	M	0 ppm	NA	100 weeks	NA	NA	subcutis	fibroma	3/91 4/154
								pancreas	adenoma	7/97 7/160
								pituitary	adenoma	19/97 43/157
								peritoneum	mesothelioma	2/97 3/160
								spleen	leukemia[d]	13/97 38/160
inhal-ation	rat/F344	F	100 ppm	96 weeks	98 weeks	NR	vapor	spleen	leukemia[d]	15/26 (P<0.001) 27/80 (P<0.001)
			33 ppm	96 weeks	98 weeks	NR	vapor	spleen	leukemia[d]	14/48 (P<0.01) 24/80 (P<0.01)
			10 ppm	96 weeks	98 weeks	NR	vapor	spleen	leukemia[d]	11/54 (P<0.05) 14/80 (NS)
			0 ppm[g]	NA	98 weeks	NA	NA	spleen	leukemia[d]	11/115 22/156

Table A. Animal

Reference: Snelling et al., 1981 (cont.)

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

QUALITY OF EVIDENCE

Strengths of Study: Multiple exposure levels were administered by a natural route over a significant portion of the lifespan.

Weaknesses of Study: All rats became infected with sialodacryoadenitis virus during the 15th exposure month.

Overall Adequacy: Adequate

[a] Exposures were 6 hours/day, 5 days/week.
[b] Exposures were temporarily terminated during weeks 64 and 65 to permit recovery from sialodacryoadenitis virus infection.
[c] Pooled control data given. Incidence of tumors in rats at final sacrifice listed first. Combined incidence of tumors in rats at final sacrifice and rats dying spontaneously or euthanized when moribund listed second.
[d] Mononuclear cell leukemia
[e] Examined only if gross lesions were present (except flank region which was routinely examined microscopically).
[f] Data from the 33 and 10 ppm groups were not statistically analyzed because tissues wsere not examined from all rats (e.g., only gross lesions were examined).
[g] Two untreated air groups were exposed.

Table A. Animal

Agent: Ethylene Oxide

Reference: Snelling et al., 1984

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)
inhal-ation	rats/ F344	F	100 ppm	730 days	730 days	99.9%	air	hematopoetic/ brain	leukemia/ gliomas	32/73
			33 ppm	730 days	730 days	99.9%	air	hematopoetic/ brain	leukemia/ gliomas	27/72
			10 ppm	730 days	730 days	99.9%	air	hematopoetic/ brain	leukemia/ gliomas	15/71
			0 ppm	730 days	730 days	99.9%	air	hematopoetic/ brain	leukemia/ gliomas	23/186

QUALITY OF EVIDENCE

Strengths of Study: Both male and female rats were used. Two control groups were used.

Weaknesses of Study: Only the results which the author considered significant were reported.

Overall Adequacy: Sufficient

Comments: Dosage was 6 hrs/day, 5 days/wk.

Table A. Animal

Agent: Ethylene Oxide

Reference: Van Duuren et al., 1965

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)
dermal	mice/ Swiss Millerton	F	approx. 10 mg/ application thrice weekly[a]	life	life[b]	99.7%	acetone	skin	papilloma carcinoma	0/30 0/30
dermal	mice/ Swiss Millerton	F	0 mg/appli- cation (vehicle control)	NA	life[b]	NA	acetone	skin	papilloma carcinoma	0/60 0/60

QUALITY OF EVIDENCE

Strengths of Study: The compound was administered over the lifespan and all gross tumors were con firmed microscopically.

Weaknesses of Study: Aqueous solutions are not typical for dermal exposure. All organs were not examined.

Overall Adequacy: Adequate

[a] Approximately 0.1 ml of a 10% solution/application.

[b] Median survival times in the treated and control rats were 493 and 447 days, respectively.

NA = Not applicable

Table B. Humans

Agent: Ethylene Oxide

Reference: Hogstedt et al., 1979a

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure[a]	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected[b]	Relative Risk (P value)
inhalation	89 (1324 person years)	Swedish population	M	fulltime exposure	≥1 yr exposure, ≥10 yrs latency	total tumors	NR	9	3.4	2.7 (P<0.01)
						stomach	NR	3	0.4	7.5 (P<0.01)
						hematopoietic	leukemia	2	0.14	14.3 (P<0.01)
inhalation	NR (372 person years)	Swedish population	M	fulltime exposure	≥10 yr exposure, ≥20 yrs latency	total tumors	NR	5	1.1	4.5 (P<0.01)
						stomach	NR	1	0.13	7.7 (NS)
						hematopoietic	leukemia	1	0.04	25 (P<0.05)
inhalation	86 (1211 person years)	Swedish population	M	intermittent exposure	≥1 yr exposure, ≥10 yrs latency	total tumors	NR	3	3.4	0.9 (NS)
						stomach	NR	1	0.4	(NS)
						hematopoietic	leukemia	1	0.13	7.7 (NS)
inhalation	NR (736 person years)	Swedish population	M	intermittent exposure	≥1 yr exposure, ≥20 yrs latency	total tumors	NR	3	2.6	1.2 (NS)
						stomach	NR	1	0.3	3.3 (NS)
						hematopoietic	leukemia	1	0.1	10 (NS)
inhalation	66 (955 person years)	Swedish population	M	unexposed	≥1 yr exposure, ≥10 yrs latency	total tumors	NR	1	2.0	0.5 (NS)
						stomach	NR	0	NA	NA
						hematopoietic	leukemia	0	NA	NA
inhalation	NR (603 person years)	Swedish population	M	unexposed	≥10 yr exposure, ≥20 yrs latency	total tumors	NR	1	1.6	0.6 (NS)
						stomach	NR	0	NA	NA
						hematopoietic	leukemia	0	NA	NA

Table B. Humans

Reference: Hogstedt et al., 1979a

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure[a]	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected[b]	Relative Risk (P value)

QUALITY OF EVIDENCE

Strengths of Study: Adequately controlled mortality study.

Weaknesses of Study: Subjects were exposed to a variety of other chemicals, some that are documented animal carcinogens (see Footnote a). Exposure durations and concerntrations were uncertain. Group sizes were small in the subcohort with ≥10 years employment and 20 years induction-latency.

Overall Adequacy: Adequate

Comments: The observed increases cannot be attributed definitely to ethylene oxide alone.

[a] Ethylene oxide production workers who were exposed to estimated ethylene oxide levels of <25 mg/m^3 (with occasional exposures up to the odor threshold (1300 mg/m^3) during 1941-1947. The workers were also exposed to ethylene chlorohydrin (approx. 5 mg/m^3), ethylene dichloride (approx. 100.05 mg/m^3), bis(2-chloroethyl) ether (approx. 0.05mg/m^3) and ethylene (approx. 600 mg/m^3); it is possible that up to 1000 times these concentrations may have occurred momentarily. Exposure time was estimated as a slightly more than 1 hour/shift. From 1950 to 1963, exposure to chemicals other than ethylene oxide decreased because of production changes, and exposure to ethylene oxide increased (10-50 mg/m^3 with peaks above the odor threshold). Subsequnt years were characterized by a lower ethylene oxide exposure (approx. 1-10 mg/m^3 with higher peaks), but also by exposure to proplene oxide (10-25 mg/m^3, occasionally 120-150 mg/m^3).

[b] The expected number of deaths due to malignanoise were calculated from the cause-, sex-, and age-specific Swedish national death rates from respective 5-year age categories.

NR = Not reported; NS = Not significant

Table B. Humans

Agent: Ethylene Oxide

Reference: Hogstedt et al., 1979b

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure[a]	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected[b]	Relative Risk (P value)
inhal-ation	230	U.S. population	M,F	20 ± 10 ppm	48-yrs	hematopoietic	leukemia	3	0.2	15 (NS)

QUALITY OF EVIDENCE

Strengths of Study: Exposure concentrations and components were fairly well characterized.

Weaknesses of Study: The cohort was small, and the duration of exposure was short.

Overall Adequacy: Limited

Comments: One of the subjects with leukemia had "some occasional contact" with benzene in laboratory work.

[a] Workers were employed in a small Swedish factory that sterilized hospital equipment. Seven people (4 males, 3 females) were sterilizer operators, 70 (68 females, 2 males) were exposed via outgassing from treated boxes in a storage hole for 8 hours/day, and 153 other workers (101 females, 52 males) were employed in neighboring rooms.

Table B. Humans

Agent: Ethylene Oxide

Reference: Morgan et al., 1981

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure[a]	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Standard Mortality Ratio[b]
inhal-	767	U.S.	M	<10 ppm[a]	5-18 years	All malignant	neoplasms	11	15.24	72 (NS)
ation	(13,969	population				pancreas	cancer	3	0.80	375 (NS)
	person-					bladder	cancer	1	0.31	322 (NS)
	years)					brain/CNS	cancer	2	0.70	285 (NS)
						lymphatic	Hodgkin's disease	2	0.35	571 (NS)
						hematopoietic	leukemia	0	0.70	0 (NS)

QUALITY OF EVIDENCE

Strengths of Study: The subjects were employed in a plant that is one of the largst and oldest producers of ethylene oxide in the United States.

Weaknesses of Study: Cohort size was small, and exposures were poorly characterized. Additional tests of significance demonstrated a relationship between ethylene oxide and the incidence of Hodgkins disease and pancreatic cancer[c].

Overall Adequacy: Limited

[a] The subjects had potential exposures to ethylene oxide at a Texaco Chemical Company plant that continuously produced ethylene oxide. A recent (1977) industrial hygiene survey indicated time-weighted average concentrations "well below" the OSHA 50 ppm limit; detectable concentrations were routinely <10 ppm.

[b] Each of these standard mortality ratios (number of tumors observed/number of tumors expected x 100) has a lower 95% confidence limit under 100 (i.e., not significantly elevated).

[c] EPA evaluation of the Morgan data, June, 1985.

Table B. Humans

Agent: Ethylene Oxide

Reference: Hogstedt et al., 1986

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure[a]	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected[b]	Relative Risk (P value)
inhal-	733	Swedish	M,F	2-300 ppm	19-48 yrs	stomach,	adenocar-	4	0.3	13
ation	(total)	population				hematopoietic,	cinoma,	2	0.5	4
						lung	leukemia,	5	0.6	8
							adenocar-	1	0.16	6
							cinoma			

QUALITY OF EVIDENCE

Strengths of Study: Three groups of exposed workers in various locations all demonstrated increased rates of cancer.

Weaknesses of Study: The cohort was relatively small, and exposures were not well defined. There were no worker cohort controls.

Overall Adequacy: Limited

Comments: The author noted that one group had an exposure to almost pure ethylene oxide compared to the cohorts used in the previous two studies.

[a] Sterilization workers from hospitals combined with production workers.