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February 19, 1997

Hasmukh Shah, Ph.D.
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. Shah:

It was a pleasure to speak to you and Wendy Sherman on February 13 concerning EPA's carcinogen risk assessment project as well as the Vinyl Institute's interest in changing the reportable quantity limit for vinyl chloride under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Some background materials expanding on the points I made during our conversation are enclosed.

I appreciate your time and agree that you, Wendy, Frank Borrelli and I should meet in early March to update each other and explore these matters in more detail. Would the afternoon of March 5 be convenient? If not, would March 4 or 7 be agreeable?

We look forward to confirming a meeting date. In the interim, if you have any comments or questions or I can be of assistance, please do not hestitate to call.

Cordially yours,

Peter

Peter L. de la Cruz

Enclosures

CMA 121594

UNITED STATES
ENVIRONMENTAL PROTECTION
AGENCY

OHEA-C-073-194
JUNE 1988
FINAL

RESEARCH AND DEVELOPMENT

EVALUATION OF THE POTENTIAL CARCINOGENICITY OF VINYL CHLORIDE (75-01-4)

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

PREPARED BY

CARCINOGEN ASSESSMENT GROUP
OFFICE OF HEALTH AND
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CMA 121600

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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.

CMA 121601

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

CMA 121602

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.

CMA 121603

ABSTRACT

Vinyl Chloride 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 vinyl chloride is estimated to be 18.1 $(mg/kg/day)^{-1}$, 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, vinyl chloride is assigned a "HIGH" hazard ranking for the purpose of RQ adjustment.

CMA 121604

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Table 2-1. DERIVATION OF POTENCY FACTOR (F) 2-2

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1.0 WEIGHT OF EVIDENCE

1.1 ANIMAL STUDIES

There are many reports on the carcinogenicity of vinyl chloride in animals (Maltoni, 1977a; IARC, 1979; U.S. EPA, 1980; Feron et al., 1981). Due to the limitations of this project, only the most substantial studies will be emphasized and used as a basis for evaluating carcinogenic risk.

A report by Viola et al. (1971) indicated an increased risk of skin carcinoma, lung carcinoma, and osteochondromas in Wistar rats treated with 30,000 ppm vinyl chloride by inhalation. Since then, studies by Maltoni (1977b), Maltoni et al. (1981), Lee et al. (1978), Hong et al. (1981), and Feron et al. (1981) have been the predominant sources of information on the carcinogenicity of vinyl chloride in animals.

Maltoni (1977b) reported an increased incidence of hepatic angiosarcoma and renal nephroblastoma in Sprague-Dawley rats treated by inhalation or gavage. Kidney nephroblastomas were seen in animals treated with 10,000 and 6,000 ppm by inhalation, and 50 and 16.65 mg/kg vinyl chloride by gavage. An increased incidence of liver angiosarcoma was reported in groups treated with as little as 100 ppm vinyl chloride by inhalation and at both dose levels by gavage. Maltoni et al. (1981) reported kidney nephroblastomas in groups treated with 25 ppm vinyl chloride, while control groups had none. Liver angiosarcomas were evident in groups treated with 10 ppm by inhalation. No similar tumors were reported in rats treated with 5, 1, or 0.0 ppm vinyl chloride. In groups of Swiss mice treated with 50, 250, 500, 2,500, 6,000, and 10,000 ppm vinyl chloride, Maltoni et al. (1981) reported a dose-related incidence of liver angiosarcomas and lung tumors. In Golden Hamsters treated at the same levels by inhalation, papillomas and acanthomas of the forestomach were produced by vinyl chloride exposure.

CMA 121606

In groups of 36 male and 36 female CD rats, lung and liver hemangiosarcomas were produced in groups treated with 250 and 1,000 ppm vinyl chloride (Lee et l., 1978). This study showed that females of this strain were more susceptible to the carcinogenic effect of vinyl chloride. Rats treated with 50 or 0.0 ppm vinyl chloride developed no similar tumors. Lee et al. (1978) also reported an increased incidence of bronchioloalveolar adenoma and hepatic hemangiosarcoma in male and female CD-1 mice treated with 50, 250, and 1,000 ppm vinyl chloride by inhalation for six hours/day, five days/week.

In a study examining the carcinogenic effect of vinyl chloride at various doses (50, 250, and 1,000 ppm) by inhalation for various durations of treatment (six or ten months treatment period for rats; one, three, or six months treatment period for mice), Hong et al. (1981) reported elevated numbers of liver and lung hepatocellular carcinomas, hemangiosarcomas, and bronchioloaveolar tumors in rats treated with 250 ppm vinyl chloride for six to ten month duration. All four tumor types showed a significant dose-related response in rats. In mice, only hemangiosarcomas showed a dose-related response. One month of treatment at 250 or 1,000 ppm vinyl chloride for six hours/day, five days/week, followed by a 12 month latency period, was sufficient to produce an increase incidence of bronchioloalveolar tumors in mice.

In a study completed by Feron (1981), groups of 60 to 80 female Wistar rats were exposed to a target dose of 0, 20, 60, or 200 ppm vinyl chloride in the diet. The exposure period and the study length were both 144 weeks. The incidences of tumors from the four dose levels were 2/57 (control), 26/58, 42/59, 56/57. At the three exposure levels, there were 4, 8, and 32 multiple tumors in a single animal at each of the respective levels. None of the control had multiple tumors at a single site. The presence of multiple tumors at a single site adds to the weight of evidence that vinyl chloride is carcinogenic.

CMA 121607

1.2 HUMAN STUDIES

Many case reports and epidemiology studies on the carcinogenicity of vinyl chloride are reported in recent reviews (IARC, 1979,; U.S. EPA, 1980; Infante, 1981). For this document, only those studies presenting sufficient data on the exposed population and a substantial number of cancer cases will be reviewed for the assessment of carcinogenic risk.

Infante (1981) reviewed epidemiological data that indicates an association between liver cancer, brain cancer, lung cancer, and hematopoietic and lymphatic cancers, and vinyl chloride exposure. Waxweliler et al. (1976) reported seven of 136 deaths were due to biliary and liver cancer in 1,287 workers exposed to vinyl chloride for >5 years. All seven occurred following a 15 year latency period. The expected number of cases in this group was 0.4 ($P<0.01$). Similarly, three brain and central nervous system cancers were reported after a 15 year latency, while only 0.6 were expected ($P<0.05$). Respiratory system cancer deaths numbered 11, while 5.7 were expected ($P<0.05$). Lymphatic and hematopoietic system cancer occurred in three vinyl chloride-exposed workers, which is suggestive of an increased incidence (1.7 expected), but is not statistically significant.

A cohort study of 750 workers exposed to vinyl chloride found 4 liver/pancreatic cancers, two of which were confirmed liver angiosarcomas, compared to 0.68 expected for the group exposed for <10 years ($P=0.005$) (Bryen et al., 1976). An additional case of hepatic hemangiosarcoma that had occurred after the data were complied and was, therefore, not included in the reported cases, was reported in this study. Two cases of brain cancer were reported, compared to 0.33 expected ($P<0.05$). The increased incidence of lung cancer (3 observed versus 1.78 expected) was not statistically significant.

Fox and Collier (1977) examined the mortality of 7,409 workers exposed to vinyl chloride in the production of polyvinyl chloride (PVC). This study examined eight factories involved in the production of PVC. A total of four deaths due to liver cancer were reported, compared to 1.64 expected. Three of these

CMA 121608

cases occurred in a factory involved with PVC production since 1944 (the longest period of those factories examined), while only 0.13 would have been expected ($P<0.01$) (Infante, 1981). Infante (1981) notes that 75% of the study cohort in this report were employed for more that ten years.

Examining 161 deaths among vinyl chloride workers, Monson et al. (1974) reported eight liver and biliary cancers (0.7 expected; 11.0 risk ratio) five brain cancers (1.2 expected; 42 risk ratio), 13 lung cancers (7.9 expected; 1.6 risk ratio), 13 digestive tract cancers (8.3 expected; 1.5 risk ratio), and five lymphatic and hematopoietic cancers (3.4 expected; 1.5 risk ratio). The authors did not report statistical comparisons of these data but note an excess frequency of liver, lung, and brain cancers. It is also reported that the frequency of all cancers is increasing with length of exposure and latency.

1.3 WEIGHT-OF-EVIDENCE ASSESSMENT

Vinyl chloride has been shown to be a carcinogen in rats, mice, and hamsters. It produced a high incidence of liver, kidney, lung, and brain tumors (Maltoni et al., 1982; Feron, 1981) in a dose-related response when administered by oral or inhalation routes. Similar carcinogenic effects have been shown in vinyl chloride-exposed workers. The predominant target organs are the liver, brain, lung, and lympho-hematopoietic system, but a general non-specific carcinogenic effect has been suggested. Thus, using the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a) criteria for evaluating the overall weight of evidence to humans 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.

CMA 121609

2.0 POTENCY

The potency factor (F) for vinyl chloride is estimated to be 18.1 $(mg/kg/day)^{-1}$, placing it in potency group 2 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 vinyl chloride.

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Table 2-1. Derivation of Potency Factor(F) Agent: Vinyl Chloride

REFERENCE:	Feron et al., 1981			
EXPOSURE ROUTE:	oral			
SPECIES:	rat			
STRAIN:	Wistar			
SEX:	F			
VEHICLE OR PHYSICAL STATE:	diet			
BODY WEIGHT:[a]	0.20 kg			
DURATION OF TREATMENT:	1008 days			
DURATION OF STUDY:	1008 days			
LIFE SPAN OF ANIMAL:[b]	1008 days			
TARGET ORGAN:	liver and lung			
TUMOR TYPE:	angiosarcoma and hepatocellular carcinomas			
EXPERIMENTAL DOSES/EXPOSURE	200 ppm	60 ppm	20 ppm	0.0 ppm
TRANSFORMED DOSES:[c] (mg/kg/day)	14.1	5.0	1.7	0.0
TUMOR INCIDENCE:	56/57	42/59	26/58	2/57
ANIMAL POTENCY: $(mg/kg/day)^{-1}$	2.565			
HUMAN POTENCY:[d] $(mg/kg/day)^{-1}$	18.1			

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[a] Estimated
[b] Assumed
[c] Data were taken directly from Table 1 on page 319 of the Feron et al., 1981 reference.
[d] Human potency = animal potency x $(70\ kg/\ 0.20\ kg)^{1/3}$

3.0 HAZARD RANKING

Based on the weight-of-evidence, Group A for vinyl chloride, and the potency factor (F) of 18.1 $(mg/kg/day)^{-1}$, vinyl chloride receives a hazard ranking of "HIGH."

CMA 121612

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CMA 121614

APPENDIX

SUMMARY OF SIGNIFICANT HUMAN AND/OR ANIMAL STUDIES

Table A. Animal

Agent: Vinyl Chloride

Reference: Feron et al. 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)
oral	rat/ Wistar	M	20 ppm (1.7 mg/kg/day)	135 weeks	135 weeks	99.7%	diet	liver	neoplastic nodule carcinoma angiosarcoma	1/58 (NS) 1/58 (NS) 0/58 (NS)
oral	rat/ Wistar	M	60 ppm (5.0 mg/kg/day)	135 weeks	135 weeks	99.7%	diet	liver	neoplastic nodule carcinoma angiosarcoma	7/56 (P = 0.007) 2/56 (NS) 6/56 (P = 0.014)
oral	rat/ Wistar	M	200 ppm (14.1 mg/kg/day)	135 weeks	135 weeks	99.7%	diet	liver	neoplastic nodule carcinoma angiosarcoma	23/59 (P < 0.001) 8/59 (P = 0.004) 27/59 (P < 0.001)
oral	rat/ Wistar	M	0.0ppm (controls)	135 weeks	135 weeks	99.7%	diet	liver	neoplastic nodule carcinoma angiosarcoma	0/55 0/55 0/55
oral	rat/ Wistar	F	20 ppm (1.7 mg/kg/day)	144 weeks	144 weeks	99.7%	diet	liver	neoplastic nodule carcinoma angiosarcoma	26/58 (P < 0.001) 4/58 (NS) 0/58 (NS)
oral	rat/ Wistar	F	60 ppm (5.0 mg/kg/day)	144 weeks	144 weeks	99.7%	diet	liver	neoplastic nodule carcinoma angiosarcoma	39/59 (P < 0.001) 19/59 (P < 0.001) 2/59 (NS)
oral	rat/ Wistar	F	200 ppm (14.1 mg/kg/day)	144 weeks	144 weeks	99.7%	diet	liver	neoplastic nodule carcinoma angiosarcoma	44/57 (P < 0.001) 29/57 (P < 0.001) 9/57 (P < 0.0014)
oral	rat/ Wistar	F	0.0ppm (controls)	144 weeks	144 weeks	99.7%	diet	liver	neoplastic nodule carcinoma angiosarcoma	2/57 0/57 0/57

CMA 121616

Table A. Animal

Agent: Vinyl Chloride

Reference: Hong 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/CD	M,F	50 ppm	6 or 10 months[c]	18 or 22 months[c]	99.8%	air/vapor	liver	hepatocellular carcinoma	0/66
									hemangiosarcoma	0/66
								lung	bronchioloalveolar tumor	0/66
									hemangiosarcoma	0/66
i	rat/CD	M,F	250 ppm	6 or 10 months[c]	18 or 22 months[c]	99.8%	air/vapor	liver	hepatocellular carcinoma	2/68
									hemangiosarcoma	5/68
								lung	bronchioloalveolar tumor	2/68
									hemangiosarcoma	2/68
i	rat/CD	M,F	1000 ppm	6 or 10 months[c]	18 or 22 months[c]	99.8%	air/vapor	liver	hepatocellular carcinoma	7/72
									hemangiosarcoma	14/72
								lung	bronchioloalveolar tumor	4/72
									hemangiosarcoma	7/72
i	rat/CD	M,F	0 ppm	6 or 10 months[c]	18 or 22 months[c]	99.8%	air/vapor	liver	hepatocellular carcinoma	1/72
									hemangiosarcoma	0/72
								lung	bronchioloalveolar tumor	0/72
									hemangiosarcoma	0/72
i	mouse/ CD-1	M,F	50 ppm	1 month	13 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/32
								liver	hemangiosarcoma	1/32

CMA 121617

Table A. Animal

Agent: Vinyl Chloride

Reference: Hong et al. 1981 (cont.)

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/ CD-1	M,F	250 ppm	1 month	13 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	19/32
								liver	hemangiosarcoma	0/32
i	mouse/ CD-1	M,F	1000 ppm	1 month	13 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	20/32
								liver	hemangiosarcoma	0/32
i	mouse/ CD-1	M,F	0 ppm	1 month	13 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/32
								liver	hemangiosarcoma	0/32
i	mouse/ CD-1	M,F	50 ppm	3 months	15 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	12/32
								liver	hemangiosarcoma	0/32
i	mouse/ CD-1	M,F	250 ppm	3 months	15 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	21/32
								liver	hemangiosarcoma	4/32
i	mouse/ CD-1	M,F	1000 ppm	3 months	15 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	5/20
								liver	hemangiosarcoma	16/20
i	mouse/ CD-1	M,F	0 ppm	3 months	15 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	2/32
								liver	hemangiosarcoma	0/32

CMA 121618

Table A. Animal

Agent: Vinyl Chloride

Reference: Hong et al, 1981 (cont.)

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/ CD-1	M,F	50 ppm	6 months	18 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/16
								liver	hemangiosarcoma	1/16
i	mouse/ CD-1	M,F	250 ppm	6 months	18 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	12/20
								liver	hemangiosarcoma	9/20
i	mouse/ CD-1	M,F	1000 ppm	6 months	18 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	14/24
								liver	hemangiosarcoma	13/24
i	mouse/ CD-1	M,F	0 ppm	6 months	18 months	99.8%	air/vapor	lung	bronchioloalveolar tumor	11/56
								liver	hemangiosarcoma	1/56

QUALITY OF EVIDENCE

Strengths of Study: Two animal species were tested. Dose and exposure levels were varied to show a dose-response. Statistics of tumor incidence with respect to dose are reported.

Weaknesses of Study: The duration of treatment was too short in all cases.

Overall Adequacy: Adequate

Comments: This study was conducted to enhance that reported by Lee et al., 1978.

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

[b] Showed dose-related response; significant at $P<0.05$

[c] Duration of exposure was for 6 months or 10 months, followed by a 12-month latency period. The results presented are for the combined treatment-duration group.

CMA 121619

Table A. Animal

Agent: Vinyl Chloride

Reference: Lee et al. 1978 (cont.)

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/ CD-1	M	50 ppm	12 months	12 months	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	8/29
								liver	hemangiosarcoma	3/29
I	mouse/ CD-1	F	50 ppm	12 months	12 months	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	4/34
								liver	hemangiosarcoma	0/34
I	mouse/ CD-1	M	250 ppm	12 months	12 months	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	10/29
								liver	hemangiosarcoma	7/29 (P<0.05)
I	mouse/ CD-1	F	250 ppm	12 months	12 months	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	12/34
								liver	hemangiosarcoma	16/34 (P<0.05)
I	mouse/ CD-1	M	1000 ppm	12 months	12 months	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	22/33
								liver	hemangiosarcoma	13/33 (P<0.05)
I	mouse/ CD-1	F	1000 ppm	12 months	12 months	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	26/36
								liver	hemangiosarcoma	18/36 (P<0.05)

QUALITY OF EVIDENCE

Strengths of Study: Three different levels of vinyl chloride were tested in two species of animals. Some statistics were reported. Vinyl chloride was quite pure. An extensive examination of organs and tissues was performed.

Weaknesses of Study: The significance of bronchioloalveolar adenoma in mice is not reported. The duration of study was short (due to mortality).

Overall Adequacy: Adequate

[a] Exposure was for 6 hours/day, 5 days/week

N/A = Not Applicable

CMA 121621

Table A. Animal

Agent: Vinyl Chloride

Reference: Maltoni, 1977b

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	NR	10,000 ppm	52 weeks	155 weeks	NR	vapor/air	liver kidney	angiosarcoma nephroblastoma	9/60 5/60
i	rat/ Sprague-Dawley	NR	6,000 ppm	52 weeks	155 weeks	NR	vapor/air	liver kidney	angiosarcoma nephroblastoma	13/60 4/60
i	rat/ Sprague-Dawley	NR	200 ppm	52 weeks	143 weeks	NR	vapor/air	liver	angiosarcoma	12/120
i	rat/ Sprague-Dawley	NR	150 ppm	52 weeks	143 weeks	NR	vapor/air	liver	angiosarcoma	5/120
i	rat/ Sprague-Dawley	NR	100 ppm	52 weeks	143 weeks	NR	vapor/air	liver	angiosarcoma	1/120
i	rat/ Sprague-Dawley	NR	0 ppm	52 weeks	143 155 weeks	NA	air only	liver kidney	angiosarcoma nephroblastoma	0/500 0/120
i	rat/ Sprague-Dawley	NR	50 mg/kg	52 weeks	136 weeks	NR	olive oil	liver kidney	angiosarcoma nephroblastoma	9/80 3/80
i	rat/ Sprague-Dawley	NR	0.0 mg/kg	52 weeks	136 weeks	NA	olive oil	liver kidney	angiosarcoma nephroblastoma	0/150 0/150

CMA 121622

Table A. Animal

Agent: Vinyl Chloride

Reference: Maltoni, 1977b (cont.)

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)

QUALITY OF EVIDENCE

Strengths of Study: A broad range of dose levels were tested. Carcinogenic response was shown by two routes of administration. Duration of study was long in all cases.

Weaknesses of Study: No statistics were reported. The sex of test animals was not reported. Data for the control group for the gavage studies is reported in Maltoni et al., 1981. Some animals were treated by gavage. The purity of vinyl chloride is not reported.

Overall Adequacy: Adequate

Comments: This study focused on different factors affecting the carcinogenic effect (animal species, strain and age, treatment duration, and exposure levels.)

[a] Exposure to vinyl chloride was for 4 hours/day, 5 days/week for 52 weeks; by gavage, once daily in olive oil 4 - 5 days/week.

NR = Not Reported

NA = Not Applicable

CMA 121623

Table A. Animal

Agent: Vinyl Chloride

Reference: Maltoni, 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	M,F	30,000 ppm	52 weeks	68 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	18/60 NR
i	rat/ Sprague-Dawley	M,F	10,000 ppm	52 weeks	135 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	7/60 5/60
i	rat/ Sprague-Dawley	M,F	6,000 ppm	52 weeks	135 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/59 5/59
i	rat/ Sprague-Dawley	M,F	2,500 ppm	52 weeks	135 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/60 6/60
i	rat/ Sprague-Dawley	M,F	500 ppm	52 weeks	135 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/60 6/60
i	rat/ Sprague-Dawley	M,F	250 ppm	52 weeks	135 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	3/59 5/59
i	rat/ Sprague-Dawley	M,F	200 ppm	52 weeks	143 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	12/120 7/20
i	rat/ Sprague-Dawley	M,F	150 ppm	52 weeks	143 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/119 11/119

CMA 121624

Table A. Animal

Agent: Vinyl Chloride

Reference: Maltoni, et al., 1981 (Cont.)

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	M,F	100 ppm	52 weeks	143 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/120 10/120
i	rat/ Sprague-Dawley	M,F	50 ppm	52 weeks	135 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/60 1/60
i	rat/ Sprague-Dawley	M,F	25 ppm	52 weeks	147 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	5/120 1/120
i	rat/ Sprague-Dawley	M,F	10 ppm	52 weeks	147 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/119 0/119
i	rat/ Sprague-Dawley	M,F	5 ppm	52 weeks	147 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/119 0/119
i	rat/ Sprague-Dawley	M,F	1 ppm	52 weeks	147 weeks	>99.9%	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/118 0/118
i	rat/ Sprague-Dawley	M,F	0 ppm	NA	135 - 147 weeks	NA	air only	liver kidney	angiosarcoma nephroblastoma	0/363 0/363
i	rat/ Sprague-Dawley	M,F	10,000 ppm	30 weeks	81 weeks	>99.9%	air/vapor	liver lung	angiosarcoma tumor	10/56 46/56

CMA 121625

Table A. Animal

Agent: Vinyl Chloride

Reference: Maltoni, et al., 1981 (Cont.)

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/ Swiss	M,F	6,000 ppm	30 weeks	81 weeks	>99.9%	air/vapor	liver lung	angiosarcoma tumor	13/60 47/60
i	mouse/ Swiss	M,F	10,000 ppm	30 weeks	81 weeks	>99.9%	air/vapor	liver lung	angiosarcoma tumor	10/56 46/56
i	mouse/ Swiss	M,F	2,500 ppm	30 weeks	81 weeks	>99.9%	air/vapor	liver lung	angiosarcoma tumor	16/59 40/59
i	mouse/ Swiss	M,F	500 ppm	30 weeks	81 weeks	>99.9%	air/vapor	liver lung	angiosarcoma tumor	14/60 50/60
i	mouse/ Swiss	M,F	250 ppm	30 weeks	81 weeks	>99.9%	air/vapor	liver lung	angiosarcoma tumor	18/60 41/60
i	mouse/ Swiss	M,F	50 ppm	30 weeks	81 weeks	>99.9%	air/vapor	liver lung	angiosarcoma tumor	1/60 6/60
i	mouse/ Swiss	M,F	0 ppm	NA	81 weeks	NA	air only	liver lung	angiosarcoma tumor	0/150 15/150
	hamster/ Syrian Golden	M,F	10,000 ppm	30 weeks	109 weeks	>99.9%	air/vapor	forestomach	papilloma/acanthoma	10/30

CMA 121626

Table A. Animal

Agent: Vinyl Chloride

Reference: Maltoni, et al., 1981 (Cont.)

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	hamster/ Syrian Golden	M,F	6,000 ppm	30 weeks	109 weeks	>99.9%	air/vapor	forestomach	papilloma/acanthoma	10/30
i	hamster/ Syrian Golden	M,F	2,500 ppm	30 weeks	109 weeks	>99.9%	air/vapor	forestomach	papilloma/acanthoma	17/30
i	hamster/ Syrian Golden	M,F	500 ppm	30 weeks	109 weeks	>99.9%	air/vapor	forestomach	papilloma/acanthoma	9/30
i	hamster/ Syrian Golden	M,F	250 ppm	30 weeks	109 weeks	>99.9%	air/vapor	forestomach	papilloma/acanthoma	4/30
i	hamster/ Syrian Golden	M,F	50 ppm	30 weeks	109 weeks	>99.9%	air/vapor	forestomach	papilloma/acanthoma	3/30
i	hamster/ Syrian Golden	M,F	0 ppm	NA	109 weeks	NA	air only	forestomach	papilloma/acanthoma	3/60

QUALITY OF EVIDENCE

Strengths of Study: Vinyl chloride was administered by inhalation, gavage, or subcutaneous or intraperitoneal injection to rats, mice, and hamsters at a broad range of doses. Extensive examinations of animals were performed. The vinyl chloride was quite pure. Duration of studies was long.

Overall Adequacy: Adequate

Comments: This report was extensive and much of the data was not reported here due to the scope of this project.

[a] Exposure was for 4 hours/day, 5 days/week

NA = Not Applicable

CMA 121627

Table A. Animal

Agent: Vinyl Chloride

Reference: Viola, et al., 1971

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/Wistar (Ar/IRE)	M	30,000 ppm	12 months	>12 months	99%	vapor/air	skin lung bone	epidermoid carcinoma carcinoma osteochondroma	15/26 6/26 5/26
i	rat/Wistar (Ar/IRE)	M	0 ppm	NA	>12 months	NA	air only	skin lung bone	epidermoid carcinoma carcinoma osteochondroma	0/25 0/25 0/25

QUALITY OF EVIDENCE

Strengths of Study: An appropriate route of administration was used. The vinyl Chloride was relatively pure. Appropriate controls were included for comparison.

Weaknesses of Study: Only male mice were tested. The duration of the study could have been longer. No statistics were complied on incidences between treated and untreated animals.

Overall Adequacy: Adequate

[a] Exposure was for 4 hours/day, 5 days/week for 12 months.

NA = Not Applicable

CMA 121628

Table A. Animal

Agent: Vinyl Chloride

Reference: Viola, et al., 1971

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/Wistar (Ar/IRE)	M	30,000 ppm	12 months	>12 months	99%	vapor/air	skin	epidermoid carcinoma	15/26
								lung	carcinoma	6/26
								bone	osteochondroma	5/26
i	rat/Wistar (Ar/IRE)	M	0 ppm	NA	>12 months	NA	air only	skin	epidermoid carcinoma	0/25
								lung	carcinoma	0/25
								bone	osteochondroma	0/25

QUALITY OF EVIDENCE

Strengths of Study: An appropriate route of administration was used. The vinyl Chloride was relatively pure. Appropriate controls were included for comparison.

Weaknesses of Study: Only male mice were tested. The duration of the study could have been longer. No statistics were complied on incidences between treated and untreated animals.

Overall Adequacy: Adequate

[a] Exposure was for 4 hours/day, 5 days/week for 12 months.

NA = Not Applicable

CMA 121628

Table 8. Humans

Agent: Vinyl Chloride

Reference: Bryen 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	750	1969 Swedish Population	M	periodically up to 15,000 ppm	>10 years	liver/ pancreas	cancer	4	0.68	P<0.005
					<1 to >10 years	brain	cancer	2	0.33	P<0.043
					<1 to >10 years	lung	cancer	3	1.78	P<0.260

QUALITY OF EVIDENCE

Strengths of Study: The Exposed population was compared to the Swedish population. The incidence of liver tumors was reported based on lengths of exposure. Statistics were complied to show significant increases in tumor incidence.

Weaknesses of Study: Specific levels of exposure are not reported. A relatively small number of cancer deaths were examined.

Overall Adequacy: Adequate

CMA 121629

Table B. - Humans

Agent: Vinyl Chloride

Reference: Monson et al., 1974

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	161	161	M	NR	NR	liver and biliary tract	cancer	8	0.7	11.0
						brain	cancer	5	1.2	4.2
						lung	cancer	13	7.9	1.6
						digestive system	cancer	13	8.3	1.6
						lymphatic and hematopoietic system	cancer	5	3.4	1.5

QUALITY OF EVIDENCE

Strengths of Study: Deaths in vinyl chloride-exposed population were compared with a comparable age/time/cause-specific reference population. The incidence of several causes of death were examined.

Weaknesses of Study: The levels of exposure and duration are not reported. No statistics are reported.

Overall Adequacy: Adequate

NR = Not reported

CMA 121630

Table B. Humans

Agent: Vinyl Chloride

Reference: Waxweiler 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	1287	U.S. death rates	M,F	NR	>5 years	liver and biliary	cancer	7	0.4	16.0 (P<0.01)
						brain and CNS	cancer	3	0.6	5.0
						lymphatic and hematopoietic	cancer	3	1.7	1.8 (NS)
						respiratory	cancer	11	5.4	1.9

QUALITY OF EVIDENCE

Strengths of Study: Tumor incidences were analyzed on the basis of latency period. Statistical analyses of different types of cancer compared to expected values were performed. The study was of workers with >5 years exposure.

Weaknesses of Study: Levels of Exposure were not available.

Overall Adequacy: Adequate

[a] Incidence of tumors after 15-year latency
NR = Not reported
NS = Not significant

CMA 121631