

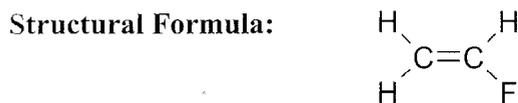
ROBUST SUMMARY FOR FLUOROETHYLENE

Existing published and unpublished data were collected and scientifically evaluated to determine the best possible study or studies to be summarized for each required endpoint. In the spirit of this voluntary program, other data of equal or lesser quality are not summarized, but are listed as related references at the end of each appropriate section, with a statement to reflect the reason why these studies were not summarized.

1.0 Substance Information

CAS Number: 75-02-5

Chemical Name: Fluoroethylene



Other Names:

- FC-1141
- 1-Fluoroethene
- 1-Fluoroethylene
- Fluoroethene
- HFC-1141
- Monofluoroethene
- Monofluoroethylene
- R 1141
- 2,4,6-Triethyleneimino-2,3,5-triazine
- Triethylenemelamine
- VF
- Vinyl Fluoride

Exposure Limits: 1 ppm (8-hour TWA), A2, suspected human carcinogen: ACGIH TLV

1 ppm (8-hour TWA)
0.5 ppm (12-hour TWA): DuPont Acceptable Exposure Limit (AEL)

1 ppm (1.88 mg/m³), (8-hour TWA), Ceiling value of
5 ppm (9.4 mg/m³) for short-term (15-minute) exposure: NIOSH

RECEIVED
OPPT 0310
03 DEC 31 AM 9:10

2.0 Physical/Chemical Properties

2.1 Melting Point

Value:	-160.5°C
Decomposition:	No Data
Sublimation:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Lide, D. R. (ed). (1994-1995). <u>CRC Handbook of Chemistry and Physics</u> , 75 th ed., p. 3-163, CRC Press Inc., Boca Raton, FL (HSDB/807).
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point:

SRC (Syracuse Research Corporation) (1988). (ENVIROFATE-0003108).

Grasselli, J. G. and W. M. Richey (1975). Chemical Rubber Company Atlas of Spectral Data and Physical Constants for Organic Compounds, 2nd ed., CRC Press, Inc., Cleveland, Ohio (ISHOW/0001184).

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 3678, John Wiley & Sons, Inc., New York.

2.2 Boiling Point

Value:	-72°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Lide, D. R. (ed). (1994-1995). <u>CRC Handbook of Chemistry and Physics</u> , 75 th ed., p. 3-163, CRC Press Inc., Boca Raton, FL (HSDB/807).
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

DuPont Co. (1999). Material Safety Data Sheet No. DU002828 (October 9).

Engineering Services Data Unit (1976). Eng. Sci. Data Item, 76004:43 (ENVIROFATE/0003109).

Weast, R. C. (1969). Chemical Rubber Company Atlas of Spectral Data and Physical Constants for Organic Compounds, 2nd ed., CRC Press, Inc., Cleveland, Ohio (ISHOW/0001185).

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 3678, John Wiley & Sons, Inc., New York.

2.3 Density

Value: Specific gravity = 0.636 (liquid under pressure)
Temperature: 21°C
Method: No Data
GLP: Unknown
Results: No additional data.
Reference: Kirk-Othmer (1991). Encyclopedia of Chemical Technology, 4th ed., p. VII 684, John Wiley and Sons, New York, NY (HSDB/807).
Reliability: Not assignable because limited study information was available.

Additional References for Density:

DuPont Co. (1999). Material Safety Data Sheet No. DU002828 (October 9).

Patty, F. (ed.) (1963). Industrial Hygiene and Toxicology: Volume II: Toxicology, 2nd ed., p. 1322, Interscience Publishers, New York (HSDB/807).

2.4 Vapor Pressure

Value: 1.98×10^4 mm Hg
Temperature: 25°C
Decomposition: No Data
Method: Calculated from experimentally derived coefficients.
GLP: Unknown
Reference: Daubert, T. E. and R. P. Danner (1989). Physical and Thermodynamic Properties of Pure Chemicals Data Compilation, Taylor and Francis, Washington, DC (HSDB/807).
Reliability: Not assignable because limited study information was available.

Additional References for Vapor Pressure:

DuPont Co. (1999). Material Safety Data Sheet No. DU002828 (October 9).

Kirk-Othmer Encyclopedia of Chemical Technology, (1991). 4th ed., John Wiley & Sons, 11:683-694 (cited in IARC (1995). IARC Monograph Series, 63:467-477).

Engineering Services Data Unit (1976). Eng. Sci. Data Item, 76004:43 (ENVIROFATE/103176).

Angus, S. et al. (1985). International Tables for the Fluid State: Chlorine, Pergamon Press, Oxford (cited in Lide, D. R. (ed.) (1994-1995). CRC Handbook of Chemistry and Physics, 75th ed., CRC Press Inc., Boca Raton, FL).

2.5 Partition Coefficient (log Kow)

Value: 1.19
Temperature: No Data
Method: Estimated
GLP: Not Applicable
Reference: Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/807).
Reliability: Not assignable because limited study information was available.

Additional References for Partition Coefficient (log Kow):

Leo, A. J. (1978). Report on the Calculation of Octanol/Water Log P Values for Structures in EPA Files (ISHOW/301092).

SRC (Syracuse Research Corporation) (1988). Calculated values (ENVIROFATE/103179).

2.6 Water Solubility

Value: 0.94 g/100 g water @ 3.4 Mpa
1.54 g/100 g water @ 6.9 Mpa
Temperature: 80°C
pH/pKa: No Data
Method: No Data
GLP: Unknown
Reference: Kirk-Othmer (1991). Encyclopedia of Chemical Technology 4th ed., 1:684, John Wiley and Sons, New York, NY.
Reliability: Not assignable because limited study information was available.

Additional References for Water Solubility:

DuPont Co. (1999). Material Safety Data Sheet No. DU002828 (October 9).

PCR Inc. (1994). Material Data Safety Sheet, Gainesville, FL (cited in IARC (1995). IARC Monograph Series, 63:467-477).

SRC (Syracuse Research Corporation) (1988). Calculated values (ENVIROFATE/103175).

Weast, R. C. (1969). Chemical Rubber Company Handbook of Chemistry and Physics, 50th ed., CRC Press, Inc., Cleveland, Ohio (ISHOW/0001187).

Lide, D. R. (ed). (1994-1995). CRC Handbook of Chemistry and Physics, 75th ed., p. 3-163, CRC Press Inc., Boca Raton, FL.

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 3678, John Wiley & Sons, Inc., New York.

2.7 Flash Point: No Data.

2.8 Flammability

Results: 2.6-21.7%
Method: No Data
GLP: Unknown
Reference: Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 3678, John Wiley & Sons, Inc., New York.
Reliability: Not assignable because limited study information was available.

Additional Reference for Flammability:

DuPont Co. (1999). Material Safety Data Sheet No. DU002828 (October 9).

3.0 Environmental Fate

3.1 Photodegradation

Concentration: Not Applicable
Temperature: Not Applicable
Direct Photolysis: Not Applicable
Indirect Photolysis: Half-life due to OH radical oxidation = 1.5 days (experimental); Half-life due to ozone oxidation = 16 days (experimental); Estimated atmospheric half-life due to the combined effects of OH radical and ozone oxidation reactions = 1.37 days
Breakdown: Not Applicable

Products:
Method: Based upon a vapor pressure of 19800 mm Hg at 25°C (Daubert and Danner, 1989), vinyl fluoride will exist in the vapor phase in the ambient atmosphere (Bidleman, 1988; SRC, n.d.). The rate constant for the vapor-phase reaction of vinyl fluoride with photochemically produced hydroxyl radicals has been experimentally determined to be 5.9×10^{-12} cm³/molecule-sec at 25°C which corresponds to an atmospheric half-life of about 1.5 days at an atmospheric concentration of 5×10^5 hydroxyl radicals per cm³ (Atkinson, 1989; SRC, n.d.). The rate constant for the vapor-phase reaction of vinyl fluoride with atmospheric ozone has been experimentally determined to be 7×10^{-19} cm³/molecule-sec at 21°C which corresponds to an atmospheric half-life of about 16 days at an atmospheric concentration of 7×10^{11} molecules per cm³ (Atkinson and Carter, 1984; SRC, n.d.).

GLP: Not Applicable

Reference: Daubert, T. E. and R. P. Danner (1989). Physical and Thermodynamic Properties of Pure Chemicals: Data Compilation, Hemisphere Pub. Corp., New York (HSDB/807).

Bidleman, T. F. (1988). Environ. Sci. Technol., 22:361-367 (HSDB/807).

Atkinson, R. (1989). J. Phys. Chem. Ref. Data, Monograph No. 1, p. 127 (HSDB/807).

Atkinson, R. and W. P. L. Carter (1984). Chem. Rev., 84:437-670 (HSDB/807).

Reliability: SRC (Syracuse Research Corporation) (n.d.). (HSDB/807). Estimated value based on accepted model.

Additional References for Photodegradation: None Found.

3.2 Stability in Water

Concentration: Not Applicable
Half-life: Not Applicable
% Hydrolyzed: Not Applicable
Method: HYDROWIN Program (v1.67) cannot estimate a hydrolysis rate constant for this chemical structure. Volatilization will be a major fate process for vinyl fluoride in water. Volatilization half-lives of 2 and 23.5 hours have been estimated for a model river (1 m deep) and a model pond

(2 m deep), respectively (Lyman et al., 1990; U.S. EPA, 1987; SRC, n.d.).

GLP: Not Applicable

Reference: Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, p. 15-15 to 15-29, Amer. Chem. Soc., Washington, DC (HSDB/801)

U.S. EPA (1987). EXAMS II Computer Simulation (HSDB/801).

Reliability: SRC (n.d.). Syracuse Research Corporation (HSDB/801). Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity):

Media: Air, Water, Soil, and Sediments

Compartment	% of total distribution	½ life (advection + reaction) (hrs)
Air	37.5	58.9
Water	61.4	360
Soil	1	720
Sediment	0.1	3240

Adsorption Coefficient: Koc = 6.35 (calculated by model)

Desorption: No Data

Volatility: Henry's Law Constant = 0.118 atm-m³/mole (HENRYWIN program)

Method: Modeled.
Based on equal emissions to air, water, and soil, using values of Vapor Press : 1.98x10⁴ mm Hg (user-entered)
Log Kow: 1.19 (KOWWIN program)

Henry's Law Constant - HENRYWIN v.3.10 module of EPIWIN v3.11 (Syracuse Research Corporation). Henry's Law Constant (HLC) is estimated by two separate methods that yield two separate estimates. The first method is the bond contribution method and the second is the group contribution method. The bond contribution method is able to estimate many more types of structures; however, the group method estimate is usually preferred (but not always) when all fragment values are available.

Koc – Calculated from Kow by the Mackay Level III fugacity model incorporated into EPIWIN v3.11 (Syracuse Research Corporation).

GLP: Environmental Distribution - Mackay Level III fugacity model, in EPIWIN v3.11 (Syracuse Research Corporation). Emissions (1000 kg/hr) to air, water, and soil compartments. Not Applicable
Reference: HENRYWIN - J. Hine and P. K. Mookerjee (1975). J. Org. Chem., 40(3):292-8 and Meylan, W. and P. H. Howard (1991). Environ. Toxicol. Chem., 10:1283-93.

Fugacity - The methodology and programming for the Level III fugacity model incorporated into EPIWIN v3.11 (Syracuse Research Corporation) were developed by Dr. Donald MacKay and coworkers and are detailed in: Mackay, D. (1991). Multimedia Environmental Models: The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press.
Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.
Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.
Reliability: Estimated values based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation:

Value:	No Data
Breakdown	
Products:	No Data
Linear Model	
Prediction:	0.7256 (Biodegrades Fast)
Non-Linear Model	
Prediction:	0.9133 (Biodegrades Fast)
Ultimate	
Biodegradation	
Timeframe:	3.1 (Weeks)
Primary	
Biodegradation	
Timeframe:	3.78 (Days)
MITI Linear Model	
Prediction:	0.611 (readily biodegradable)
MITI Non-Linear	
Model Prediction:	0.063 (Not readily biodegradable)

Breakdown
Products: No Data
Method: Modeled. BIOWIN, v4.0 module of EPIWIN v3.05 (Syracuse Research Corporation). BIOWIN estimates the probability for the rapid aerobic biodegradation of an organic chemical in the presence of mixed populations of environmental microorganisms. Estimates are based upon fragment constants that were developed using multiple linear and non-linear regression analyses.
GLP: Not Applicable
Reference: Boethling, R. S. et al. (1994). Environ. Sci. Technol., 28:459-65.
Howard, P. H. et al. (1992). Environ. Toxicol. Chem., 11:593-603.
Howard, P. H. et al. (1987). Environ. Toxicol. Chem., 6:1-10.
Tunkel, J. et al. (2000). "Predicting Ready Biodegradability in the MITI Test" Environ. Toxicol. Chem., accepted for publication.
Reliability: Estimated values based on accepted model.

Additional Reference for Biodegradation:

Jawarska, J. S. et al. (2002). SAR QSAR Environ. Res., 13(2):307-323. The CATABOL model predicts 6% of theoretical BOD after 28 days.

3.5 Bioconcentration

Value: BCF = 4.7
Method: Based upon an estimated log Kow of 1.19 (Meylan and Howard, 1995), the BCF of vinyl fluoride can be estimated to be approximately 4.7 from a regression-derived equation (Lyman et al., 1990; SRC, n.d.). This estimated BCF value suggests that bioconcentration in aquatic organisms is not an important fate process (SRC, n.d.).
GLP: Not Applicable
Reference: Meylan, W. M. and P. H. Howard (1995). J. Pharm. Sci., 84:83-92 (HSDB/801).
Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, p. 5-4, Amer. Chem. Soc., Washington DC (HSDB/801).

Reliability: SRC (Syracuse Research Corporation) (n.d.). (HSDB/801).
Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish:

Type: 96-hour LC₅₀
Species: Fish
Value: 197.1 mg/L (log₁₀ Kow of 1.19)
Method: Modeled
GLP: Not Applicable
Test Substance: Vinyl Fluoride
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210.
Reliability: Estimated value based on accepted model.

Supporting Data:

Type: 96-hour LC₅₀
Species: Fish
Value: 2.3 mg/L (log₁₀ Kow of 1.62)
Method: Modeled
GLP: Not Applicable
Test Substance: Vinyl Chloride
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210.
Reliability: Estimated value based on accepted model.

Type: 96-hour LC₅₀
Species: Zebra fish, *Brachydanio rerio*
Value: 210 mg/L (based on mean measured concentrations)
Method: The procedures used in the test were based on the

recommendations of the OECD Guideline 203, "Fish, Acute Toxicity Test", which were adapted to volatile chemicals.

Nominal concentrations of 0, 31, 63, 125, 250 and 500 mg/L were tested. Three test flasks were prepared per concentration. Two fish were added to two of the flasks and 3 fish were added to the other. Test solutions were renewed daily and fish were not fed during the test.

Mortality and behavior and appearance of fish were noted 3, 24, 48, 72, and 96 hours after test initiation. Dead fish were removed every 24 hours. The length of the smallest and largest fish at each concentration was measured at the end of the test. Dissolved oxygen concentration, temperature, and pH were measured in control flasks and flasks containing 500 mg/L before and after renewal at 24, 48, 72, and 96 hours (and at time 0 in controls). Samples of test solutions were taken before and after renewal at 0, 24, 48, 72, and 96 hours and analyzed by gas chromatography.

LC₅₀s were calculated using PROBIT of SAS. The NOEC was the highest test concentration that did not cause a significantly different response from controls during the test (Fisher's exact test).

GLP:

Test Substance:

Results:

Yes

Vinyl Chloride, purity > 99%

Measured concentrations were lower than nominal concentrations between day 0 and day 1. The measured concentrations between day 0 and day 1 were 21, 38, 70, 140 and 260 mg/L for the 31, 63, 125, 250 and 500 mg/L concentration groups, respectively. There was good agreement between nominal and analytical concentrations during last part of the experiment. Mean concentrations over 96 hour periods were 1.25 (control), 34.9, 59.4, 128, 220, and 388 mg/L for the 0, 31, 63, 125, 250, and 500 mg/L concentration groups, respectively. The biological results were based on mean measured concentrations.

NOEC for mortality = 128 mg/L.

24-hour LC₅₀ = 240 mg/L.

48-hour LC₅₀ = 210 mg/L.

72-hour LC₅₀ = 210 mg/L.

No deaths or aberrant behavior were observed over 96 hours in controls or animals exposed to 34.9, 59.4 or 128 mg/L. Aberrant behavior was observed after 3 hours of exposure to

220 or 388 mg/L. Mortality of 70% occurred in fish exposed to 220 mg/L by 96 hours. All fish exposed to 388 mg/L died within 48 hours. The minimum test concentration for 100% mortality was 388 mg/L. The length of surviving fish was not altered by exposure to vinyl chloride.

The pH ranged from 7.5-8.0. The dissolved oxygen concentration varied between 5.1 and 9.0 mg/L and the temperature ranged between 21.1 and 22.0°C.

Reference: Groeneveld, A. H. C. et al. (1993). Solvay-Duzphar Report 56635/64/92, "The Acute Toxicity of Vinyl Chloride to the Zebra fish" (February) (cited in IUCLID (2000). IUCLID Dataset, "Chloroethylene" (February 19) and Draft SIDS Dossier for Vinyl Chloride (http://www.oecd.org/document/63/0,2340,en_2649_34379_1897983_1_1_1_1,00.html accessed on 09/11/2003).

Reliability: High because a scientifically defensible or guideline method was used.

Type: 96-hour TL₅₀

Species: Bluegill, *Lepomis macrochirus*

Bass, *Micropterus salmoides*

Value: 1220 ppm (bluegill)

1060 ppm (bass)

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Test fish were an average length of 35 to 75 mm. The bluegills were maintained at a temperature of 18°C and the bass at a temperature of 13°C. Five concentrations were tested with 10 fish tested at each concentration.

Concentrations for bluegills included 682, 576, 894, 1680, and 1760 ppm. Concentrations for bass included 647, 1024, 1586, 1221, and 2185 ppm.

Bioassay vessels were lined with disposable polyethylene bags and filled with 12.5 L of well aerated, reconstituted water. After a 24-hour reconstitution period, the test material was bubbled through an air stone at a constant rate of flow for 5 determined time periods in the reconstituted water. For bluegills, the time of bubbling was 3, 5, 10, 15, and 18 minutes for the 682, 576, 894, 1680, and 1760 ppm groups, respectively. For bass, the time of bubbling was 3, 5, 10, 15, and 18 minutes for the 647, 1024, 1586, 1221, and 2185 ppm groups, respectively. Water samples to verify test

concentration were taken periodically during the test and analyzed via gas chromatography.

Fish were observed for 96 hours and all mortalities and any unusual behavior reactions were noted.

Dissolved oxygen concentrations were measured during the test. Concentrations of 4 mg/L (4 ppm) were considered to be minimal for testing. The pH was recorded when mortalities were recorded.

As a quality check, each lot of experimental fish was challenged with a reference pesticide, toxaphene.

The 96-hour tolerance levels (TL₅₀) were calculated employing the methods of Litchfield, J. T., Jr. and F. Wilcoxon (1949). J. Pharm. Exp. Ther., 96:99.

GLP:

Test Substance:

Results:

No

Vinyl chloride, purity not reported

Percent survival for the bluegills was 100, 100, 100, 0, and 0 for the 682, 576, 894, 1680, and 1760 ppm groups, respectively. Deaths occurred within 1-6 hours after dose administration.

Dissolved oxygen was 8.0 and 7.6 and pH was 7 and 7 for the 1680 and 1760 ppm bluegills, respectively, at 1-6 hours. Dissolved oxygen and pH were not reported for the other bluegill concentration levels.

Percent survival for the bass was 80, 90, 20, 0, and 0 for the 647, 1024, 1586, 1221, and 2185 ppm groups, respectively. Deaths occurred within 48, 48, 1-96, 1-48, and 1-6 hours after dose administration for the 647, 1024, 1586, 1221, and 2185 ppm groups, respectively.

Dissolved oxygen for the bass was 4.2, 4.7, 4.6-5.8, 4.1-4.2, and 7.5 for the 647, 1024, 1586, 1221, and 2185 ppm groups, respectively, at 1-6 hours. The pH was 7 for all concentration groups at 1-6 hours.

Reference:

Ethyl Corporation (1971). Industrial Bio-Test Report No. IBT A9149, "Four-day static fish toxicity studies with methyl chloride, ethyl chloride, vinyl chloride, and ethylene dichloride in bluegills and largemouth bass" (September 9) (TSCA Fiche OTS0515773 and OTS0516114).

Reliability:

High because a scientifically defensible or guideline method was used.

Additional References for Acute Toxicity to Fish: None Found.

4.2 Acute Toxicity to Invertebrates:

Type: 48-hour EC₅₀
Species: Daphnid
Value: 199.7 mg/L (log₁₀ Kow of 1.19)
Method: Modeled
GLP: Not Applicable
Test Substance: Vinyl Fluoride
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210.
Reliability: Estimated value based on accepted model.

Supporting Data:

Type: 48-hour EC₅₀
Species: Daphnid
Value: 141.5 mg/L (log₁₀ Kow of 1.62)
Method: Modeled
GLP: Not Applicable
Test Substance: Vinyl Chloride
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210.
Reliability: Estimated value based on accepted model.

Type: 24-hour LC₅₀
Species: *Daphnia magna*
Value: 80.7±1.8 ppm (corresponds to a VC concentration of 12 mg/L)
Method: The test method was based on ISO 6341-1982 – Water quality, Determination of the inhibition of the mobility of *Daphnia magna* Straus.

Newborn (age 4-24 hour) daphnids were used in the test. Ten daphnids were tested in 40 mL glass beakers containing 25 mL of the test solution in dilution water. A control group (dilution water) was also included. Three replicates of each test concentration were tested. Actual test concentrations were not reported. Mortality was recorded after 24 hours. The 24-hour LC₅₀ value was calculated by probit analysis.

Analysis of the crude effluent was done by gas chromatography.

GLP: No Data
Test Substance: Crude effluent from production of Vinyl Chloride

<u>Composition:</u>	<u>% weight</u>
Vinyl chloride	15-18
Ethyl chloride	1
1,1-dichloroethane	23
1,2-dichloroethylene	27
trichloroethanes	20
pentachloroethane	2
1,2-dichloropropane	6
others-unidentified	1

Results: No additional data. No water chemistry information was provided.
Reference: Demkowicz-Dobrzanski, K. et al. (1993). Sci. Total Environ., Suppl:1151-1158.
Reliability: Medium because a scientifically defensible method was used, but limited study information was available.

Additional References for Acute Toxicity to Invertebrates: None Found.

4.3 Acute Toxicity to Aquatic Plants:

Type: 96-hour EC₅₀
Species: Green algae
Value: 119.1 mg/L (log₁₀ Kow of 1.19)
Method: Modeled
GLP: Not Applicable
Test Substance: Vinyl Fluoride
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center,

Syracuse, NY 13210.
Reliability: Estimated value based on accepted model.

Supporting Data:

Type: 96-hour EC₅₀
Species: Green algae
Value: 25.1 mg/L (log₁₀ Kow of 1.62)
Method: Modeled
GLP: Not Applicable
Test Substance: Vinyl Chloride
Results: No additional data.
Reference: Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210.

Reliability: Estimated value based on accepted model.

Type: 7-day EC₃
Species: Green algae, *Scenedesmus quadricauda*
Value: ≥ 710 mg/L
Method: No specific test guideline was reported; however, methods used were analogous to the cell multiplication inhibition test.

Stock cultures of *Scenedesmus quadricauda* were stored in 20 mL of nutrient solution in an Erlenmeyer flask on a white surface under exclusion of daylight during continuous illumination between 2 fluorescent lamps at 27°C and 50% relative humidity. New stock cultures were prepared continually at intervals of 10 days.

Preliminary cultures, prepared in the same manner as the stock cultures, were stored for 10 days under the same conditions as the stock culture. The cell material in the preliminary culture served as the inoculation of the test cultures. The algae were separated from the culture solution by means of filtration across a membrane filter in a sterilized filter apparatus. The separated cell material was washed on the filter with sterilized, twice distilled water and taken up from the filter with sterilized, twice distilled water. The final turbidity value of the suspension was adjusted so that the extinction value in a measurement sample (further diluted with sterilized, twice distilled water) corresponded to that of a standard formazin suspension TE/F/578 nm = 20.

Test cultures were prepared by serial dilution at a constant dilution ratio according to the scheme of 40 mL test solution pre-dilution + 40 mL of twice distilled water. Consequently, each test flask initially contained 40 mL of liquid. To this was added 5 mL of stock solution, as well as 5 mL of algae suspension of the preliminary culture. To each remaining non-inoculated flask was added 5 mL of stock solution and 5 mL of bidistilled water. Contents were shaken and 10 mL from each flask were placed into Kapsenberg-style culture tubes and sealed with metal caps. These culture tubes were stored for 8 days under the same conditions of the stock cultures and were shaken daily. Following the 8 days, the small culture tubes were shaken vigorously and the extinction of the monochromatic measurement radiation Hg 578 of the cell suspension of each test culture was measured for a 10 mm layer thickness.

GLP: No Data
Test Substance: Vinyl Chloride, purity not reported
Results: No additional data.
Reference: Bringmann, G. and R. Kuehn (1977). Z. Wasser Abwasser Forsch., 10(3/4):87-98.
Reliability: Medium because a suboptimal study design was used.

Type: 72-hour EC₅₀
Species: Algae, *Chlorella sp.*
Value: 1495±79.5 ppm (corresponds to a VC concentration of 224 mg/L)
Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Algal tests were conducted in 250 mL Erlenmeyer flasks containing 90 mL of the test solution and 30 mL of the inorganic medium. Test concentrations were not reported. *Chlorella sp.* suspension (15 mL, absorbance of ~ 1.0 at wavelength 678 nm) were added to each flask. Two parameters were used as a test response. Absorbance *in vivo* was measured with a spectrophotometer at a wavelength of 678 nm. The second response, chlorophyll content, was determined via the method of Hiscox, J. D. (1979). Canad. J. Botany, 57:1332-1334.

GLP: No Data
Test Substance: Crude effluent from production of Vinyl Chloride

Composition: % weight

	Vinyl chloride	15-18
	Ethyl chloride	1
	1,1-dichloroethane	23
	1,2-dichloroethylene	27
	trichloroethanes	20
	pentachloroethane	2
	1,2-dichloropropane	6
	others-unidentified	1
Results:	No additional data. No water chemistry information was provided.	
Reference:	Demkowicz-Dobrzanski, K. et al. (1993). <u>Sci. Total Environ.</u> , Suppl:1151-1158.	
Reliability:	Medium because a scientifically defensible method was used, but limited study information was available.	

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	Oral: No Data.
Type:	Inhalation LC₅₀
Species/Strain:	Mice/Strain not specified
Exposure Time:	4 hours
Value:	690,000 ppm
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

In experiment 1, Vinyl fluoride and air were introduced with a water and mercury flowmeter. The mixture of gases was passed through the cylinder containing the experimental animals. The flow rate was at least 2000 mL/hour and the mice were exposed to the gaseous mixture for 4 hours. Survival and death were evaluated up to 24 hours after the conclusion of the experiment. Concentrations of 45, 66, 70, and 100% VF were tested. The LD₅₀ was calculated by the Reed-Meunch method. The mice that died were autopsied. Histology was performed only at the 100% VF concentration and only on the lungs.

In experiment 2, concentrations of 80 and 90% VF were tested. In this experiment, the vinyl fluoride was mixed with pure oxygen.

GLP: No
Test Substance: Vinyl fluoride, purity not specified
Results: Experiment 1: The median lethal dose was determined. The median lethal dose for VF in air was 69%. At 70% VF, 100% mortality was observed. At 66.6% VF, 30.7% mortality was observed. At concentrations of 100-71% VF, the mice died in the range of 15 minutes to 5 hours. At 66.6% VF, 3 mice died during 3 hours of exposure and 9 mice survived 24 hours. A concentration of 45% produced 1 death at 5.5 hours and 6 animals survived the exposure.

During the exposure, the mice became listless with rapid respiration. At concentrations which caused death within 15 minutes, spasm-like movements preceded death. Autopsy revealed congested internal organs, and histological examinations uncovered alterations of the alveoli and bronchioli.

Experiment 2: When VF was given in oxygen, the VF did not oxidize and the results were similar to those obtained in tests with air. The authors concluded that the suffocation of the animals was caused by lack of oxygen rather than by direct VF poisoning. VF does not decompose or oxidize spontaneously.

Reference: Kopeny, J. et al. (1964). Prac. Lek., 16(7):301-311.
Reliability: Medium because a suboptimal study design was used.

Additional References for Acute Inhalation Toxicity:

Data from these additional sources support the study results summarized above. The studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1966). Unpublished Data, "Acute Inhalation Toxicity of Pyrolysis Products" (Nov. 2) (also cited in TSCA Fiche OTS0206277 and OTS0206334).

Lester, D. and L. A. Greenberg (1950). Arch. Ind. Hyg. Occup. Med., 2:335-334 (also cited in TSCA Fiche OTS0520115).

Braker, W. and A. Mossman (1971). Matheson Gas Data Book, 5th ed., Matheson Gas Products, New Jersey (cited in TSCA Fiche OTS0523802).

Conolly, R. B. et al. (1978). Exp. Mol. Pathol., 28:25-33.

Conolly, R. B. and R. J. Jaeger (1977). Environ. Health Perspect.,

21:131-135.

Clayton, J. W., Jr. (1967). Fluorine Chem. Rev., 1:197-252 (cited in IARC (1995). IARC Monograph Series, 63:467-477).

Dilley, J. V. et al. (1974). Toxicol. Appl. Pharmacol., 27:582-590 (also cited in TSCA Fiche OTS0523802).

Lazarev, N. V. (1959). Chemical Toxins in Industry (cited in Kopency, J. et al. (1964). Prac. Lek., 16(7):301-311).

Type: **Dermal Toxicity:** No Data.

Type: **Dermal Irritation**

Species/Strain: No Data

Method: No Data

GLP: Unknown

Test Substance: Vinyl fluoride, purity not specified

Results: Vinyl fluoride may burn the skin or cause frostbite, and may cause headache or dizziness in humans.

Reference: NLM (1994). United States National Library of Medicine Hazardous Substances Data Base (HSDB), Bethesda, MD (cited in IARC (1995). IARC Monograph Series, 63:467-477 and USCG (1984). United States Coast Guard CHRIS – Hazardous Chemical Data, Volume II, U.S. Government Printing Office, Washington, DC (HSDB/807)).

Reliability: Not assignable because limited study information was available.

Additional References for Dermal Irritation: None Found.

Type: **Dermal Sensitization:** No Data.

Type: **Eye Irritation**

Species/Strain: No Data

Method: No Data

GLP: Unknown

Test Substance: Vinyl fluoride, purity not specified

Results: Vinyl fluoride may burn the eyes and may cause headache or dizziness in humans.

Reference: NLM (1994). United States National Library of Medicine Hazardous Substances Data Base (HSDB), Bethesda, MD (cited in IARC (1995). IARC Monograph Series, 63:467-477).

Reliability: Not assignable because limited study information was available.

Additional References for Eye Irritation: None Found.

5.2 Repeated Dose Toxicity

Type:	90-Day Inhalation Study
Species/Strain:	Rats/Crl:CD [®] BR Mice/Crl:CD [®] -1(ICR)BR
Sex/Number:	Male and female/15 per group
Exposure Period:	Approximately 90 days
Frequency of Treatment:	6 hours/day, 5 days/week, weekends and holidays excluded
Exposure Levels:	0, 200, 2000, 20,000 ppm
Method:	The procedures used in the test were based on the recommendations of the following guideline: US EPA Pesticide Assessment Guidelines, Subdivision F, 82-4.

Groups of 15 male and 15 female rats and mice were exposed 6 hours a day for approximately 90 days to 200, 2000, or 20,000 ppm of VF. Ten male and 10 female rats and mice were designated for final sacrifice after an approximate 90 day test period. The remaining 5 rats and mice/group were designated for cell proliferation studies. Food and water were available to the rats *ad libitum* except during exposures. Upon receipt, the rats were 22 days of age and the mice were 29 days of age.

Rats were exposed whole-body to the vapor. Atmospheres of VF were generated by metering VF from a compressed-gas cylinder into the air supply systems of 3 test chambers. d-Limonene stabilizer was removed from VF vapor by passage over 2 silica-gel traps. The chambers were operated in a one-pass, flow-through mode with air flow rates adequate to provide sufficient oxygen for test animals, to prevent contamination from volatiles derived from animal excreta, and to enable adequate distribution of VF in the chambers. Filtered air, alone, was metered in a similar manner into the control chamber. Even distribution of VF in the chamber was tested and verified. During exposure, relative humidity of the chamber air and chamber temperature were measured. Air flow rates were monitored continuously and readings were recorded. Chamber atmospheres were quantitatively analyzed for VF by gas chromatography. VF vapor was checked daily for the presence of d-limonene by gas chromatography.

All rats were weighed and individually handled and carefully examined for abnormal behavior and appearance once weekly throughout the study. Cage-site examinations to detect moribund or dead rats and abnormal behavior and appearance were conducted at least once daily throughout the exposure period. The amount of food consumed by each test animal during each weighing interval was determined throughout the study. Ophthalmological examinations were performed during the pretest period on all rats received for the study and again prior to the 90-day sacrifice for those rats and mice designated for the 90-day sacrifice. During the pretest period, approximately 45 days after study initiation, and prior to study termination (days 86-89) hematological, clinical chemical, and urine analytical evaluations were conducted on survivors in the 90-day sacrifice subgroups. Approximately 18 hematological parameters were measured or calculated in rats and mice and 17 clinical chemistry parameters were measured or calculated in rats. On the day prior to each bleeding time, an overnight urine specimen was collected from the rats and approximately 10 urine chemistry parameters were measured or calculated. Gross and histopathological evaluations were conducted on 10 rats/sex/exposure group and 10 mice/sex/exposure group after 93-96 days on test. Approximately 50 organs and/or tissues were saved for microscopic examinations. Eight organ weights were recorded.

After 93 days on test, groups of 5 rats and 5 mice per group were implanted with osmotic minipumps containing radiolabeled thymidine and were exposed for an additional 5 days to measure cell proliferation in liver, kidney, lung, and nasal cavity tissues.

Body weights, body weight gains, organ weights (absolute and relative) and clinical laboratory measurements were analyzed by a one-way analysis of variance. When the test for differences among test group means was significant, pairwise comparisons between test and control groups were made with the Dunnett's test. Cell proliferation data were first evaluated by the Wilk-Shapiro test for normality, F-test for equivalent variances, and then Student's T or Mann-Whitney U tests for comparisons of parametric or non-parametric data, respectively.

GLP: Yes
Test Substance: Vinyl fluoride, purity 99.99%
Results: Mean daily chamber concentrations in the control, low-,

intermediate-, and high-concentration groups were 0, 198.2, 2005.1, and 19,841.2 ppm VF, respectively. Mean chamber temperatures were 23.2, 22.8, 22.6, and 21.7°C for the 0, 200, 2000, and 20,000 ppm groups, respectively. Mean relative humidity was 58.5, 58.8, 58.8, and 58.9% for the 0, 200, 2000, and 20,000 ppm groups, respectively.

VF exposure at concentrations up to 20,000 ppm had no significant effects on body weight, body weight gain, food consumption, food efficiency, clinical observations, or clinical ophthalmological evaluations.

Results of the histopathological, clinical chemical, and hematological evaluations showed no significant effects of VF exposure at any concentration following either 45 or 90 days of exposure.

A concentration-related increase in fluoride ion in the urine was observed in male and female rats at 45 and 90 days of exposure. This finding and the nature of the concentration-response curve for urinary fluoride excretion suggested a saturation of VF metabolism at concentrations greater than 2000 ppm.

VF exposure resulted in concentration-related increases in cell proliferation in livers of male and female rats and mice and in olfactory nasal mucosa of male and female mice. These effects were considered biologically important at all concentrations.

There were no effects on the standard endpoints of toxicity up to 20,000 ppm. However, VF induced cell proliferation changes indicative of toxicity at concentrations of 200, 2000, and 20,000 ppm. Thus, a no-observable-effect level was not established for this study.

Reference: DuPont Co. (1989). Unpublished Data, Haskell Laboratory Report No. 549-88, "Subchronic Inhalation Toxicity: 90-Day Study with Vinyl Fluoride in Rats and Mice" (August 16) (also cited in TSCA Fiche OTS0520666, OTS0521270, OTS0522820, and OTS0544301).

Reliability: Bogdanffy, M. S. et al. (1990). Fundam. Appl. Toxicol., 15:394-406.
High because a scientifically defensible or guideline method was used.

Type:	Oncogenicity Inhalation Study
Species/Strain:	Rats/Crl:CD [®] BR Mice/Crl:CD [®] -1(ICR)BR
Sex/Number:	Male and female/95 per group
Exposure Period:	2 years for rats 18 months for mice
Frequency of Treatment:	6 hours/day, 5 days/week, weekends and holidays excluded
Exposure Levels:	0, 25, 250, and 2500 ppm
Method:	The procedures used in the test were based on the recommendations of the following guideline: Test Guideline 40 CFR 798.3300.

Groups of 95 male and 95 female rats and mice were exposed 6 hours a day, 5 days a week for up to 18 months (mice) or 24 months (rats) to 25, 250, or 2500 ppm of VF. Food and water were available to the rats *ad libitum* except during exposures. At study start, the rats were approximately 40 days of age and the mice were approximately 47 days of age.

Animals were exposed whole-body to the vapor. Atmospheres of VF were generated by metering VF from a compressed-gas cylinder into the air supply systems of 3 test chambers. d-Limonene stabilizer was removed from VF vapor by passage over 2 silica-gel traps. The chambers were operated in a one-pass, flow-through mode with air flow rates adequate to provide sufficient oxygen for test animals, to prevent contamination from volatiles derived from animal excreta, and to enable adequate distribution of VF in the chambers. Filtered air, alone, was metered in a similar manner into the control chamber. Even distribution of VF in the chamber was tested. During exposure, the temperature, relative humidity, and air flow in each chamber were monitored continuously and were recorded. Chamber oxygen content was measured. Chamber atmospheres were quantitatively analyzed for VF by gas chromatography. VF vapor was checked daily for the presence of d-limonene by gas chromatography.

All rats and mice were weighed and individually handled and carefully examined for abnormal behavior and appearance once per week during the first 3 months of the study and once every other week for the remainder of the study. Cage-site examinations to detect moribund or dead animals and abnormal behavior and appearance were

conducted at least once daily throughout the study.

Ophthalmological examinations were performed during the pretest period on all animals received for the study and on all surviving rats prior to their final sacrifices (test days 574, 651, and 707). Surviving mice in the control and low-concentration groups were examined prior to their final sacrifices (test days 519 and 545 for the females and males, respectively). Final ophthalmological examinations were not performed on mice in the intermediate- and high-concentration groups.

Clinical laboratory evaluations (including hematology, clinical chemistry, and urine analyses) were conducted on rats approximately 3, 6, 12, 18, and 24 months after study initiation. Ten rats from each group were randomly selected for the first evaluation. These same rats were evaluated at the 6- and 12-month evaluation time points and were designated for the 12-month sacrifice. After approximately 18 and 24 months, 10 rats were randomly selected from each group. Following clinical evaluation, these rats were sacrificed. Due to early sacrifices, only the control and low-concentration groups were available for clinical evaluation at the 24-month evaluation period.

Hematological evaluations were conducted on mice (10/group) approximately 3, 6, 12, and 18 months after study initiation. Due to early sacrifices, only the control and low concentration groups were available for clinical evaluation at 18 months. Approximately 10 hematological parameters were measured or calculated in rats and mice and 17 clinical chemistry parameters were measured or calculated in rats. On the day prior to each bleeding time, an overnight urine specimen was collected from the rats and approximately 10 urine chemistry parameters were measured or calculated.

Gross and histopathological evaluations were conducted on 10 rats/sex/exposure group after 12 and 18 months on test. All surviving rats in the 2500 ppm group were sacrificed on test day 585 and all surviving rats in the 250 ppm groups were sacrificed on test day 657. All surviving rats in the 0 and 25 ppm groups were sacrificed after 24 months on test. Ten mice/sex/group were sacrificed at 6 months. All surviving male mice in the 2500 and 250 ppm groups were sacrificed on test days 375 and 412, respectively. All surviving female mice in the 2500 and 250 ppm groups were sacrificed on test days 450 and 459, respectively. All

surviving mice in the 0 and 25 ppm groups were sacrificed at 18-months. Approximately 50 organs and/or tissues were saved for microscopic examinations. Six organ weights were recorded. Selected organs from 5 rats and 5 mice per group were evaluated for gross and microscopic observations and for cell proliferation at approximately 2 weeks, 3 months, and 12 months of exposure.

Multiple group comparisons of mean body weight, body weight gain, organ weight, and clinical laboratory measurements were analyzed by a one-way analysis of variance. When the test for differences among test group means was significant, pairwise comparisons between test and control groups were made with the Dunnett's test. When early mortality reduced the test groups to only control and low-concentration, mean body weight and body weight gain were compared using Student's t-test.

Incidence of clinical observations were evaluated by the Fisher's Exact test. Survival among groups was compared using the log-rank test. Incidences of selected microscopic lesions were evaluated by the Cochran-Armitage trend test and/or Fisher's exact test.

Bartlett's test for homogeneity of variances was performed on the clinical laboratory data and, if significant, was followed by non-parametric procedures.

GLP:

Yes

Test Substance:

Vinyl fluoride, purity >99.9%

Results:

All chamber analyses indicated that concentrations were within 1% of target concentrations. Mean chamber concentrations were 0, 25.0, 250.3, and 2500.2 ppm for the 0, 25, 250, and 2500 ppm groups, respectively. Mean chamber temperature was 22.0, 23.1, 22.8, and 22.4°C for the 0, 25, 250, and 2500 ppm groups, respectively. Mean chamber relative humidity was 52.7, 60.7, 55.4, and 56.4% for the 0, 25, 250, and 2500 ppm groups, respectively. Mean chamber airflow was 1060.2, 868.4, 933.2, and 1015.8 L/min for the 0, 25, 250, and 2500 ppm groups, respectively.

Survival was decreased in male rats and mice of the 250 and 2500 ppm groups, and female rats and mice of all vinyl fluoride-exposed groups compared to controls.

Survival of Rats and Mice Exposed to Vinyl Fluoride				
Male Rats				
Concentration (ppm)				
Test Days	0	25	250	2500
1-583	68a	70	62	27
1-652	58	57	28	b
1-722	42	33	c	b
Female Rats				
Concentration (ppm)				
Test Days	0	25	250	2500
1-583	67	57	43	25
1-652	50	42	28	b
1-722	40	25	c	b
Male Mice				
Concentration (ppm)				
Test Days	0	25	250	2500
1-372	80	86	43	29
1-400	77	86	30	d
1-540	49	34	e	d
Female Mice				
Concentration (ppm)				
Test Days	0	25	250	2500
1-442	84	49	37	33
1-456	84	43	29	f
1-512	80	30	g	f
a All data are presented as % Survival b This group was sacrificed on test day 586. c This group was sacrificed on test day 657. d This group was sacrificed on test day 375. e This group was sacrificed on test day 412. f This group was sacrificed on test day 450. e This group was sacrificed on test day 459.				

Slight decreases in mean body weight gain (6-15%) were noted among rats of the 25 and 250 ppm groups, but not the 2500 ppm groups, when evaluated through final sacrifice. Mean body weight gain of 2500 ppm male mice was decreased 17% when evaluated through final sacrifice.

There were no unique or unusual clinical signs that were associated with vinyl fluoride toxicity. The only possible

exception was an increased incidence of “weak” and “colored discharge eye(s)” among the 25 ppm female rats compared to controls. Female mice exposed to VF had increased incidences of masses of the side. This observation is related to the increased incidence of mammary gland neoplasms, primarily adenocarcinomas, present in all treated groups of female mice (see below).

There were no ophthalmoscopic observations that occurred with an incidence suggestive of a compound-related effect in either species.

There were no biologically significant effects on hematological, clinical chemical, or urinalysis parameters measured in rats or mice at any of the evaluations. Urinary fluoride excretion was concentration- and time-dependent, although the dose relationship appeared to plateau at concentrations ≥ 250 ppm.

There were no compound-related changes in mean final body weight or mean final absolute or relative organ weight in rats or mice. Due to differences in final euthanasia dates of the 250 and 2500 ppm rats relative to the 25 ppm and control groups, statistical comparisons were not performed on organ weights collected at the final sacrifice.

At necropsy, the following test substance-related gross observations were observed in rats: masses, nodules, discoloration and hemorrhage of the liver; mass/nodules and discoloration of the lungs, and fluid in the peritoneal cavity; masses of the head, face, and periaural area; and abscesses of the face. Microscopically, these lesions were correlated with hepatic hemangiosarcoma, hepatocellular adenoma and carcinoma, foci of clear cell and basophilic alteration and sinusoidal dilatation, and Zymbal’s gland tumors. The incidences of these lesions were concentration-related in all exposed groups. Hepatic hemangiosarcoma appeared to be the sentinel lesion in rats. The first hepatic hemangiosarcoma appeared on test day 362. Early mortality was primarily related to hemorrhage from hepatic hemangiosarcoma.

The incidences of tumors (discussed above) can be found in the following tables. Incidence levels are the total combined incidence for all sacrifices.

Tumor Incidence in Rats Exposed to Vinyl Fluoride				
<u>Male Rats</u>				
	<u>Control</u>	<u>25 ppm</u>	<u>250 ppm</u>	<u>2500 ppm</u>
Hepatic Hemangiosarcoma	0/80	5/80	30/80	20/80
Hepatocellular Adenomas and Carcinomas	5/80	10/80	10/80	7/80
Foci of clear cell alteration	25/80	34/80	36/80	41/80
Foci of basophilic alteration	14/80	24/80	31/80	46/80
Sinusoidal dilatation	6/80	23/80	25/80	21/80
Zymbal Gland Tumors	0/80	2/80	3/80	11/80
<u>Female Rats</u>				
	<u>Control</u>	<u>25 ppm</u>	<u>250 ppm</u>	<u>2500 ppm</u>
Hepatic Hemangiosarcoma	0/80	8/80	19/80	15/80
Hepatocellular Adenomas and Carcinomas	0/80	4/80	9/80	8/80
Foci of clear cell alteration	12/80	15/80	26/80	31/80
Foci of basophilic alteration	21/80	35/80	33/80	44/80
Sinusoidal dilatation	10/80	42/80	36/80	29/80
Zymbal Gland Tumors	0/80	0/80	1/80	12/80

Several other lesions were noted to be secondary to vinyl fluoride-induced neoplasms and not primary lesions. Lesions secondary to hemangiosarcoma-induced hemorrhage and hemolysis included increased erythropoiesis in the spleen and bone marrow and eosinophilic droplets/pigment in renal tubular epithelium. Acute necrosis in the liver was likely the result of acute tissue hypoxia following hemorrhage into the peritoneal cavity. Metastatic hemangiosarcomas in the lungs

were associated with pulmonary hemorrhage, edema, and histiocytosis. All other lesions were considered spontaneous and unrelated to vinyl fluoride exposure.

At necropsy, the following test substance-related gross observations were observed in mice: nodules, masses, and discoloration of the lung, and fluid in the pleural cavity; masses of the peritoneal cavity and hemorrhage, cysts, masses, discoloration, and nodules of the liver; and mammary gland masses. Microscopically, these lesions were correlated with bronchioloalveolar adenoma and hyperplasia; hepatic hemangiosarcoma and hepatocellular hyperplasia with angiectasis and peliosis; and mammary gland adenocarcinoma and hyperplasia. The incidences of these lesions were concentration-related in all exposed groups. Bronchioloalveolar adenoma appeared to be the sentinel lesion in mice; the first appeared on test day 89. Early mortality was primarily related to hemorrhage from hepatic hemangiosarcoma. The first hepatic hemangiosarcoma appeared on test day 162. Increased incidences of adenomas of the Harderian glands were present in all treated groups of mice relative to the controls. Incidences were greater in male groups compared to female groups.

The incidences of tumors (discussed above) can be found in the following tables. Incidence levels are the total combined incidence for all sacrifices.

Tumor Incidence in Mice Exposed to Vinyl Fluoride				
<u>Male Mice</u>				
	<u>Control</u>	<u>25 ppm</u>	<u>250 ppm</u>	<u>2500 ppm</u>
Hepatic Hemangiosarcoma	1/81	16/80	42/80	42/81
Harderian Gland Adenoma	3/81	13/81	12/81	31/81
Bronchioalveolar adenoma	11/81	45/80	52/80	56/81
Bronchioalveolar hyperplasia	2/81	17/80	26/80	40/81
Hepatocellular hyperplasia with angeictasis and peliosis	0/81	18/80	43/80	36/81
<u>Female Mice</u>				
	<u>Control</u>	<u>25 ppm</u>	<u>250 ppm</u>	<u>2500 ppm</u>
Hepatic Hemangiosarcoma	0/81	13/81	25/80	32/81
Mammary Gland neoplasms (adenoma, adenocarcinoma, fibroadenoma combined)	0/77	22/76	20/78	20/77
Harderian Gland Adenoma	1/81	7/81	6/80	12/81
Bronchioalveolar adenoma	9/81	24/80	47/80	53/81
Bronchioalveolar hyperplasia	1/81	5/80	27/80	36/81
Hepatocellular hyperplasia with angeictasis and peliosis	2/81	18/80	37/80	37/81

Several other lesions were noted to be secondary to vinyl

fluoride induced neoplasms and not primary lesions. Lesions secondary to hemangiosarcoma-induced hemorrhage and hemolysis included erythropoiesis in the spleen and bone marrow and pigment in renal tubular epithelium. Acute necrosis in the liver and, less commonly, the kidneys were likely the result of acute tissue hypoxia following hemorrhage into the peritoneal cavity. Increased granulopoiesis in the liver, spleen, and bone marrow of female mice exposed to vinyl fluoride was secondary to extensive necrosis and inflammation within vinyl-fluoride induced mammary tumors. Lymphoid atrophy in the spleen was most often due to effacement of the white pulp by erythro- or granulopoiesis. In some cases, lymphoid atrophy was likely secondary to chronic stress. Localized areas of chronic passive congestion or histiocytosis in the lungs occurred secondary to large bronchiolar tumors. A decrease in the incidences of amyloid in a number of organs in treated groups of mice was considered the result of early deaths in these groups. Such was also the case for peripheral retinal atrophy. All other lesions were considered spontaneous and unrelated to vinyl fluoride exposure.

There were no increases in cell proliferation of the organs of rats or mice examined that were consistent and could be related to VF exposure. Mild increases were noted in the liver of male mice, but large standard deviations precluded meaningful conclusions.

The spectrum of vinyl fluoride-induced tumors is similar to that induced by other monohaloethylenes in rats and mice. Under the conditions of this study, vinyl fluoride was carcinogenic in male and female rats and mice at concentrations greater than or equal to 25 ppm. A no-observable adverse effect level was not determined in this study.

Reference: DuPont Co. (1992). Unpublished Data, Haskell Laboratory Report No. 480-91, "Oncogenicity Study with Vinyl Fluoride: Long-Term Inhalation Study in Rats and Mice" (July 17) (also cited in TSCA Fiche [OTS0522368](#), [OTS0523344](#), [OTS0523344-1](#), [OTS0523344-2](#), [OTS0523344-3](#), [OTS0522368-1](#), [OTS0532940](#), [OTS0532943](#), [OTS0532944](#), [OTS0538078](#), and [OTS0572977](#)).

Bogdanffy, M. S. et al. (1995). *Fundam. Appl. Toxicol.*, 26:223-238.

Reliability: Bogdanffy, M. S. et al. (1993). The Toxicologist, 13(1):69.
High because a scientifically defensible or guideline method was used.

Additional References for Repeated Dose Toxicity:

Data from these additional sources support the study results summarized above. The studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1956). Unpublished Data, Haskell Laboratory Report No. 34-56, "Toxicity of Vinyl Fluoride Monomer" (August 15) (also cited in TSCA Fiche OTS0215048, OTS0206334, and OTS0215232)

Bolt, H. M. et al. (1981). Arch. Toxicol., 47:71-73.

DuPont Co. (1998). Unpublished Data, "Results of Cell Proliferation Study with Vinyl Fluoride" (May 11).

5.3 Developmental Toxicity: No Data for Vinyl Fluoride.

Supporting Data: Study 1

Species/Strain: Rat/Sprague Dawley
Sex/Number: Female/25 per group
Route of Administration: Inhalation
Exposure Period: Gestation Days 6-19
Frequency of Treatment: 6 hours/day
Exposure Levels: 0, 10, 100, 1100 ppm
Method: No specific test guideline was reported; however, the study was designed to meet or exceed guidelines of US EPA, 1985; OECD, 1981; and EEC, 1988.

After a 2-week acclimation period, female rats were mated with males. Females were considered to have mated if sperm was observed microscopically in the vaginal smear and/or a vaginal plug was observed. The day on which evidence of mating was observed was defined as Day 0 of gestation. Rats weighed an average of 213 g on gestation day 0. Exposure concentrations were verified analytically.

During exposures, all animals were housed in stainless steel, wire mesh cages within a 6 m³ stainless steel and glass whole-body

exposure chamber. The temperature and relative humidity in the chambers during exposure were maintained within 16-28°C and 29-79%, respectively. Vinyl chloride was delivered from gas cylinders to a gas regulator. The regulator was attached to flowmeters that delivered flow rates of 12.36 mL/min, 128.3 mL/min, and 1312 mL/min for the 10, 100, and 1100 ppm exposure groups, respectively.

Animals were observed twice daily and given detailed physical exams daily on gestation days 0 and 6-20. Body weights were recorded on days 0, 6, 9, 12, 15 and 20 of gestation and food consumption was recorded over gestation days 0-6, 6-9, 9-12, 12-15, and 15-20. Animals were sacrificed on day 20 and given a postmortem examination which included weighing of the gravid uterus, kidneys, and liver. The ovaries were evaluated for the number of corpora lutea and uteri for implants. Fetuses were removed, weighed, sexed, and evaluated for external abnormalities. One half were processed for visceral examination and the other for skeletal examination.

GLP: Yes
Test Substance: Vinyl chloride, purity > 99.9%.
Results: The exposure concentrations determined by IR and gas spectrometry were 10.8±1.1, 102±10, and 1110±43 ppm for the 10, 100, and 1100 ppm groups, respectively.

Maternal Toxicity: No mortalities occurred in any group. Pregnancy rate for the control, 10, 100 and 1100 ppm groups were 92, 96, 88, and 96%, respectively. Slight changes in body weight gain seen in treated animals were not treatment-related (see table below). No maternal toxicity was observed at the 10 ppm level. Increases in relative kidney weight occurred in the 100 and 1100 ppm groups (0.006±0.0005 in both groups vs. 0.005±0.004 in control), and increased relative liver weight was noted at 1100 ppm (0.043±0.0024 vs. 0.041±0.0023 in control). There was no effect of treatment on pre- and post-implantation loss or the number of corpora lutea, implants, fetuses, or resorptions.

Fetal Toxicity: There was no effect of treatment on sex ratio, fetal body weight, or number or type of malformations observed. Additional information on these parameters is tabulated below.

Body Weight Gains and Litter Size in Female Rats Exposed to Vinyl Chloride				
Parameter	0 ppm	10 ppm	100 ppm	1100 ppm
Body Weight Gain ^a	110±13.5	100±13.8*	101±14.0*	99±10.4*
Implantation sites	14.2±1.38	12.9±1.80	13.1±2.55	13.3±2.30
Live fetuses	13.8±1.64	12.4±1.84	12.9±2.57	12.7±2.27
Fetal body weight	3.4±0.17	3.4±0.17	3.4±0.22	3.3±0.22
a Gestation Days 6-20 p<0.05				

Fetal Malformations Following Exposure to Vinyl Chloride				
Parameter	0 ppm	10 ppm	100 ppm	1100 ppm
Number examined, fetuses (litters)				
gross	318 (23)	297 (24)	283 (22)	305 (24)
soft tissue	167 (23)	155 (24)	147 (22)	158 (24)
skeletals	151 (23)	142 (24)	136 (22)	147 (24)
Gross cranio-rachischisis	0	0	0	1(1)
Soft tissue distended lateral ventricles	0	0	1(1)	0
Skeletals Malformations	0	0	0	0

Reference:

Thornton, S. R. et al. (2002). Toxicological Sciences, 68(1):207-219.

Huntingdon Life Sciences (1998). Developmental Toxicity Study Final Report, Study No. 96-4080, Submitted to Chemical Manufacturer's Association, Arlington VA, January 30, 1998, "Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats" (cited in draft SIDS Initial Assessment Report for Vinyl Chloride accessed via http://www.oecd.org/document/63/0,2340,en_2649_34379_1897_983_1_1_1_1,00.html).

US EPA (1985). Environmental Protection Agency Toxic Substances Control Act Test Guidelines. Final Rule. Fed. Regist. 40 (CFR Part 798), pp. 39426-39433.

OECD (1981). Guidelines for Testing of Chemicals, Section 4, Health Effects. Organization for Economic Cooperation and Development.

EEC (1988). Methods for the Determination of Toxicity. European Economic Community, Off. J. European Communities, 31(L133).

Reliability: High because a scientifically defensible or guideline method was used.

Supporting Data: Study 2

Species/Strain: Rat/Sprague-Dawley

Sex/Number: Female/16-31 per group

Route of Administration: Inhalation

Exposure Period: Gestation Days 6-15

Frequency of Treatment: 7 hours/day

Exposure Levels: 0, 500, 2500 ppm with and without 15% ethanol

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Twenty eight animals (controls) were exposed to air and 31 animals were exposed to 500 ppm vinyl chloride (VC) by inhalation in the first experiment. Nineteen animals (controls) were exposed to air, 16 animals were exposed to 2500 ppm VC by inhalation, and 16 animals were exposed to 2500 ppm VC by inhalation plus 15% ethanol in drinking water in the second experiment. Rats weighed approximately 250 g at study initiation.

Exposures were conducted in 3.7 m³ chambers under dynamic airflow conditions. The atmosphere was generated by diluting gaseous vinyl chloride with filtered room air. The actual exposure concentration was measured with infrared spectrophotometer. The day on which a vaginal plug or sperm was seen in a vaginal smear was considered to be Day 0 of pregnancy.

Food consumption was measured every 3 days and body weights

were recorded on days 6, 10, 16, and 21. Animals were sacrificed on day 21 of gestation. The number and position of live, dead and resorbed fetuses, sex, weight and length (crown-rump) and external and skeletal condition of fetuses were measured. Soft tissues of one-third of each litter were examined microscopically.

The Fishers exact probability test was used to evaluate the incidence of resorption among litters. Body weights, body measurements and maternal liver weights were analyzed using ANOVA and a Dunnett's test. The incidence of fetal anomalies was analyzed using a Wilcoxon test.

GLP: No Data
Test Substance: Inhibited vinyl chloride monomer from Matheson Gas Products, Joliet, IL, purity not reported
Results: Maternal Toxic Effects: The percentage of pregnancy for the 0, 500, 0, 2500, and 2500 ppm with ethanol groups was 96, 94, 95, 100, and 94%, respectively. Decreased weight gain was found in rats exposed to 500 ppm vinyl chloride (VC). Decreased feed consumption and increased absolute and relative liver weight were found in animals exposed to 2500 ppm VCM. There was no significant effect of exposure on maternal death.

There was no significant effect of exposure on the number of litters, number of implantation sites/dam, number of implantations or litters resorbed, or percent pregnant. The number of corpora lutea/dam and pregnancy wastage (the number of corpora lutea minus the number of implants) decreased in rats exposed to 500 ppm VC, but not 2500 ppm VC. No significant effect of exposure on number of live fetuses/litter or sex ratio was noted. A significant decrease in fetal body weight and an increase in crown-rump length were observed in animals exposed to 500 ppm VCM, but not 2500 ppm VC. See the table below for additional information on reproductive indices.

Reproductive Indices of Rats Exposed to Vinyl Chloride					
	Experiment 1		Experiment 2		
Concentration (ppm):	0	500	0	2500	2500 [^]
Number of Litters:	28	31	19	16	16
Corpora lutea per dam:	15±3	13±2	14±2	15±2	14±2
Implantations per dam:	12±2	13±2	12±2	14±2	12±2
No. of Resorptions/ Litters with resorptions:	4/4	11/9	9/6	6/4	7/4
Total No. of Fetuses:	NR	NR	NR	NR	NR
Total No. of Live Fetuses per Litter:	12±2	12±2	12±2	13±2	12±2
Mean Fetal Weight (g):	5.67	5.44	5.59	5.62	5.34
Fetal crown-rump length (mm):	42.6	43.6	43.6	43.3	42.4
Sex Ratio (males: females):	52:48	50:50	49:51	53:47	51:49
[^] With 15% ethanol in drinking water NR = Not Reported					

No effect on the overall incidence of gross, soft-tissue, or skeletal anomalies was noted. The incidence of unilateral or bilateral dilated ureters was increased in animals exposed to 2500 ppm VC, but not 2500 ppm VC + ethanol. An increased incidence of rib spurs was noted in animals exposed to 500 ppm VC, but not 2500 ppm VC. In general, effects were augmented in animals exposed to VC and ethanol. See table below for additional details on the anomalies observed.

Incidence of Anomalies in Rats Exposed to Vinyl Chloride					
Parameters	Experiment 1		Experiment 2		
	0	500	0	2500	2500^
Number examined, fetuses (litters)					
Gross	339 (28)	387 (31)	229 (19)	214 (16)	188 (16)
Soft tissues	113 (28)	129 (31)	76 (19)	73 (16)	63 (16)
Skeletals	337 (28)	387 (31)	229 (19)	214 (16)	188 (16)
Fetuses affected (%) (litters affected (%))					
<u>Gross Anomalies</u>					
Omphalocele	0	1 (3)	0.4 (5)	0	0.5 (6)
<u>Soft Tissue Anomalies</u>					
Microphthalmia	0	0	0	0	2 (6)
Dilated ureter (uni or bilateral)	2 (7)	2 (6)	5 (10)	27 (50)*	5 (19)**
Small kidney	0	0	0	0	2 (6)
<u>Skeletal Tissue Anomalies</u>					
Sternebrae unfused	0	1 (6)	3 (32)	0.5 (6)	1 (12)
Ribs spurs	1 (4)	9 (52)*	0.4 (5)	0	0.5 (6)
Vertebrae missing cervical centra	0.3 (4)	2 (16)	14 (68)	12 (69)	35 (69)
Skull delayed ossification	16 (61)	12 (61)	18 (58)	6 (31)	3 (25)
Skull unfused	0	0	53 (90)	3 (12)	2 (12)
^ With 15% ethanol in drinking water * p<0.05 from control; ** p<0.05 from VC alone					

The authors did not consider effects seen at 2500 ppm to be significant, and concluded that 2500 ppm produced no adverse developmental effects. Effects noted at 500 ppm VC were not considered to be of significance since they were not observed at 2500 ppm, and controls for the 500 ppm group had lower values for variables in question compared to controls for the 2500 ppm VC group.

The NOAEL for maternal toxicity was < 500 ppm.
The NOAEL for developmental toxicity was 2500 ppm.

Reference: John, J. A. et al. (1977). Toxicol. Appl. Pharmacol., 39:497-513.

Reliability: Medium because a suboptimal study design was used.

Supporting Data: Study 3

Species/Strain: Mouse/CF-1

Sex/Number: Female/7-26 per group

Route of

Administration: Inhalation

Exposure

Period: Gestation Days 6-15

Frequency of

Treatment: 7 hours/day

Exposure

Levels: 0, 50, 500 ppm with and without 15% ethanol

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Twenty one animals (controls) exposed to air, 20 animals exposed to 50 ppm vinyl chloride (VC) by inhalation, and 16 animals exposed to VC by inhalation plus 15% ethanol in drinking water were used in the first experiment. Twenty six animals (controls) exposed to air, 19 animals exposed to 500 ppm VC by inhalation, and 7 animals exposed to 500 ppm VC by inhalation plus 15% ethanol in drinking water were used in the second experiment. Mice weighed approximately 25-30 g at study initiation.

Exposures were conducted in 3.7 m³ chambers. The atmosphere was generated by diluting gaseous vinyl chloride with filtered room air. The actual exposure concentration was measured with an infrared spectrophotometer. The day on which a vaginal plug or sperm was seen in a vaginal smear was considered to be Day 0 of pregnancy. Animals were sacrificed on day 18 of gestation.

Food consumption was measured every 3 days and maternal body weight was recorded on days 6, 12, 15, and 18. The number and position of live, dead and resorbed fetuses, sex, weight and length (crown-rump) and external and skeletal condition of fetuses were determined. Soft tissues of one-third of each litter were examined microscopically.

The Fishers exact probability test was used to evaluate the incidence of resorption among litters. Body weights, body measurements, and maternal liver weights were analyzed using ANOVA and a Dunnett's test. The incidence of fetal anomalies was analyzed using a Wilcoxon test.

December 18, 2003

GLP: No Data
Test Substance: Inhibited vinyl chloride monomer from Matheson Gas Products, Joliet, IL, purity not reported
Results: Maternal Toxic Effects: The percentage of pregnancy for the 0, 50, 50 with ethanol, 0, 500, and 500 ppm with ethanol groups was 57, 74, 57, 88, 72, and 31%, respectively. Decreased weight gain occurred in mice exposed to 500 ppm VC. Decreased feed consumption and decreased absolute liver weight was observed in animals exposed to 500 ppm VC. Seventeen percent of mice exposed to 500 ppm VC died (compared to 0% of controls).

There was an increase in the incidence of resorptions in mice exposed to 500 ppm VC (13% vs. 7% in controls). Litter size was reduced in mice exposed to 500 ppm VC. Decreased numbers of live fetuses/litter and fetal weight occurred in mice exposed to 500 ppm VC. There was no significant effect of VC exposure on the sex ratio. See the table below for additional information on reproductive indices.

Reproductive Indices of Mice Exposed to Vinyl Chloride						
	Experiment 1			Experiment 2		
Concentration (ppm):	0	50	50 [^]	0	500	500 [^]
Number of Litters:	21	20	16	26	19	7
Corpora lutea per dam:	NR	NR	NR	NR	NR	NR
Implantations per dam:	12 _± 2	12 _± 4	11 _± 4	14 _± 2	13 _± 2	10 _± 6 ^{**}
No. of Resorptions/ Litters with resorptions:	40/14	18/11	19/11	26/15	33/15	13/6
Total No. of Fetuses:	NR	NR	NR	NR	NR	NR
Total No. of Live Fetuses per Litter:	10 _± 4	11 _± 4	10 _± 4	12 _± 2	11 _± 2 [*]	8 _± 6 ^{**}
Mean Fetal Weight (g):	1.00	1.02	0.84 ^{**}	1.07	0.99 [*]	0.78 ^{**}
Fetal crown-rump length (mm):	23.0	24.2 [*]	22.4 ^{**}	23.7	23.6	21.2 ^{**}
Sex Ratio (males: females):	50:50	50:50	48:52	54:46	52:48	64:36
[^] Also treated with 15% ethanol in drinking water [*] p<0.05 from control; ^{**} p<0.05 from VCM alone NR = Not Reported						

There was no significant effect of VC exposure on the overall incidence of gross, soft tissue, or skeletal anomalies. The incidence of unfused sternebrae, and delayed ossification in skull and sternebrae increased in animals exposed to 500 ppm VC. In general, effects were augmented in animals exposed to VC and ethanol. See the table below for additional details on the anomalies observed.

Incidence of Anomalies in Mice Exposed to Vinyl Chloride						
Parameters	Experiment 1			Experiment 2		
	0	50	50 [^]	0	500	500 [^]
Number examined, fetuses (litters)						
Gross	221(20)	220(20)	153(14)	325(26)	215(19)	56(5)
Soft tissues	74(20)	75(20)	50(14)	107(26)	73(19)	19(5)
Skeletals	221(20)	220(20)	153(14)	325(26)	215(19)	56(5)
Fetuses affected (%) (litters affected (%))						
<u>Gross Anomalies</u>						
Exencephaly	0	0	0	1(8)	1(10)	2(20)
Anophthalmia	0	0	0	0	0	2(20)
Cleft palate	1 (10)	1 (10)	2(21)	0	1(5)	4(40)
<u>Soft tissue Anomalies</u>						
Small thymus	0	0	4 (7)	0	0	0
<u>Skeletal tissue Anomalies</u>						
Sternebrae unfused	3(20)	3(25)	13(57)**	2(19)	9(42)*	34(80)**
Sternebrae delayed ossification	7(50)	4(35)	44(100)**	1(12)	6(42)*	43(100)**
No. 5 sternebra missing	0	0	3(21)	0	1(10)	7(40)**
Ribs extra	4(30)	5(30)	0.6(7)	3(31)	3(32)	14(60)**
Ribs spurs	4(35)	5(40)	2(21)	4(31)	3(21)	14(80)**
Vertebrae forked atlas	0.4(5)	1(10)	4(36)**	0	0	4(20)
Vertebrae missing cervical centra	0	0	0	00	1(10)0	38(60)**
Vertebrae delayed ossification of cervical arches	0	0	1(14)	0	0	5(40)**
Skull delayed ossification	9(35)	8(37)	40(100)**	13(54)	30(58)*	70(100)**
Skull unfused occipital	0	0.7(5)	24(50)**	1(12)	5(21)	11(20)
[^] also treated with 15% ethanol in drinking water * p<0.05 from control; ** p<0.05 from VCM alone						

The authors concluded that none of the fetal effects noted at 500 ppm were adverse. Although the number of resorptions in mice treated with 500 ppm was greater than concurrent controls, it was not greater than historical controls.

The NOAEL for maternal toxicity was 50 ppm.

The NOAEL for developmental toxicity was 500 ppm.

Reference: John, J. A. et al. (1977). Toxicol. Appl. Pharmacol., 39:497-513.

Reliability: Medium because a suboptimal study design was used.

Supporting Data: Study 4

Species/Strain: Rabbit/New Zealand White

Sex/Number: Female/5-20 per group

Route of

Administration: Inhalation

Exposure

Period: Gestation Days 6-18

Frequency of

Treatment: 7 hours/day

Exposure 0, 500, 2500 ppm with 15% ethanol and 2500 ppm without

Levels: 15% ethanol

Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Eighteen animals (controls) were exposed to air and 20 animals were exposed to 500 ppm vinyl chloride (VC) by inhalation in the first experiment. Eleven animals (controls) were exposed to air, 5 animals were exposed to 2500 ppm VC by inhalation, and 16 animals were exposed to 2500 ppm VC by inhalation plus 15% ethanol in drinking water in the second experiment. Rabbits weighed approximately 3.5-4.5 kg at study initiation.

The exposures were conducted in 3.7 m³ chambers. The atmosphere was generated by diluting gaseous vinyl chloride with filtered room air. The actual exposure concentration was measured with an infrared spectrophotometer. Day of mating was considered to be Day 0 of pregnancy. Animals were sacrificed on day 29 of gestation.

Food consumption was measured every 2 days and body weights were recorded on days 6, 12, 18, 22, and 29. The number and position of live, dead and resorbed fetuses, sex (based on examination of external genitalia), weight and length (crown-rump) and external and skeletal condition of fetuses were

measured. Soft tissues of one-third of each litter were examined microscopically.

The Fishers exact probability test was used to evaluate incidence of resorption among litters. Body weights, body measurements, and maternal liver weights were analyzed using ANOVA and a Dunnett's test. The incidence of fetal anomalies was analyzed using a Wilcoxon test.

GLP: No Data
Test Substance: Inhibited vinyl chloride monomer from Matheson Gas Products, Joliet, IL, purity not reported
Results: Maternal Toxic Effects: The percentage of pregnancy for the 0, 500, 0, 2500, and 2500 ppm with ethanol groups was 100, 95, 100, 86, and 95%, respectively. Decreased feed consumption occurred in animals exposed to 500 pm VC, but was unaffected in the 2500 ppm VC exposure group. Decreased numbers of corpora lutea/dam and implantation sites/dam were seen in animals exposed to 500 ppm VC, but not 2500 ppm VC. A decreased number of live fetuses/litter was seen in animals exposed to 500 ppm VC, but not 2500 ppm VC. See the table below for additional information on reproductive indices.

Reproductive Indices of Rabbits Exposed to Vinyl Chloride					
	Experiment 1		Experiment 2		
Concentration (ppm):	0	500	0	2500	2500 [^]
Number of Litters:	18	19	11	5	16
Corpora lutea per dam:	9 _{±1}	8 _{±1} *	10 _{±2}	10 _{±7}	10 _{±2}
Implantations per dam:	9 _{±1}	8 _{±1} *	8 _{±2}	8 _{±4}	9 _{±2}
No. of Resorptions/ Litters with resorptions:	10/8	14/6	19/7	10/4	79/14
Total No. of Fetuses:	NR	NR	NR	NR	NR
Total No. of Live Fetuses per Litter:	8 _{±1}	7 _{±2} *	6 _{±3}	6 _{±4}	4 _{±4}
Mean Fetal Weight (g):	35.23	34.13	36.46	33.77	32.48
Fetal crown-rump length (mm):	91.0	92.6	92.6	87.1	87.7
Sex Ratio (males: females):	53:47	50:50	61:39	50:50	43:57
[^] also treated with 15% ethanol in drinking water * p<0.05 from control; ** p<0.05 from VCM alone NR = Not Reported					

No significant effect of exposure on overall incidence of gross, soft tissue or skeletal anomalies was noted. A significant increase in the incidence of delayed ossification of 5th sternebra and an increase in crown-rump length in animals exposed to 500 ppm VC, but not 2500 ppm VC was observed. In general, effects were augmented in animals exposed to VC and ethanol. See the table below for additional details on the anomalies observed.

Incidence of Anomalies in Rabbits Exposed to Vinyl Chloride					
	Experiment 1		Experiment 2		
Concentration (ppm)	0	500	0	2500	2500 [^]
Number examined, fetuses (litters)					
Gross	152 (18)	136 (18)	69 (9)	32 (4)	70 (9)
Soft tissue	50 (18)	47 (18)	24 (9)	10 (4)	25 (9)
Skeletals	152 (18)	136 (18)	69 (9)	32 (4)	70 (9)
Fetuses affected (%) (litters affected, %)					
<u>Gross Anomalies</u>					
Cleft palate	0	0	0	0	1 (11)
<u>Soft tissue Anomalies</u>					
Dilated renal pelvis	0	0	0	0	8 (11)
Dilated cerebral ventricle	0	0	0	10 (25)	0
Enlarged right atrium of heart	0	0	0	0	8 (11)
<u>Skeletal Tissue Anomalies</u>					
Sternebrae delayed ossification #5	28 (77)	38 (94)*	20 (44)	16 (75)	24 (67)
[^] also treated with 15% ethanol in drinking water * p<0.05 from control; ** p<0.05 from VCM alone					

Fetal effects seen at 500 ppm were not considered to be of significance since they were not observed at 2500 ppm. Since the decrease in litter size at 500 ppm VC was associated with a decrease in corpora lutea (which was established prior to day 6 of gestation), this effect is probably not due to exposure to vinyl chloride.

The NOAEL for maternal toxicity was < 500 ppm.
 The NOAEL for developmental toxicity was 2500 ppm vinyl chloride (VC).

Reference: John, J. A. et al. (1977). Toxicol. Appl. Pharmacol., 39:497-513.
 Reliability: Medium because a suboptimal study design was used.

Supporting Data: Study 5

Species/Strain: Rat/CFY
Sex/Number: Female/13 to 28 per group
Route of Administration: Inhalation
Exposure Period: 6-9 days during 1st, 2nd, or 3rd trimester
Frequency of Treatment: 24 hours/day
Exposure Levels: 4000 mg/m³ (1500 ppm)
Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

Pregnant rats were exposed to air, vinyl chloride, air + Trypan Blue s.c. (2 times), vinyl chloride + Trypan Blue s.c. (2 times) during days 1-9, 8-14, and 14-21 of gestation, respectively. The rats were mated in a harem system. The day of finding sperm in the vaginal smear was considered the first day of gestation. Body weights were recorded once per week. On day 21 of gestation, animals were sacrificed. The number, position of fetuses living, dead, or resorbed were noted. Fetal weight was recorded. Half of the fetuses of each mother were dissected after fixation under the stereomicroscope. The other half of the fetuses underwent a skeletal examination.

Arithmetic means and standard errors were calculated. Student's t-test was used for statistical comparison. Affected over total fetus ratios were calculated. Mann-Whitney U-test was used for the statistical comparison of the ratios obtained.

GLP: No Data
Test Substance: Vinyl chloride, purity not reported
Results: Maternal weight gain was decreased in females exposed on days 14-21 of gestation. Relative liver weight values were increased in dams exposed on days 1-9 or 8-14. No pathological changes in the liver of rats exposed to vinyl chloride were observed at the light microscope level.

The number of resorbed fetuses as well as fetal loss were significantly increased in the group exposed to vinyl chloride during days 1-9 of gestation. Fetal weight was unaffected. None of the fetal malformations or skeletal anomalies observed were attributed to vinyl chloride.

Litter Size and Fetal Loss Following Exposure to Vinyl Chloride		
Parameter	0 ppm	1500 ppm
Exposure Days 1-9		
litter size	13.15±0.64	11.68±0.38
fetal loss (%)	1.7	5.5*
Exposure Days 8-14		
litter size	11.29±0.61	13.36±0.37
fetal loss (%)	3.18	4.54
Exposure Days 14-21		
litter size	11.78±0.94	11.18±0.74
fetal loss (%)	5.8	5.4
* p<0.05		

Reference: Ungvary, G. et al. (1978). *Toxicology*, 11:45 –54.
 Reliability: Medium because a suboptimal study design was used.

5.4 Reproductive Toxicity:

Reproductive Toxicity Study 1

Species/Strain: Rats/Crl:CD®BR
 Mice/Crl:CD®-1(ICR)BR
 Sex/Number: Male and female/15 per group
 Route of Administration: Inhalation
 Exposure Period: Approximately 90 days
 Frequency of Treatment: 6 hours/day, 5 days/week, weekends and holidays excluded
 Exposure Levels: 0, 200, 2000, 20,000 ppm
 Method: A 90-day inhalation study was conducted in male and female rats and mice (see section 5.2 for details on the study design). The procedures used in the test were based on the recommendations of the following guideline: US EPA Pesticide Assessment Guidelines, Subdivision F, 82-4.

Terminal sacrifice (10 animals/sex/group) occurred after 93-96 days on test. All animals underwent both gross and microscopic examinations. Reproductive organs in the histopathological evaluation included testes, epididymides, prostate, seminal vesicles, mammary gland, ovaries, uterus, and vagina. The testes and ovaries were weighed.

GLP: Yes
 Test Substance: Vinyl fluoride, purity 99.99%

Results: No compound-related effects on the reproductive organs of either male or female rats or mice were observed. See section 5.2 for additional subchronic toxicity study results.

Reference: DuPont Co. (1989). Unpublished Data, Haskell Laboratory Report No. 549-88, "Subchronic Inhalation Toxicity: 90-Day Study with Vinyl Fluoride in Rats and Mice" (August 16) (also cited in TSCA Fiche [OTS0520666](#), [OTS0521270](#), [OTS0522820](#), and [OTS0544301](#)).

Bogdanffy, M. S. et al. (1990). *Fundam. Appl. Toxicol.*, 15:394-406.

Reliability: High because a scientifically defensible or guideline method was used.

Reproductive Toxicity Study 2

Species/Strain: Rats/Crl:CD[®]BR
Mice/Crl:CD[®]-1(ICR)BR

Sex/Number: Male and female/95 per group

Route of Administration: Inhalation

Exposure Period: 2 years for rats
18 months for mice

Frequency of Treatment: 6 hours/day, 5 days/week, weekends and holidays excluded

Exposure Levels: 0, 25, 250, and 2500 ppm

Method: An oncogenicity inhalation study was conducted in male and female rats and mice (see section 5.2 for details on the study design). The procedures used in the test were based on the recommendations of the following guideline: Test Guideline 40 CFR 798.3300.

Interim sacrifices (10 rats/sex/group) were conducted at 12 and 18 months. Due to early mortality, final sacrifice of rats of the 2500 and 250 ppm groups occurred on test days 586 and 657, respectively. Control and 25 ppm rats were sacrificed at approximately 24 months. An interim sacrifice of 10 mice per group was conducted at 6 months. Early mortality among mice of the 2500 and 250 ppm groups resulted in final sacrifice on test days 375 and 412 for males, respectively, and test days 450 and 459 for females, respectively. Control and 25 ppm mice were sacrificed at approximately 18 months. All animals underwent both gross and microscopic examinations. Reproductive organs in the histopathological evaluation included testes, epididymides, prostate, seminal vesicles, mammary gland, ovaries, uterus, and vagina. The testes and ovaries were weighed.

GLP: Yes
Test Substance: Vinyl fluoride, purity >99.9%
Results: No compound-related effects on the reproductive organs of either male or female rats or male mice were observed. Mammary gland masses were observed in the female mice. Microscopically, these lesions were correlated with mammary gland adenocarcinoma and hyperplasia. Incidences of these lesions were 0/77, 22/76, 20/78, and 20/77 for the 0, 25, 250, and 2500 ppm groups, respectively. See section 5.2 for additional chronic toxicity study results.
Reference: DuPont Co. (1992). Unpublished Data, Haskell Laboratory Report No. 480-91, "Oncogenicity Study with Vinyl Fluoride: Long-Term Inhalation Study in Rats and Mice" (July 17) (also cited in TSCA Fiche [OTS0522368](#), [OTS0523344](#), [OTS0523344-1](#), [OTS0523344-2](#), [OTS0523344-3](#), [OTS0522368-1](#), [OTS0532940](#), [OTS0532943](#), [OTS0532944](#), [OTS0538078](#), and [OTS0572977](#)).
Bogdanffy, M. S. et al. (1995). *Fundam. Appl. Toxicol.*, 26:223-238.
Bogdanffy, M. S. et al. (1993). *The Toxicologist*, 13(1):69.
Reliability: High because a scientifically defensible or guideline method was used.

Reproductive Toxicity Study 3

Species/Strain: Rats/CDF(F-344)CrIBr[®]
Sex/Number: Male/15 per group
Route of Administration: Inhalation (nose-only)
Exposure Period: 6 hours/day
Frequency of Treatment: 1, 2, or 5 consecutive days
Exposure Levels: 0, 20,000 ppm
Method: The procedures used in this unscheduled DNA test were based on the recommendations of the following guidelines: EPA Health Effects Guideline 40 CFR Part 798. Additional method details can be found in Section 5.5.

At approximately 2, 6, or 24 hours after exposure, testicular cells were prepared from 5 animals in both the control and 20,000 ppm groups. Testicular cells from animals of the positive control group and its corresponding vehicle control were prepared 1-2 hours following treatment. Rats were anesthetized and 1 testis from each animal was removed and

placed in a sterile dish containing enriched Krebs/Ringer bicarbonate solution (EKRB). The testes were decapsulated and the seminiferous tubules were washed in EKRB. Tubules were enzymatically digested and then gently drawn up in a pipette to produce a cell suspension. Viability and cell density were determined.

Individual wells containing medium were inoculated with approximately 6×10^6 viable testicular cells. Cells were cultured in Williams E medium supplemented with fetal bovine serum, L-glutamine, penicillin, streptomycin, and [methyl- ^3H]thymidine. Cultures were incubated in a humidified atmosphere at $33 \pm 1^\circ\text{C}$ for 18 to 24 hours.

To determine whether vinyl fluoride inhibited DNA repair, separate testicular cell cultures from either air control or vinyl fluoride-exposed animals were treated *in vitro*. Isolated cells from animals sacrificed 2 and 6 hours following the 1- and 5-day exposures were tested.

Following incubation, cell viability was determined by trypan blue exclusion. Cells were fixed in formaldehyde and refrigerated. Fixed cells were washed with PBS. Aliquots of each cell suspension were placed on microscope slides. Slides were washed in cold tap water and dried by washing in methanol. When dry, slides were dipped into undiluted nuclear track emulsion, dried, and stored frozen for 2-3 weeks to expose the emulsion. Slides were then developed and stained with Gills hematoxylin.

Slides were examined in a blind manner. Cells meeting the following criteria were scored for UDS: 1) cells with normal morphology, 2) cells free of debris or staining artifacts, and 3) cells free of overlapping cells.

Grain counts were made under a 100X oil immersion light microscope with a 10X eye piece. Silver grains were counted using a colony counter interfaced via a TV camera to a microscope. Three slides per animal and 25 cells per slide were scored for a total of 75 cells per animal.

GLP: Yes
Test Substance: Vinyl fluoride, purity >99.9%
Results: Negative. Vinyl fluoride was not toxic to testicular cells. Following isolation, testicular cell viability ranged from 91-100% for the air-exposed group and 91-99% for the vinyl fluoride-exposed animals. UDS was not observed at any

Reference: time post-exposure following any exposure period.
DuPont Co. (1990). Unpublished Data, Haskell Laboratory Report No. 727-90, "Determination of Unscheduled DNA Synthesis in Rat Spermatocytes Following *In Vivo* Exposure to Vinyl Fluoride by Inhalation" (December 13) (also cited in TSCA Fiche OTS0532955).

Reliability: Bentley, K. S. et al. (1992). Environ. Mol. Mutagen., 19(Suppl. 20):5.
High because a scientifically defensible or guideline method was used.

Additional References for Reproductive Toxicity: None Found.

5.5 Genetic Toxicity:

Type: *In vitro* Bacterial Reverse Mutation Assay
Tester Strain: *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, and TA100

Exogenous
Metabolic
Activation: With and without Aroclor[®]-induced rat liver S9
Exposure
Concentrations: 0, 1, 5, 10, 25%
Method: No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study.

The standard Ames plate test was modified for testing a gaseous chemical. To a sterile test tube, placed in a 43°C heating block, the following were added: agar (containing histidine, biotin, and NaCl), indicator organisms, and the metabolic activation mixture (if appropriate). The plates, with lids removed, were placed side by side on a perforated shelf in a desiccator, which was then sealed. After evacuation of the air, a known volume of the test gas was introduced into the desiccator. The pressure was normalized and the desiccator was placed on a magnetic stir plate in a room maintained at 37°C. A magnetic stirrer with vanes was placed in the base of each desiccator to ensure adequate dispersion of the chemical. After incubating for 9 hours, the plates were removed, their lids replaced, and they were incubated at 37°C for an additional 64 hours. The number of his⁺ revertant colonies were counted and recorded. A positive control chemical (ethylene oxide) was tested similarly in each experiment. Three replicates were plated

for each tester strain in the presence and absence of the exogenous metabolic activation system at each test substance concentration.

The S9 mix contained S9 fraction, MgCl₂, glucose-6-phosphate, NADP, sodium phosphate buffer, and H₂O.

Criteria for determining positive and negative findings and statistical methods were not reported.

GLP: No
Test Substance: Vinyl fluoride, purity not reported
Results: Negative
Remarks: The treatment slightly increased the frequency of histidine revertants in strain TA100. Because this increase was less than 2-fold and was not dose-related, the authors concluded that the effect was not biologically significant and the test compound was not mutagenic in *Salmonella*.

No data were obtained for strain TA1538 due to contamination of the culture on that test day.

Reference: SRI International (1979). SRI Project No. LSU-7558-13, “*In Vitro* Microbiological Mutagenicity Assays of Vinyl Fluoride” (September), TSCA Fiche OTS0523803.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Bacterial Reverse Mutation Assay:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1976). Unpublished Data, Haskell Laboratory Report No. 252-76, “*In Vitro* Microbial Mutagenicity Studies of Ethylene, Fluoro” (April 5) (also cited in TSCA Fiche OTS0215048 and OTS0215232). VF was not mutagenic in the TA1535, TA100, TA1537, TA1538, and TA98 strains of *Salmonella typhimurium* when tested according to the protocol for the Ames test using a six-hour incubation period. Two concentration levels, 20 and 40% of VF, were tested. The test substance contained 0.25±0.10% d-limonene, which was tested and was not active in the mutagen screen. The extreme toxicity of limonene to the tester strains prevented the testing of a wide range of doses.

DuPont Co. (1978). Unpublished Data, Haskell Laboratory Report No. 728-78, “Mutagenic Activity of Ethylene, Fluoro- in the *Salmonella*/Microsome Assay” (April 9) (also cited in TSCA Fiche OTS0215048, OTS0215232, OTS0000557-0, OTS0522771, OTS0539802, and OTS0523782). VF was tested at concentrations

of 0, 5, 10, 20, and 40%, and using a 48-hour incubation period in strains TA1535, TA1537, TA98, and TA100. It was negative in 3 strains, but was found to induce a statistically significant mutagenic response in strain TA1535 in the presence of an activation system. However, when this study was evaluated by DuPont, it was concluded that the low magnitude of the response (1.4, 1.6, 1.9, 1.4, and 2.1 times the spontaneous frequency in successive trails) renders the response biologically insignificant. According to current data evaluation criteria for strain TA1535, the mutagenic response needs to be ≥ 3.0 times the spontaneous frequency in order to be judged positive (DuPont Co. (2003). Memo from M. Donner to Study File (December 12)).

DuPont Co. (1978). Unpublished Data, Personal communication D. Krahn to B. Ramirez, M.D., November 16. VF was reported to be mutagenic for *Escherichia coli* (Landry, M. M. and R. Fuerst (1968). Dev. Ind. Microbiol., 9:370-380). Evaluation of this study by a Haskell genetic toxicologist did not support this conclusion.

Landry, M. M. and R. Fuerst (1968). Dev. Ind. Microbiol., 9:370-380.

Type:	<i>In vitro</i> CHO/HPRT Assay
Cell Type:	CHO/HPRT cells, BH4 clone of the CHO-K1 cell line.
Exogenous Metabolic	
Activation:	With and without Aroclor [®] -induced rat liver S9
Exposure	
Concentrations:	0, 20, 40, 60, 80, 100%
Method:	No specific test guideline was reported; however, a scientifically defensible approach was used to conduct the study. The CHO/HPRT assay used was an adaptation of a method developed primarily by Dr. A. W. Hsie at the Oak Ridge Laboratory.

Preliminary cytotoxicity studies, with and without activation, were conducted to select the concentrations for the mutagenicity studies.

For the negative control which is listed as a concentration of 0, nitrogen was present. The positive control agents used in the study included ethylmethane sulfonate (EMS) and vinyl chloride (VCl).

Approximately 5×10^5 cells were seeded per 25 cm² flask in culture medium. The next day the culture medium was removed and the treatment medium was added. Specially designed glass chambers were used to expose the cell cultures to the vinyl fluoride. A separate chamber was used

for each concentration level. Immediately prior to the exposure period, the tissue culture flasks were uncapped and placed into the exposure chamber. A pair of flow meters was used to generate the appropriate vinyl fluoride-nitrogen and VCL-air mixtures. The chamber was sealed after flushing with the gas mixture at a flow rate of 10 L/min for 1 minute. Negative control chambers were flushed at the same flow rate with nitrogen. Atmospheric samples were taken at the beginning and end of the exposure period and analyzed with gas chromatography.

The cells were incubated with the test mixture for 18-19 hours without activation or 5 hours with activation. Treatment flasks were incubated on a rocker panel to maximize contact between cells and test mixture. After incubation, the flasks were flushed with nitrogen or air (VCL treatment) before the treatment medium was removed. The cells treated without activation were subcultured immediately after treatment while the cells treated with activation were incubated in culture medium for 21-26 hours before subculturing.

At the time of subculturing, an aliquot of cells was plated to assess cytotoxicity and the rest were plated to allow expression of the mutant phenotype. To assess cytotoxicity, 200 cells were plated per dish (6 dishes) from each flask of cells in the study. These dishes were incubated for 7 days and the colonies were stained and counted. Cell survival was determined by dividing the total number of colonies by the total number of cells plated and was expressed both as the percent plated and as the percent of the solvent control survival.

For expression of the mutant phenotype, treated cells were plated and allowed to recover for 7 days, during which they were subcultured twice, if survival was sufficient. On the 7th day, the cells were plated to assess cell survival and the frequency of 6-TG-resistant cells. To identify the 6-TG-resistant cells, cells were plated in culture medium containing 6-TG. The cells were incubated for 6-8 days and the colonies were stained and counted.

Three mutagenicity trials were performed with and without activation.

Mutant frequency data were transformed prior to analysis.

The analysis used a 2 variable (dose and experiment) ANOVA model. In 1 analysis, the t-test was used to determine whether a dose caused a significant increase in mutant frequency. In the 2nd analysis, an ANOVA was used to evaluate a dose-response relationship. Linear, quadratic, and higher order effects were tested by an F-test.

A test sample was classified as positive when: 1) the mutant frequency of 1 or more of the sample concentrations tested was significantly greater than that of the negative control, where significance was judged at the 0.01 level, and 2) the correlation between the mutant frequency and the concentration of the test sample was significantly greater than 0, where significance was judged at the 0.01 level.

A test sample was classified as negative when: 1) the mutant frequency of none of the sample concentrations tested was significantly greater than the mutant frequency of the negative control, where significance was judged at the 0.01 level, and 2) the correlation between the mutant frequency and the concentration of the test sample was not significantly greater than 0, where significance was judged at the 0.01 level.

GLP: Yes
Test Substance: Vinyl fluoride, purity 99.99%
Results: Positive
Remarks: Data from the 1st trial without activation was not used in the statistical analyses because the actual test concentrations could not be accurately determined. In the 2nd and 3rd trials without activation, no significant increase in the mutant frequency at any of the concentrations was observed and no positive dose-response was seen.

Although no statistically significant increases in mutant frequencies were demonstrated in either trial with activation when analyzed separately, combined analyses indicated a significant increase at the 60% level. A large standard deviation between the negative control values in the 2nd trial made interpretation of the results difficult. Therefore, a 3rd trial was conducted. The combined statistics of all 3 trials indicated significant increases in mutant frequencies at all concentrations (20-100% vinyl fluoride). A positive quadratic dose-response was also statistically evident.

Reference: DuPont Co. (1986). Unpublished Data, Haskell Laboratory Report No. 344-86, "Mutagenicity Evaluation of Vinyl Fluoride in the CHO/HPRT Assay" (August 18) (also cited

in TSCA Fiche [OTS0510276](#), [OTS0000557-0](#),
[OTS0523823](#), [OTS539801](#), and [OTS0523849](#)).

Bentley, K. S. et al. (1992). *Environ. Mol. Mutagen.*,
19(Suppl. 20):5.

Reliability: High because a scientifically defensible or guideline method was used.

Type: ***In vitro* Chromosome Aberration Assay**
Cell Type: Chinese Hamster Ovary (CHO) cells, BH4 clone of the CHO-K1 cell line.

Exogenous
Metabolic

Activation: With and without Aroclor[®]-induced rat liver S9
Exposure Concentrations: Non-activated cytotoxicity assessment: 0, 23, 48, 71.5, 96.3%
Activated cytotoxicity assessment: 0, 27, 52.1, 61.3, 97.0%

Non-activated chromosome aberration trial 1: 0, 8.1, 42.9, 72.3, 104.1%

Non-activated chromosome aberration trial 2: 0, 8.8, 46.5, 77.8, 111.4%

Activated chromosome aberration trial 1: 0, 8.3, 25.9, 49.6, 75.1%

Activated chromosome aberration trial 2: 0, 12.3, 35.4, 63.3, 91.3%

Method: The procedures used in the test were based on the recommendations of the following guidelines: EPA Health Effects Guideline 50 CFR Part 798, Subpart 798.5375 and OECD Guideline No. 473.

Preliminary cytotoxicity studies, with and without activation, were conducted to select vinyl fluoride concentrations and fixation times for the chromosome aberration studies.

For the negative control which is listed as a concentration of 0, nitrogen was present. The positive control agents used in the study included ethylmethane sulfonate (EMS) and vinyl chloride (VCl).

Cytotoxicity Assessment:
Approximately 5×10^5 cells were seeded per 25 cm² flask in culture medium. The next day the culture medium was removed and the treatment medium was added. Specially designed glass chambers were used to expose the cell

cultures to the vinyl fluoride. A separate chamber was used for each concentration level. Immediately prior to the exposure period, the tissue culture flasks were uncapped and placed into the exposure chamber. A pair of flow meters was used to generate the appropriate vinyl fluoride-nitrogen and VCL-air mixtures. The chamber was sealed after flushing with the gas mixture at a flow rate of 5-10 L/min for 1-2 minutes. Negative control chambers were flushed at the same flow rate with nitrogen. Atmospheric samples were taken at the beginning and end of the exposure period and analyzed with gas chromatography.

The cells were incubated with the test mixture for 5 hours without activation or 2 hours with activation. Treatment flasks were incubated on a rocker panel to maximize contact between cells and test mixture. After incubation, the flasks were flushed with air, the treatment medium was removed, and the flasks were rinsed with fresh culture medium. Fresh medium containing 5-bromodeoxyuridine (BudR) was added and incubation was continued for 24-26 hours. Colcemid[®] was added to the medium approximately 2-3 hours before the end of this incubation period to arrest metaphase cells.

Cells from pairs of like-treated flasks were collected by mitotic shake-off and pooled in centrifuge tubes to form 2 "replicate" samples for harvest. The cells were incubated for 15 minutes in a hypotonic solution at 37°C, and fixed in 2 changes of ice cold 3:1 mixture of methanol and glacial acetic acid. Centrifugation was required between each of these steps and after the final fixation step. Cells were resuspended in fixative, dropped onto microscope slides, and dried on a 60°C slide warmer. A modified fluorescence-plus-Giemsa technique was used to differentially stain sister chromatids. After rinsing, the slides were exposed to fluorescent light bulbs for 20 minutes with Giemsa in buffer, and then rinsed again. Slides were cleared and coverslipped.

Fifty to 100 metaphase cells per concentration were scanned and scored. Cell cycle delay was judged.

Chromosome Aberration Studies:

Culture seeding, treatments, and cell harvests were conducted as described above except that: 1) BudR was omitted from the medium, 2) the test concentrations and fixation times were different, and 3) positive indicators were included. Slides were stained for 7 minutes with Giemsa in

phosphate buffer, cleared, coverslipped, and coded for blind scoring.

Metaphase cells were analyzed for structural chromosome aberrations at 1000X magnification. For each trial, 100 cells (50 per replicate) were initially analyzed from each test level and from the negative control. Fifty cells (25 per replicate) were analyzed from the positive control. The aberrations observed were categorized as chromatid- and chromosome-type aberrations and break- or exchange-type aberrations. Chromatid and isochromatid breaks were also recorded.

A Mann-Whitney U test comparing each treatment level with the negative control was used to evaluate the data for aberrations per cell. The percent abnormal cells and percent cells with more than one aberration were evaluated with a Fisher Exact test to compare treatment level with the negative control.

Assessment of a test material as clastogenic was based on 1) its ability to produce a statistically significant increase in chromosomal aberrations in test cultures as compared with the negative control cultures at a minimum of 1 level, and/or 2) its ability to induce a significant dose-response. Either of these effects must be reproducible.

A test article which produced neither a statistically positive response at a minimum of 1 test level nor a significant dose-related increase in chromosome aberrations was considered non-clastogenic.

GLP:	Yes
Test Substance:	Vinyl fluoride, purity 99.99%
Results:	Positive
Remarks:	Under non-activated conditions, cytotoxicity studies showed a significant cell cycle delay only at the relatively high concentration of 96.3% vinyl fluoride (in nitrogen). With activation, moderate cell cycle delay was observed at 52.1%, and severe cell cycle delay was evident at $\geq 61.3\%$ vinyl fluoride.

In the chromosome aberration studies, equivocal results were obtained following 5-hour non-activated treatments. After 2-hour treatments with S9, significant chromosome aberration induction was seen at concentrations ranging from 8.3-63.3% vinyl fluoride.

December 18, 2003

Reference: DuPont Co. (1986). Unpublished Data, Haskell Laboratory Report No. 621-86, "Evaluation of Vinyl Fluoride in the *In Vitro* Assay for Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells" (October 16) (also cited in TSCA Fiche OTS0513353, OTS0539803, and OTS0523824).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for *In vitro* Clastogenicity: None Found.

Type: *In vivo* Mouse Micronucleus Assay
Species/Strain: Mice/ CrI:CD[®]-1(ICR)BR
Sex/Number: Male and female/15 per sex per concentration (control, low, and intermediate group), 18 per sex for the high group
Route of Administration: Whole-body inhalation
Concentrations: 0, 50,000, 200,000, 400,000 ppm
Method: The procedures used in the test were based on the recommendations of the following guidelines: EPA Health Effects Guideline 50 CFR Part 798, Subpart 798.5395 and draft OECD Guideline No. 424.

The positive control agent used in the study was cyclophosphamide (CP).

Mice, approximately 8 weeks old and weighing 31-38 g (males) and 23-29 g (females), were placed into wire-mesh baskets (sexes separate). The baskets were stacked in approximately 30-L cylindrical glass exposure chambers. Mice were exposed to either air (control) or the test substance for 6 hours. Concurrent with the initiation of these exposures, 5 male and 5 female mice were dosed by intraperitoneal injection with 20 mg/kg CP, the positive control.

Atmospheres of vinyl fluoride gas in air were generated by metering pure vinyl fluoride gas from a cylinder with flow meters into 3-neck glass mixing flasks. The pure gas was diluted to the desired concentrations by adding air at the flasks. The diluted vinyl fluoride was added to the tops of the 30-L cylindrical glass exposure chambers. Where appropriate, pure oxygen was added to maintain the atmospheric oxygen content at an acceptable level. For the control chamber, approximately 9 L/min of air was pumped into the top of a similar exposure chamber. The atmospheric

concentration of vinyl fluoride in each exposure chamber was monitored at approximately 30-minute intervals and analyzed via gas chromatography. Chamber temperatures were monitored with thermometers, relative humidity was measured with a humidity indicator, and chamber oxygen concentrations were monitored via an oxygen monitor.

Mice were observed for clinical signs of toxicity during exposure. Surviving mice were weighed and observed daily until sacrifice. Approximately 24, 48, and 72 hours after initiation of exposure, mice were sacrificed (5 per sex per time period for the control, low, and intermediate dose groups, 6 per sex per time period for the high group). The positive control mice were sacrificed at 24 hours after dosing.

Immediately following sacrifice, the marrow from both femurs of each animal was aspirated and flushed into prewarmed (37°C) fetal bovine serum. The marrow button was collected by centrifugation. Most of the supernatant was removed and the cells were resuspended in the remaining 1-2 drops of serum. An automatic blood smearing instrument was used to make the bone marrow smears. Three slides per animal were prepared and fixed in absolute methanol. The slides were stained in acridine orange in phosphate buffer, followed by phosphate buffer rinses. Immediately prior to scoring, the slides were coverslipped.

Representative slides from each animal were examined in a blind manner. One thousand PCEs per animal were scored for the presence of micronuclei. The number of micronucleated NCEs seen in the optic fields scored for PCEs was also recorded. The ratio of PCEs to NCEs was determined for each animal.

Treatment effects were examined for each sex separately. A Cochran-Armitage test for trend across exposure groups was performed. An analysis of variance (ANOVA) of treatment level and time was also performed. Where the F-test for treatment level was significant, pairwise comparisons were made between each treatment group and the concurrent control using Dunnett's test.

GLP: Yes
Test Substance: Vinyl fluoride, purity 99.99%
Results: Equivacol in male mice
Positive in female mice

Remarks:

Exposure chamber conditions for the vinyl fluoride treatments ranged from 24-25°C and 34-54% relative humidity. Oxygen content in the low level chamber was 21%. In the intermediate and high level chambers oxygen content was 18 and 17-18%, respectively, for the first 3 hours of exposure, after which pure oxygen was added until the oxygen content stabilized at 20-21%. The control chamber temperature was 24°C, relative humidity was 82%, and the oxygen content was 21%.

Actual vinyl fluoride concentrations were 50,100, 191,000, and 388,000 for the 50,000, 200,000, and 400,000 ppm groups, respectively.

During exposure, all mice in the vinyl fluoride groups had a reduced response to sound. Mice exposed to 191,000 ppm were more active than the controls. Soon after the onset of exposure to 388,000 ppm, mice were less active than controls, were grooming excessively and staggering, and had red ocular discharge. Later during exposure, all mice were hyperactive and were grooming excessively as indicated by frantic preening, licking, and scratching. At 24-hours post initiation, 1 male mouse in the 191,000 ppm and 1 male mouse in the 388,000 ppm group exhibited ruffled fur; this condition was still present in the 388,000 mouse at 48 hours. Additionally, at 48 hours, 1 male in the 50,100 ppm level was hyperactive. No clinical signs were observed at the 72-hour observation period.

Significant weight loss was seen in the low dose group males at the 72-hour sacrifice time and in the high dose group males at the 48-hour and 72-hour sacrifice times. Females from the high dose group had significant weight loss at the 24-hour sampling time.

No significant depression of PCE:NCE ratios was seen in any vinyl fluoride treated group at any of the sampling times. Additionally, no statistically significant increases of concentration-related trends in MN-PCEs were seen at the 48- or 72-hour sampling times.

At the 24-hour sacrifice time, the females showed a statistically significant concentration-related trend in the proportion of micronucleated PCEs, although no single test concentration gave significant increases over controls. The males in the low and high exposure groups exhibited

increased frequencies of MN-PCEs as compared to the concurrent control group. These increases were not statistically significant.

To further investigate the responses at the 24-hour sampling time, an additional 1000 PCEs per animal were evaluated for both the males and females. Based on the total of 2000 PCEs, female exposed to the intermediate and high levels of vinyl fluoride (191,000 and 388,000 ppm) showed statistically significant increases in the frequency of micronucleated polychromatic erythrocytes as compared to controls. A significant concentration-related trend was also present. The 24-hour treated males also showed increased frequencies of micronucleated polychromatic erythrocytes; however, these increases were not statistically significant.

Reference: DuPont Co. (1987). Unpublished Data, Haskell Laboratory Report No. 293-87, "Mouse Bone Marrow Micronucleus Assay of Vinyl Fluoride" (July 31) (also cited in TSCA Fiche OTS0515661 and OTS0536879).

Bentley, K. S. et al. (1992). Environ. Mol. Mutagen., 19(Suppl. 20):5.

Reliability: High because a scientifically defensible or guideline method was used.

Type: ***In vivo* Dominant Lethal Mutation Study**

Species/Strain: Rats/Crl:CD[®]

Sex/Number: Male/40 per group

Route of Administration: Inhalation

Concentrations: 0, 200, 2000, 20,000 ppm

Method: The procedures used in the test were based on the recommendations of the following guidelines: EPA Health Effects Guideline 40 CFR Part 798, Subpart 798.5450 and Federal Register, Vol. 40, Part 799.1700.

Groups of 40 sexually mature male rats were exposed 6 hours a day for 5 days to 0, 200, 2000, or 20,000 ppm of vinyl fluoride. A 5th group (positive control) of 40 sexually mature male rats was dosed with a single intraperitoneal injection of 0.2 mg/kg triethylenemelamine (TEM) in sterile saline on the final exposure day of the other groups.

Vinyl fluoride atmospheres were generated by metering concentrated vinyl fluoride gas from cylinders into 1.4 m³ exposure chambers where the vinyl fluoride was mixed with

the chamber air supply to the desired vinyl fluoride concentration. The vinyl fluoride sample was stabilized with d-limonene which was removed from the vinyl fluoride by trapping in silica gel prior to entry of vinyl fluoride into the exposure chamber. The atmospheric concentration of vinyl fluoride was determined at approximately 30 minute intervals using gas chromatography.

Beginning 2 days after exposure/dosing was completed, each male rat was co-housed with 1 sexually mature, nulliparous, unexposed female. They were cohoused for a maximum of 5 days or until copulation was verified by the presence of a copulatory plug, at which time the females were housed separately. Females without evidence of copulation were assumed to have copulated on the last day of cohabitation. The day of copulation was designated as Day 0 of gestation (Day 0G). This procedure was repeated weekly, using different females, for 8 consecutive weeks.

Females were weighed and clinical signs recorded on Days 0G and 14G. They were sacrificed on Day 14G. The uterine contents were examined to determine the number of total implantations, resorptions, and live and dead embryos. The ovaries were examined to determine the number of corpora lutea. Preimplantation loss was calculated as the difference between the number of corpora lutea and the number of implantations.

Males were weighed and clinical signs were recorded daily during exposure and weekly thereafter. All males were sacrificed 10-11 days after the final day of mating. Testes were examined for gross abnormalities, weighed, and preserved in Bouin's fixative. Testes were not examined histologically.

Clinical signs data, mortality, mating incidence and fertility incidence were analyzed statistically with the Cochran-Armitage test for linear trend and the Fisher's exact test. Body weights, body weight changes, and organ weights were analyzed via linear combination of dose ranks from ANOVA and Dunnett's test when the one-way ANOVA was significant. Mean number of corpora lutea, mean preimplantation loss, mean early resorptions, mean dead embryos, mean total non-viable embryos, mean live embryos, mean total implantations, percent pre-implantation loss, and percent post-implantation loss were analyzed via

the Jonckheere's test and Mann-Whitney U test.
GLP: Yes
Test Substance: Vinyl fluoride, purity 99.99%
Results: Negative
Remarks: The 5-day exposure concentration means for the low, intermediate, and high concentration groups were 195±17.7, 2006±158, and 19,325±821 ppm, respectively.

VF exposure had no adverse effects with respect to mortality rate, body weight gain, clinical signs of toxicity, or mating or fertility indices of the adult rats.

Pregnancy rates and pre- and post-implantation losses were similar in control and treated dams. The number pregnant ranged from 30-38 females per group throughout the study. Fertility was significantly lower for females mated to the 20,000 ppm group compared to control females during mating week 3. However, this was attributed to the relatively high fertility rate observed in the control rats that week. The fertility in the 20,000 ppm group (75%) was within the range of historical control fertility (52-98%) found with this species at this laboratory and therefore the lower fertility was not considered a treatment-related effect.

The vinyl fluoride exposure did not increase the frequency of dominant-lethal mutations, indicating that VF was not mutagenic to germ cells in the male rat. The NOEL was 20,000 ppm.

Reference: DuPont Co. (1988). Unpublished Data, Haskell Laboratory Report No. 237-88, "Dominant Lethal Mutation Study of Vinyl Fluoride in Rats" (September 19) (also cited in TSCA Fiche OTS0000665, OTS0522785, OTS0522790, and OTS0536879).

Chromey, N. C. et al. (1990). The Toxicologist, 10(1):55 (Abstract 218).

Bentley, K. S. et al. (1992). Environ. Mol. Mutagen., 19(Suppl. 20):5.

Reliability: High because a scientifically defensible or guideline method was used.

Type: **Unscheduled DNA Synthesis in Rat Spermatocytes**
Species/Strain: Rats/CDF(F-344)CrIBr[®]
Sex/Number: Male/15 per group
Route of Inhalation (nose-only)

December 18, 2003

Administration:
Concentrations: 0, 20,000 ppm
Method: The procedures used in the test were based on the recommendations of the following guideline: EPA Health Effects Guideline 40 CFR Part 798.

Groups of 15 male rats were exposed via inhalation to either air or 20,000 ppm vinyl fluoride for a period of 6 hours per day for 1, 2, or 5 consecutive days. During the exposures, rats were individually restrained in perforated, polycarbonate cylinders with conical nosepieces. The restrainers were inserted into side ports of a specially designed polycarbonate exposure chamber so that only the nose of each rat protruded into the chamber.

A vapor atmosphere of vinyl fluoride was generated by metering the test material from the gas cylinder into a glass mixing flask. Conditioned, filtered house-line air was added to the flask to dilute the test material to the desired concentration. The vinyl fluoride/air mixture then flowed into the exposure chamber. Baffles were placed in the airstream to promote uniform distribution of the test atmosphere within the chamber.

Chamber air flow was monitored by flowmeters. Chamber temperature was targeted at $23\pm 2^{\circ}\text{C}$ and was monitored with a thermometer. Relative humidity was targeted at $50\pm 10\%$ and was measured with a psychrometer. Chamber oxygen concentration was targeted for at least 19% and was measured with an oxygen monitor. The atmospheric concentration of vinyl fluoride was determined at approximately 30-minute intervals during each exposure period and analyzed via gas chromatography.

Conditioned, filtered, house-line air was used as the negative control. Phosphate buffered saline (PBS), administered by intraperitoneal injection, was the vehicle control for the positive control group. Methyl methanesulfonate (MMS) was administered via intraperitoneal injection as the positive control.

At approximately 2, 6, or 24 hours after exposure, testicular cells were prepared from 5 animals in both the control and 20,000 ppm groups. Testicular cells from animals administered the positive control and its corresponding vehicle control were prepared 1-2 hours following treatment.

Rats were anesthetized and 1 testis from each animal was removed and placed in a sterile dish containing enriched Krebs/Ringer bicarbonate solution (EKRB). The testes were decapsulated and the seminiferous tubules were washed in EKRB. Tubules were enzymatically digested and then gently drawn up in a pipette to produce a cell suspension. Viability and cell density were determined.

Individual wells containing medium were inoculated with approximately 6×10^6 viable testicular cells. Cells were cultured in Williams E medium supplemented with fetal bovine serum, L-glutamine, penicillin, streptomycin, and [methyl- ^3H]thymidine. Cultures were incubated in a humidified atmosphere at $33 \pm 1^\circ\text{C}$ for 18 to 24 hours.

To determine whether vinyl fluoride inhibited DNA repair, separate testicular cell cultures from either air control or vinyl fluoride-exposed animals were treated *in vitro* with MMS prepared in PBS. Isolated cells from animals sacrificed 2 and 6 hours following the 1- and 5-day exposures were tested.

Following incubation, cell viability was determined by trypan blue exclusion. Cells were fixed in formaldehyde and refrigerated. Fixed cells were washed with PBS. Aliquots of each cell suspension were placed on microscope slides. Slides were washed in cold tap water and dried by washing in methanol. When dry, slides were dipped into undiluted nuclear track emulsion, dried, and stored frozen for 2-3 weeks to expose the emulsion. Slides were then developed and stained with Gills hematoxylin.

Slides were examined in a blind manner. Cells meeting the following criteria were scored for UDS: 1) cells with normal morphology, 2) cells free of debris or staining artifacts, and 3) cells free of overlapping cells.

Grain counts were made under a 100X oil immersion light microscope with a 10X eye piece. Silver grains were counted using a colony counter interfaced via a TV camera to a microscope. Three slides per animal and 25 cells per slide were scored for a total of 75 cells per animal.

Average nuclear grains per cell was calculated for each slide. The mean nuclear grains per cell and the standard error of the mean were calculated for each animal. The percent of

cells in repair was also calculated. Statistical analysis was conducted using the animal as the experimental unit. A one-way analysis of variance was performed.

The test material was considered positive if 1) the mean nuclear grains per cell for a group of animals exposed to the test material was statistically greater than the mean for the corresponding control group and 2) the average percent of cells undergoing repair for those animals was 10% or greater. The test material was considered negative if 1) the mean nuclear grains per cell for all groups of animals exposed to the test material was not statistically greater than the mean for the corresponding control group and 2) the average percent of cells undergoing repair was < 10%.

GLP: Yes
Test Substance: Vinyl fluoride, purity 99.99%
Results: Negative
Remarks: Average chamber concentrations of vinyl fluoride were within 3% of the targeted 20,000 ppm. The range of individual samples for the 1- and 2-day exposures were within 10% of target. For the 5-day exposure; however, the range of measurements was 9% below target and 20% above target. The animals were considered to be sufficiently exposed to vinyl fluoride since excursions outside the 10% target range were at concentrations above 20,000 ppm. Chamber temperature was 22-23°C for the control group and 21-23°C for the vinyl fluoride group. Relative humidity was 40-52% for the control group and 46-58% for the vinyl fluoride group. Oxygen content for exposures was maintained between 20.0-20.4% for the control group and 20.1-20.2% for the vinyl fluoride group.

Weight losses were observed in both the air- and vinyl fluoride-exposed groups for all harvest times following the 2-day exposure and at the 24-hour harvest following the 1- and 5-day exposures. There were no statistically significant differences in body weight loss for any exposure length or harvest time when analyzed by one-way analysis of variance.

A red discharge from the eyes and nose was noticed when air- and vinyl fluoride-exposed animals were removed from the exposure chambers.

Vinyl fluoride was not toxic to testicular cells. Following isolation, testicular cell viability ranged from 91-100% for the air-exposed group and 91-99% for the vinyl fluoride-

Reference: exposed animals. UDS was not observed at any time post-exposure following any exposure period.
DuPont Co. (1990). Unpublished Data, Haskell Laboratory Report No. 727-90, "Determination of Unscheduled DNA Synthesis in Rat Spermatocytes Following *In Vivo* Exposure to Vinyl Fluoride by Inhalation" (December 13) (also cited in TSCA Fiche OTS0532955).

Reliability: Bentley, K. S. et al. (1992). Environ. Mol. Mutagen., 19(Suppl. 20):5.
High because a scientifically defensible or guideline method was used.

Type: *In vivo* DNA Repair Assay
Species/Strain: Rats/Sprague Dawley (F-344/NHSD)
Sex/Number: Male/4 per group per exposure period
Route of Administration: Inhalation (nose-only)
Concentrations: 0, 20,000 ppm
Method: No specific test guideline was reported; however, the procedures used in the test were based on the procedures of Skare, J. A. and K. R. Schrotel (1984). Mutat. Res., 130:295-303.

Groups of 4 male rats were designated into treatment (vinyl fluoride) or control (shame or positive control) groups for 3 different exposure periods. Exposures were conducted for a period of 6 hours on 1, 2, or 5 consecutive days. Sham controls received filtered outside air only.

Vinyl fluoride gas containing d-limonene as a stabilizer was generated from a pressurized tank connected to the exposure modules via Teflon tubing. Prior to entering the exposure modules, the gas was cleared of d-limonene by trapping on silica gel. Filtered outside air was used to dilute the gas before entering the exposure chambers. The test atmosphere and dilution air were directed through a calibrated rotometer prior to entering the exposure module. Flow rates were adjusted during exposure to maintain appropriate concentrations within 10% of the target. The exposure units consisted of a flat polycarbonate cylinder (~ 360 mL). Rats were held in cylindrical tubes which aligned the heads of the animals with conical shaped openings on the exposure chamber. The nose of each animal protruded into the chamber for nose-only inhalation. On each day, the atmosphere in the test exposure module was sampled

approximately every 60 minutes and analyzed via GLC. The oxygen content in the chambers was measured via an oxygen indicator. Temperature and humidity were measured using a hygrometer. The air flow per exposure module was adjusted to approximately 3.6-6.1 L/min.

Methyl methanesulfonate (MMS) and triethylenemelamine (TEM) were administered via intraperitoneal injection as the positive controls. Calcium and magnesium free-Hanks' Balanced Salt Solution (CMF-HBSS), administered by intraperitoneal injection, was the solvent and vehicle control for the positive control groups.

All animals were weighed prior to treatment. Clinical observations, including mortality and pharmacotoxic signs, were recorded prior to exposure and immediately after exposure on Days 1, 2, 3, 4, and 5. Animals were checked for mortality and moribundity at least once daily.

Rats were anesthetized and 1 testis from each animal was removed. Testicular cells were harvested 2, 6, and 24 hours after daily exposures of 1, 2, and 5 days to analyze the testicular DNA for DNA single strand breaks and DNA cross links. The alkaline elution procedure of Skare and Schrotel was used to detect DNA single strand breaks. DNA X-irradiation and the photofluorometric DNA assay was used to detect DNA cross links. The photofluorometric DNA assay used was a modification of the assay described by Kissane, J. M. and E. J. Robins (1958). J. Biol. Chem., 223:184-188.

The extent of single strand breaks was measured by comparing the elution rate of the testicular DNA derived from cells treated with the test material to the elution rate of DNA from sham exposed cells. The test material was judged to be positive if it induced a significant increase in the mean elution rate over the control elution rate. A one-tailed t-test was employed to compare the mean elution rates.

The extent of DNA cross links was measured by comparing the mean elution rate of X-irradiated testicular DNA from cells treated with the test material to the mean elution rate of X-irradiated testicular DNA from sham exposed cells. The test material was judged positive if it induced a significant decrease in the mean elution rate of X-irradiated samples

over the control elution rate. A one-tailed t-test was employed to compare the mean elution rates.

GLP: Yes
Test Substance: Vinyl fluoride, purity > 99.9%
Results: Negative
Remarks: For each day during the 3 exposure periods, the concentration of vinyl fluoride was within 10% of the target concentration and ranged from 18,106 to 21,680 ppm. The stabilizer, d-limonene, was not detected in any of the test modules. The oxygen content of the atmosphere in the test and sham-exposure modules ranged from 20.0-21.5% and 19.0-21.5%, respectively. The temperature in the test exposure modules ranged from 67.8-74.2°F, while the relative humidity ranged from 41.7-72.1%. Temperature and relative humidity in the sham-exposure modules ranged from 67.2-74.0°F and 30.4-70.0%, respectively.

Immediately following exposure, sham and treated animals appeared hunched and ataxic with secretions from the eyes (red) and stained coat (brown/yellowish brown) along the hindquarters. Observations recorded after exposure were limited to secretions from the eyes/nose (reddish brown or clear to pink) and/or stained coat (brown) along the hindquarters of sham and treated animals.

The results of the alkaline elution assays to detect DNA single strand breaks indicated that the test material did not cause a significant increase in single strand breaks in testicular DNA. A statistically significant increase in elution rate was found at 1 of 9 time points. However, the difference in rate was very small and not repeated at any other time point in the study. Therefore, it was not considered to be biologically significant.

In addition, the results of the alkaline elution assays to detect DNA cross links indicated that the test material did not cause cross links in testicular DNA. A statistically significant decrease in elution rate was found at 1 of 9 time points. Since the difference in rate was very small and was apparently the result of a low control value at the last elution time point, it was not considered to be of biological significance.

Reference: DuPont Co. (1991). Unpublished Data, Haskell Laboratory Report No. 203-91, "Detection of DNA Damage in Rat Testicular DNA by Alkaline Elution Following *In Vivo* Inhalation Exposure to Vinyl Fluoride" (March 15) (also

cited in TSCA Fiche OTS0000806 and OTS0532956).

Bentley, K. S. et al. (1992). Environ. Mol. Mutagen., 19(Suppl. 20):5.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for *In vivo* Genetic Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Hazleton Laboratories (1988). Unpublished Data, Project No. 10212-0-461, "Mutagenicity Test on Vinyl Fluoride, *Drosophila Melanogaster* Sex-Linked Recessive Lethal Test" (August 12) (cited in TSCA Fiche OTS0000557-1, OTS0522785, OTS0522809, OTS0536884, and OTS0536879 and Bentley, K. S. et al. (1992). Environ. Mol. Mutagen., 19(Suppl. 20):5). VF induced sex-linked recessive lethal mutations in *Drosophila melanogaster* exposed to an atmospheric concentration of 50% for 24 hours.

DuPont Co. (1991). Unpublished Data, Letter to EPA, August 12. Lactating rats were exposed with their 10-day-old pups 6 hours a day, 5 days a week, for 2 weeks to 25, 250, or 2500 ppm of VF. At the end of the exposure period, livers were collected from the pups and analyzed for 7-oxoethyldeoxyguanosine DNA adducts. Adducts were found in the liver of all the exposed pups and ranged from approximately 17 to 30 pmoles/mg DNA. Liver samples were also collected from rats similarly exposed to VF for approximately 2 or 52 weeks. Adducts were also found in the livers of all 3 groups of exposed rats. No difference was found in the level of adducts between the 2-week and the 52-week groups. The dose-response for DNA adducts observed in both studies suggests saturation of metabolic activation near 250 ppm. When compared with similar data for vinyl chloride, VF appears to be 1/3 to 1/4 less efficient than vinyl chloride in producing adducts.