

SCREENING-LEVEL HAZARD CHARACTERIZATION Methallyl chloride (CASRN 563-47-3)

The High Production Volume (HPV) Challenge Program¹ was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

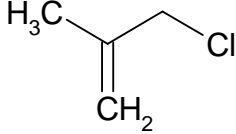
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p>563-47-3</p>
<p>Chemical Abstract Index Name</p>	<p>1-Propene, 3-chloro-2-methyl-</p>
<p>Structural Formula</p>	
<p style="text-align: center;">Summary</p> <p>CASRN 563-47-3 is a colorless liquid with moderate water solubility and high vapor pressure. It is expected to have moderate mobility in soil. Volatilization of 1-Propene, 3-chloro-2-methyl- is considered high based on its Henry's Law constant. The rate of hydrolysis was not measured; however, based on data for a structurally similar compound, the rate of hydrolysis of methallyl chloride may be slow to moderate. The rate of atmospheric photooxidation is considered moderate. It is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute toxicity to rats via oral, inhalation and dermal routes is low. An oral combined repeated-dose/reproductive/developmental toxicity screening test in rats showed epithelial hyperplasia in non-glandular stomach in both sexes at 180 mg/kg-bw/day. The NOAEL for systemic toxicity was 60 mg/kg-bw/day. An increase in post-implantation loss and decreased number of live pup at birth were seen at 180 mg/kg-bw/day with a NOAEL for reproductive toxicity at 60 mg/kg-bw/day. The NOAEL for developmental toxicity was 180 mg/kg-bw/day based on no effects at the highest dose tested. In the long term studies in rats and mice (103 weeks) rats showed decreased body weight at 75 mg/kg-bw/day and above with a LOAEL of 75 mg/kg-bw/day. Mice showed nephropathy/nephrosis and effects on nasal cavity at 100 mg/kg-bw/day. The NOAELs for systemic toxicity were not established in these studies. Methallyl chloride did not induce gene mutation in bacterial cells <i>in vitro</i> and chromosomal aberrations in mammalian cells <i>in vivo</i>. Methallyl chloride did induce tumors in rats and mice in carcinogenicity studies at moderate doses.</p> <p>No measured data for environmental effects were available. The estimated 96-hour LC₅₀ of this chemical for fish is 7.6 mg/L, the estimated 48-hour EC₅₀ for aquatic invertebrates is 20.2 mg/L, and the estimated 96-hour EC₅₀ for aquatic plants is 171.3 mg/L.</p> <p>Acute toxicity to fish, aquatic invertebrates and aquatic plants were identified as data gaps under the HPV Challenge Program.</p>	

The sponsor, The FMC Corporation, submitted a Test Plan and Robust Summaries to EPA on December 28, 2000, for methallyl chloride (CASRN 563-47-3). EPA posted the submission on the RTK HPV Challenge Website on February 13, 2001 (<http://www.epa.gov/chemrtk/pubs/summaries//methal/c12875tc.htm>). EPA comments on the original submission were posted to the website on March 7, 2001. Public comments were also received and posted to the website. The sponsor submitted three revisions to the submission which were posted on the RTK HPV Challenge Website on June 19, 2001, August 9, 2001 and February 23, 2004.

1. Chemical Identity

1.1 Identification and Purity

The HPV submission⁴ for this chemical did not include information on purity in the Test Plan. However, the robust summaries identified the purity of the test material to be 93- 99% (February 2004).

1.2 Physical-Chemical Properties

The physical-chemical properties of 2-methyl-1,3-propanediol are summarized in Table 1. Methallyl chloride is a colorless liquid with moderate water solubility and high vapor pressure.

Property	Value
CASRN	563-47-3
Molecular Weight	90.55
Physical State	Clear colorless liquid
Melting Point	<0°C (measured)
Boiling Point	70°C (measured)
Vapor Pressure	102.3 mm Hg at 20°C (measured)
Water Solubility	180 mg/L at 25°C (measured)
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	8.7×10 ⁻³ atm·m ³ /mole (measured)
Log K _{ow}	2.29 (measured)

¹FMC Corporation. February 23, 2004. Revised Robust Summary and Test Plan for 1-Propene, 3-Chloro-2-Methyl-. <http://www.epa.gov/chemrtk/pubs/summaries/methal/c12875tc.htm>.

⁴ The FMC Corporation (2000) Methallyl Chloride, CASRN 563-47-3
<http://www.epa.gov/chemrtk/pubs/summaries//methal/c12875tc.htm>

2. General Information on Exposure

2.1 Production Volume and Use Pattern

Production Volume, Use, and Release Information

Methallyl Chloride had an aggregated production and import volume in the United States of 10 million to 50 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include processing as an intermediate in other basic organic chemical manufacturing. Information from the HSDB indicates that the chemical is primarily used as an intermediate in the production of insecticides, plastics, pharmaceuticals, as well as a fumigant for grains, tobacco and soil. The Extended High Production Volume submission for this chemical indicates that the chemical is used as a chemical intermediate.

2.2 Environmental Exposure and Fate

The chemical is on the Toxics Release Inventory. The total release reporting in 2006 from all reporting sites is 5,963 pounds. This total includes 103 pounds from fugitive emissions and remainder as point source air emissions. There were no releases reported to water or landfill.

The environmental fate properties are provided in Table 2. Methallyl chloride is a colorless liquid with moderate water solubility and high vapor pressure. It is expected to have moderate mobility in soil. Volatilization of 1-Propene, 3-chloro-2-methyl- is considered high based on its Henry's Law constant. The rate of hydrolysis was not measured; however, based on data for a structurally similar compound, the rate of hydrolysis of methallyl chloride may be slow to moderate. The rate of atmospheric photooxidation is considered moderate. It is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	Value
Photodegradation Half-life	3.2 hours (estimated)
Hydrolysis Half-life	8 days at pH 7 (data for 1-propene, 3-chloro-) ²
Biodegradation	71% after 28 days (readily biodegradable); 99% in 28 days (readily biodegradable) ³
Bioconcentration	BCF = 16.2 (estimated) ⁴
Log K _{oc}	2.1
Fugacity (Level III Model)	Air = 5.67% Water = 66.1% Soil = 27.9% Sediment = 0.342%
Persistence ⁵	P1 (low)
Bioaccumulation ⁵	B1 (low)

¹FMC Corporation. February 23, 2004. Revised Robust Summary and Test Plan for 1-Propene, 3-Chloro-2-Methyl-
<http://www.epa.gov/chemrtk/pubs/summaries/methal/c12875tc.htm>.

²HSDB. 2008. Hazardous Substances Data Bank. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search>. Accessed October 23, 2008.

³National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law.
http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

⁴U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA.
<http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

⁵Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3. Human Health Hazard

The human health hazard data are summarized in Table 3.

Acute Oral Toxicity

Sprague-Dawley rats (10/sex/dose) were administered methallyl chloride as a 10% v/v solution in corn oil at doses of 1001, 1183, 1367 and 1639 mg/kg-bw for males and 719, 841, 994 and 1365 mg/kg-bw for females.

LD₅₀ (male) = 1149 mg/kg-bw

LD₅₀ (female) = 848 mg/kg-bw

Acute Inhalation Toxicity

Sprague-Dawley rats (5/sex/concentration) were exposed (whole-body) for 4 hours to a nominal concentration of 6.3 mg/L methallyl chloride. No mortality was seen during the 4-hour observation period.

LC₅₀ > 6.3 mg/L

Acute Dermal Toxicity

New Zealand White rabbits (10) were dermally exposed to 2000 mg/kg-bw of methallyl chloride by direct contact with clipped, abraded skin under occluded conditions for 24 hours. No mortality was seen. Erythema and edema were seen on all 10 rabbits during the study.

LD₅₀ > 2000 mg/kg-bw

Repeated-Dose Toxicity

(1) In a combined repeated-dose/reproductive/developmental toxicity screening test, Wistar rats (10/sex/dose) were administered methallyl chloride in corn oil via gavage at doses of 0, 20, 60 or 180 mg/kg-bw/day for 54 days. At 180 mg/kg-bw/day, effects on total bilirubin and liver enzymes in females were observed (nature of effects not indicated). Histopathological examination revealed treatment-related epithelial hyperplasia in non-glandular stomach in both sexes.

LOAEL = 180 mg/kg-bw/day (based on histopathology of the non-glandular stomach)

NOAEL = 60 mg/kg-bw/day

(2) In a carcinogenicity assay, F344/N rats (50/sex/dose) were administered methallyl chloride via gavage at 0, 75 or 150 mg/kg-bw/day 5 days/week for 103 weeks. Evidence of systemic toxicity at 75 and 150 mg/kg-bw/day included decreased body weights for males at the high dose and a marginal decrease in survival in male rats.

LOAEL (male) = 75 mg/kg-bw/day (based on decreased body weight)

NOAEL (male) = Not established

NOAEL (female) = 150 mg/kg-bw/day (based on no effects at the highest dose tested)

(3) In a carcinogenicity assay, B6C3F1 mice (50/sex/dose) were administered methallyl chloride via gavage at 0, 100 and 200 mg/kg-bw/day, 5 days/week for 103 weeks. Inflammation of the nasal cavity and nephropathy/nephrosis were greater in the two dosed groups than in controls.

LOAEL = 100 mg/kg-bw/day (based on effects on nasal cavity and nephropathy/nephrosis)

NOAEL = Not established

Reproductive/Developmental Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test in rats described previously, treatment with 180 mg/kg-bw/day caused an increase in post-implantation loss and thereby decreased number of live pups at birth.

LOAEL (systemic toxicity) = 180 mg/kg-bw/day (based on histopathology of the non-glandular stomach)

NOAEL (systemic toxicity) = 60 mg/kg-bw/day

LOAEL (reproductive toxicity) = 180 mg/kg-bw/day (based on increase in post-implantation loss and decreased number of live pups at birth)

NOAEL (reproductive toxicity) = 60 mg/kg-bw/day

NOAEL (developmental toxicity) = 180 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

In an Ames bacterial reverse mutation test, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to methallyl chloride at concentrations of 16, 80, 400, 800 and 1000 µg/mL with metabolic activation and 5, 20, 100, 325 and 650 µg/mL without metabolic activation. Sealed incubation chambers were used. Methallyl chloride did not induce a positive response in any of the tester strains with or without metabolic activation.

Methallyl chloride was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

In a micronucleus assay, male and female NMRI mice were exposed to the test substance via gavage at single doses of 501 mg/kg-bw (male) or 631 mg/kg-bw (female). Methallyl chloride did not show any clastogenic activity at 24, 48 or 72 hours post-application.

Methallyl chloride was not clastogenic in this assay.

Genetic Toxicity – Other

In vitro

Chinese hamster ovary (CHO) cells were exposed to methallyl chloride in the presence and absence of metabolic activation in a sister chromatid exchange (SCE) assay. The test concentrations were 8, 20, 40, 60 and 80 µg/mL with metabolic activation and 25, 50, 75, 125 and 250 µg/mL without metabolic activation. A concentration-related increase in SCE/metaphase frequency in the absence of metabolic activation was observed. Methallyl chloride is considered a weak inducer of SCEs.

Methallyl chloride weakly induced sister chromatid exchange in this assay.

Additional Information

Carcinogenicity

(1) In the 2-year carcinogenicity assay described previously, F344/N rats had an increased incidence of forestomach basal cell hyperplasia in both sexes. Squamous cell papillomas were increased in all male rats and high-dose female rats, and there was a slight increase of squamous cell carcinomas in male rats at the high dose. Renal tubular cell adenocarcinomas were seen in male rats at both dose levels and transitional cell papillomas of the urinary bladder (high-dose male rats) and renal tubular cell adenomas (low-dose male rats) were also observed. Furthermore, inflammation of the nasal cavity and nephropathy/nephrosis were greater in the two dosed groups than in controls. There were lower incidences of adrenal gland pheochromocytoma and thyroid C-cell adenomas or combined carcinomas in all treated male rats.

Under the conditions of this bioassay, methallyl chloride was carcinogenic in both male and female F344 rats.

(2) In the carcinogenicity study in B6C3F1 mice described previously, increased forestomach inflammation was seen in male and female mice with an increased incidence of forestomach basal cell hyperplasia in both sexes. Squamous cell papillomas were also seen in both sexes and at both dose levels. An increased incidence of squamous cell carcinomas was found in both sexes at both dose levels and there was evidence of metastasis to other organs.

Under the conditions of this bioassay, methallyl chloride was carcinogenic in both male and female B6C3F1 rats.

Conclusion: The acute toxicity to rats via oral, inhalation and dermal routes is low. An oral combined repeated-dose/reproductive/developmental toxicity screening test in rats showed epithelial hyperplasia in non-glandular stomach in both sexes at 180 mg/kg-bw/day. The NOAEL for systemic toxicity was 60 mg/kg-bw/day. An increase in post-implantation loss and decreased number of live pup at birth were seen at 180 mg/kg-bw/day with a NOAEL for reproductive toxicity at 60 mg/kg-bw/day. The NOAEL for developmental toxicity was 180 mg/kg-bw/day based on no effects at the highest dose tested. In the long term studies in rats and mice (103 weeks) rats showed decreased body weight at 75 mg/kg-bw/day and above with a LOAEL of 75 mg/kg-bw/day. Mice showed nephropathy/nephrosis and effects on nasal cavity at 100 mg/kg-bw/day. The NOAELs for systemic toxicity were not established in these studies. Methallyl chloride did not induce gene mutation in bacterial cells *in vitro* and chromosomal aberrations in mammalian cells *in vivo*. Methallyl chloride did induce tumors in rats and mice in carcinogenicity studies at moderate doses.

4. Environmental Effects – Aquatic Toxicity

The environmental hazard data are summarized in Table 3.

EPA considered the aquatic toxicity data inadequate because methallyl chloride is a highly volatile chemical and all tests were conducted in open exposure systems where the concentration of methallyl chloride fluctuated greatly. Predictions for acute toxicity were instead made using ECOSAR v. 1.00a.

Acute Toxicity to Fish

A 96-hour LC₅₀ value for fish exposed to methallyl chloride was estimated by ECOSAR v. 1.00a.

96-h LC₅₀ = 7.6 mg/L (estimated)

Acute Toxicity to Aquatic Invertebrates

A 48-hour LC₅₀ value for *Daphnia* exposed to methallyl chloride was estimated by ECOSAR v. 1.00a.

48-h LC₅₀ = 20.2 mg/L (estimated)

Acute Toxicity to Aquatic Plants

A 96-hour EC₅₀ value for algae exposed to methallyl chloride was estimated by ECOSAR v. 1.00a.

96-h EC₅₀ = 171.3 mg/L (estimated)

Conclusion: The estimated 96-hour LC₅₀ of this chemical for fish is 7.6 mg/L, the estimated 48-hour EC₅₀ for aquatic invertebrates is 20.2 mg/L, and the estimated 96-hour EC₅₀ for aquatic plants is 171.3 mg/L.

Acute toxicity to fish, aquatic invertebrates and aquatic plants were identified as data gaps under the HPV Challenge Program.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL Methallyl chloride (563-47-3)
Summary of Human Health Data	
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	1149 (male); 848 (female)
Acute Inhalation Toxicity LC₅₀ (mg/L)	> 6.3
Acute Dermal Toxicity LD₅₀ (mg/kg-bw)	> 2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 60 (54-d) LOAEL = 180 (54-d) NOAEL = Not established LOAEL = 75 (2-year)
Reproductive/Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day) Systemic/Reproductive Toxicity	NOAEL = 60 (54-d) LOAEL = 180 (54-d)
Genetic Toxicity - Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity - Chromosomal Aberrations <i>In vivo</i>	Negative
Genetic Toxicity - Other <i>In vitro</i>	Weakly Positive
Additional Information Carcinogenicity	Positive
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC₅₀ (mg/L)	7.6 (estimated)
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	20.2 (estimated)
Aquatic Plants 72-h LC₅₀ (mg/L)	171.3 (estimated)