Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals

Methallyloxyphenol (CASRN 4790-71-0)
(9th CI and CA Index Name: Phenol, 2-[(2-methyl-2-propen-1-yl)oxy]-)

Contents:

BACKGROUND

Screening-level hazard, exposure and risk characterizations for high production volume chemicals (HPV) are important contributions to the chemicals cooperation work being done in North America[1] through the EPA Chemical Assessment and Management Program (ChAMP)[2]. These screening-level characterizations are developed by EPA for individual chemicals or chemical categories to support initial Risk-Based Prioritizations (RBPs) for HPV chemicals. These screening-level characterizations are technical documents intended primarily to inform the Agency's internal decision-making process. Accordingly, they are written for assessment professionals and assume a degree of technical understanding. Each of the support documents is described below.

The Risk-Based Prioritizations are found in an accompanying document and are written for a general audience. They present EPA's initial thinking regarding the potential risks presented by these chemicals and future possible actions that may be needed.

Hazard Characterizations for HPV Chemicals

EPA's screening-level hazard characterizations are based primarily on the review of the summaries of studies and other information submitted by the chemical sponsor(s) under the HPV Challenge Program[3]. These studies included in the scope of the HPV Challenge comprise the Screening Information Data Set (SIDS) of the Organization for Economic Cooperation and Development (OECD)[4], an internationally recognized battery of tests that provides the basic data necessary to make an initial evaluation of a chemical's hazards and fate. In preparing the initial hazard characterizations, EPA also consulted a variety of reliable sources[5] for additional relevant information and 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 an HPV submission, EPA also searched publicly available databases[6] for information entered from one year prior to the HPV submission through May 2008. The screening-level hazard characterization is performed according to established EPA guidance[7]. A more detailed description of the hazard characterization process is available on the EPA website[8].

With respect to chemicals for which internationally-accepted OECD SIDS Initial Assessment Profiles (SIAP) and Initial Assessment Reports (SIAR) were available, EPA did not generate its own screening-level hazard characterization, but did check for and incorporate updated information in the risk characterization.

Exposure Characterizations for HPV Chemicals

EPA recently received exposure-related data on chemicals submitted in accordance with the requirements of Inventory Update Reporting (IUR)[9]. The 2006 IUR submissions pertain to chemicals manufactured in

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[1] U.S. EPA – U.S. Commitments to North American Chemicals Cooperation: http://www.epa.gov/hpv/pubs/general/sppframework.htm.
[2] U.S. EPA – ChAMP information: http://www.epa.gov/champ/.
[3] U.S. EPA – HPV Challenge Program information: http://www.epa.gov/hpv.
[4] U.S. EPA – Technical Guidance Document, OECD SIDS Manual Sections 3.4 and 3.5: http://www.epa.gov/chemrtk/pubs/general/sidsappb.htm.
[5] U.S. EPA – Public Database Hazard Information: http://www.epa.gov/hpvis/hazardinfo.htm.
[6] U.S. EPA – Public Database Update Information: http://www.epa.gov/chemrtk/hpvis/updateinfo.htm.
[7] U.S. EPA – Risk Assessment Guidelines: http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[8] U.S. EPA – About HPV Chemical Hazard Characterizations: http://www.epa.gov/hpvis/abouthc.htm.
[9] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm.

(including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. The reports include the identity, the quantity, and the physical form of the chemical manufactured or imported, and the number of workers reasonably likely to be exposed during manufacture of the chemical. For chemicals manufactured or imported in quantities of 300,000 pounds or more at a single site, additional reported information includes: the industrial processing and uses of the chemical; the number of industrial processing sites and workers reasonably likely to be exposed to the chemical at those sites; the consumer and commercial uses of the chemical; and an indication whether the chemical was used in products intended for use by children under 14 years of age.

EPA's screening-level exposure characterizations are based largely on the information submitted under the IUR reporting, although other exposure information submitted to the Agency (for example, in HPV submissions) or readily available through a limited set of publicly accessible databases[10] was also considered. The screening-level exposure characterizations identify a potential (high, medium, or low) that each of five populations – the environment, the general population, workers, consumers, and children – might be exposed to the chemical. In most cases, this potential doesn't address the quantity, frequency, or duration of exposure, but refers only to the likelihood that an exposure could occur.

In many instances EPA is not able to fully disclose to the public all the IUR exposure-related data reviewed or relied upon in the development of the screening-level documents because some of the material was claimed as confidential business information (CBI) when it was submitted to the Agency. These CBI claims do limit the Agency's ability to be completely transparent in presenting some underlying exposure and use data for chemicals in public documents. EPA does consider all data, including data considered to be CBI, in the screening-level exposure and risk characterization process, and endeavors whenever possible to broadly characterize supporting materials claimed as confidential in ways that do not disclose actual CBI.

Risk Characterizations for HPV Chemicals

EPA combines the information from the screening-level exposure characterization with the screening-level hazard characterization to develop a qualitative screening-level risk characterization, as described in the Agency's guidance on drafting risk characterizations[11]. These screening-level risk characterizations are technical documents intended to support subsequent priority-setting decisions and actions by OPPT. The purpose of the qualitative screening-level risk characterization is two-fold: to support initial risk-based decisions to prioritize chemicals, identify potential concerns, and inform risk management options; and to identify data needs for individual chemicals or chemical categories.

These initial characterization and prioritization documents do not constitute a final Agency determination as to risk, nor do they determine whether sufficient data are available to characterize risk. Recommended actions reflect EPA's relative judgment regarding this chemical or chemical category in comparison with others evaluated under this program, as well as the uncertainties presented by gaps that may exist in the available data.

[10] U.S. EPA – Summary of Public Databases Routinely Searched: http://www.epa.gov/chemrtk/hpvis/pubdtsum.htm.
[11] U.S. EPA – Risk Characterization Program: http://www.epa.gov/osa/spc/2riskchr.htm.

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Methallyloxyphenol (CAS No. 4790-71-0)
[9th CI Name: Phenol, 2-[(2-methyl-2-propenyl)oxy-]

September 2008

Prepared by

Risk Assessment Division
Economics, Exposure and Technology Division
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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR Methallyloxyphenol (CAS No. 4790-71-0)

1. Physical-Chemical Properties and Environmental Fate

Methallyloxyphenol is a liquid at room temperature with a moderate vapor pressure and high water solubility. It is expected to partition primarily to water and soil in the environment. It is moderately mobile in soil and moderately volatile from moist soil and water. Its rate of hydrolysis is considered negligible under environmental conditions. The rate of vapor-phase photooxidation in the ambient atmosphere is rapid with respect to the hydroxyl radical and moderate with respect to ozone. It did not degrade in a ready biodegradation test; however, based on estimated biodegradability and professional judgment, it is expected to have low persistence in the environment (P1). The estimated bioconcentration factor (BCF) of 25.3 indicates that methallyloxyphenol has a low potential to bioaccumulate (B1).

2. Hazard Characterization

Aquatic Organism Toxicity. Acute toxicity of methallyloxyphenol to fish and aquatic invertebrates is high and to aquatic plants is low.

Human Health Toxicity. The acute oral toxicity of methallyloxyphenol to rats is low. Repeat-dose and reproductive toxicity studies are not required for the HPV Challenge Program because methallyloxyphenol is a closed-system intermediate (CSI). A combined reproductive/developmental toxicity study in rats showed no reproductive, developmental, or parental systemic toxicity. Methallyloxyphenol was mutagenic *in vitro*, but did not induce chromosomal aberrations *in vivo*.

3. Exposure Characterization

There are no 2002 or 2006 Inventory Update Rule (IUR) submissions for methallyloxyphenol (CAS # 4790-71-0).

Potential for Exposures to Human and the Environment:
Based on the information considered and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a low relative ranking for each of the potentially exposed groups (including workers, general population, consumers and children) and the environment. In 2003, EPA reviewed the information in the HPV submission and test plan and determined that the HPV chemical satisfied the guidance to demonstrate that the chemical is a closed system intermediate. The use of this chemical solely as an intermediate to produce other chemicals in enclosed vessels is expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. No information on commercial/consumer uses is available in the IUR or any other sources.

4. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this screening-level and qualitative risk characterization and will be used for prioritizing substances for future work in the Chemical Assessment and Management Program (ChAMP).

Risk Statement and Rationale

The Agency has reviewed the information in the HPV submission or test plan and determined that the HPV chemical satisfies the guidance to demonstrate that the chemical is a closed system intermediate (CSI). Methallyloxyphenol is manufactured and processed in closed systems that are expected to significantly reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. Therefore, there is a low concern for potential risks to aquatic organisms and the general population from environmental releases, and also to workers, consumers, and children.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Methallyloxyphenol (CAS No. 4790-71-0)
[9th CI Name: Phenol, 2-[(2-methyl-2-propenyl)oxy-]

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SCREENING-LEVEL HAZARD CHARACTERIZATION
Methallyloxyphenol
(Phenol, 2-[(2-methyl-2-propenyl)oxy]- , CAS No. 4790-71-0)

Introduction

The sponsor, FMC Corporation, submitted a Test Plan and Robust Summaries to EPA for methallyloxyphenol (CAS Number 4790-71-0, 9th CI Name: phenol, 2-[(2-methyl-2-propenyl)oxy) on December 28, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 3, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/methyall/c13458tc.htm). EPA comments on the original submission were posted to the website on were submitted on July 31, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 8, 2002, September 29, 2002, and December 30, 2004, which were posted to the ChemRTK website on July 24, 2002, October 17, 2002, and February 3, 2005, respectively.

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. 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 2004 to May 2008: the NLM databases (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health effects is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

The sponsor proposed reduced health testing, claiming that methallyloxyphenol is a closed-system intermediate (CSI). EPA's evaluation of the original and revised/updated information indicated that the chemical meets the guidance to support the CSI claim for this chemical. Methallyloxyphenol is produced at a single site, is consumed in the in-process reaction to make another substance, and there are no offsite shipment. Therefore, EPA has determined that the chemical qualifies for reduced testing – waiving of repeated-dose and reproductive toxicity testing for the purposes of the HPV Challenge Program.

Hazard Characterization

Methallyloxyphenol is a liquid at room temperature with a moderate vapor pressure and high water solubility. It is expected to partition primarily to water and soil in the environment. It is moderately mobile in soil and moderately volatile from moist soil and water. Its rate of hydrolysis is considered negligible under environmental conditions. The rate of vapor-phase photooxidation in the ambient atmosphere is rapid with respect to the hydroxyl radical and moderate with respect to ozone. It did not degrade in a ready biodegradation test; however, based on estimated biodegradability and professional judgment, it is expected to have low persistence in the environment (P1). The estimated bioconcentration factor (BCF) of 25.3 indicates that methallyloxyphenol has a low potential to bioaccumulate (B1).

Acute toxicity of methallyloxphenol to fish and aquatic invertebrates is high and to aquatic plants is low.

The acute oral toxicity of methallyloxphenol to rats is low. Repeat-dose and reproductive toxicity studies are not required for the HPV Challenge Program because methallyloxphenol is a closed-system intermediate (CSI). A combined reproductive/developmental toxicity study in rats showed no reproductive, developmental, or parental systemic toxicity. Methallyloxphenol was mutagenic *in vitro*, but did not induce chromosomal aberrations *in vivo*.

Melting point was identified as a data gap under the HPV Challenge Program; however, methallyloxphenol is a liquid at room temperature.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of methallyloxyphenol are summarized in Table 1a, while its environmental fate properties are given in Table 1b. The structure of the compound is provided in the Appendix.

Physical-Chemical Properties Characterization

Methallyloxyphenol is a liquid at room temperature. It has a moderate vapor pressure and high water solubility.

Table 1a. Physical-Chemical Properties of Methallyloxyphenol[1]

Property	Value
CAS Reg. No.	4790-71-0
Molecular Weight	164.21
Physical State	Liquid
Melting Point	Liquid at room temperature
Boiling Point	Undergoes Claisen rearrangement before reaching boiling point at atmospheric pressure
Vapor Pressure	0.02 mm Hg at 25°C (mathematical extrapolation from higher temperature vapor pressure data)
Water Solubility	1830 mg/L at 20°C (measured)
Henry's Law Constant	2.36×10^{-3} atm-m^3/mol (estimated)[2]
Log K_{ow}	2.47 (measured)

[1] FMC Corporation. 2004. Revised Robust Summary and Test Plan for Methallyloxyphenol. http://www.epa.gov/chemrtk/pubs/summaries/methyall/c13458tc.htm.

[2] US 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.

Environmental Fate Characterization

Methallyloxyphenol is expected to partition primarily to water and soil, according to the results of a Level III fugacity model. It is moderately mobile in soil. The Henry's Law constant indicates that methallyloxyphenol is moderately volatile from moist soil and water. Its rate of hydrolysis is considered negligible under environmental conditions (pH 5-9). The rate of vapor-phase photooxidation in the ambient atmosphere is rapid with respect to the hydroxyl radical and moderate with respect to ozone. The estimated bioconcentration factor (BCF) of 25.3 indicates that methallyloxyphenol has a low potential to bioaccumulate (B1). It did not degrade in a ready biodegradation test; however, based on estimated biodegradability and professional judgment, it is judged to have low persistence in the environment (P1).

Table 1b. Environmental Fate Characteristics of Methallyloxyphenol[1]	
Property	**Value**
Photodegradation Half-Life	OH half-life = 1.5 hours (estimated) O_3 half-life = 22.9 hours (estimated)[2]
Hydrolysis Half-Life	184 days at 37°C and pH 1.2 534 days at 20°C and pH 9 100 days at 37°C and pH 9
Biodegradation	0 % after 28 days (not readily biodegradable)
Bioconcentration	BCF = 25.3 (estimated) [2]
Direct Photolysis	Not significant
Log K_{oc}	2.1 (estimated)[2]
Fugacity (Level III Model)	Air = 85 % Water = 8.4 % Soil = 5 % Sediment = 47 %
Persistence[3]	P1 (low)
Bioaccumulation[3]	B1 (low)

[1] FMC Corporation. 2004. Revised Robust Summary and Test Plan for Methallyloxyphenol. http://www.epa.gov/chemrtk/pubs/summaries/methyall/c13458tc.htm.

[2] US 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

[3] 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) Page 60194–60204.

Conclusion: Methallyloxyphenol is a liquid at room temperature with a moderate vapor pressure and high water solubility. It is expected to partition primarily to water and soil in the environment. It is moderately mobile in soil and moderately volatile from moist soil and water. Its rate of hydrolysis is considered negligible under environmental conditions. The rate of vapor-phase photooxidation in the ambient atmosphere is rapid with respect to the hydroxyl radical and moderate with respect to ozone. It did not degrade in a ready biodegradation test; however, based on estimated biodegradability and professional judgment, it is expected to have low persistence in the environment (P1). The estimated bioconcentration factor (BCF) of 25.3 indicates that methallyloxyphenol has a low potential to bioaccumulate (B1).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

(1) Sheepshead minnow (*Cyprinodon variegates*, 10/replicate) were exposed to methallyoxyphenol at measured concentrations of 0, 2.3, 4.4, 8.8, 18 or 38 mg/L under flow-through conditions for 96 hours. Mortality ranged from 5% at 4.4 mg/L to 100% at 18 and 38 mg/L.
96-h LC_{50} = 9.8 mg/L

(2) Atlantic silverside (*Menidia menidia*, 10/replicate) were exposed to methallyoxyphenol at measured concentrations of 0, 0.684, 1.42, 2.96, 6.16 or 11.6 mg/L under flow-through conditions for 96 hours. The mortality was 5% at 0.684 mg/L and 100% at 11.6 mg/L.
96-h LC_{50} = 4.6 mg/L

(3)Marine spot (*Leiostomus* xanthurus, 5/replicate) were exposed to methallyoxyphenol at nominal concentrations of 0, 0.065, 0.125, 0.25, 0.50 or 1.0 mg/L for 96 hours. Partial loss of equilibrium was noted in four out of ten fish at 1.0 mg/L at 24 hours. There was 100% mortality at 1.0 mg/L at 48 hours.
96-h LC_{50} = 0.71 mg/L

Acute Toxicity to Aquatic Invertebrates

(1) *Mysidopsis bahia* (10/replicate) were exposed to methallyoxyphenol at measured concentrations of 0, 527, 660, 1080, 1363 or 2307 µg/L under flow-through conditions for 96 hours.
96-h LC_{50} = 1.327 mg/L

(2) *Mysidopsis bahia* (10/replicate) were exposed to methallyoxyphenol at measured concentrations of 0, 255, 417, 643, 880 and 2255 µg/L under flow-through conditions for 96 hours.
96-h LC_{50} = 1.130 mg/L

(3) *Mysidopsis bahia* (10/replicate) were exposed to methallyoxyphenol at measured concentrations of 67, 138, 257, 495 or 1053 µg/L under flow-through conditions for 96 hours. After 96 hours, mortality ranged from 10% at 67 µg/L to 100% at 1053 µg/L. Partial loss of equilibrium was observed at the 24 hour observation period at 138 µg/L.
48-h LC_{50} = 0.520 mg/L
96-h LC_{50} = 0.201 mg/L

(4) *Mysidopsis bahia* (10/replicate) were exposed to methallyoxyphenol at nominal concentrations of 0.23, 0.39, 0.65, 1.1, 1.8 or 3.0 mg/L under static conditions for 96 hours. After 96 hours, mortality ranged from 10% at and below 0.39 mg/L to 100% at and above 1.8 mg/L.
96-h LC_{50} = 0.81 mg/L

Toxicity to Aquatic Plants

Skeletonema costatum were exposed to methallyloxyphenol (68% purity) at measured concentrations of 0, 3.45, 10.59, 19.43, 37.64 or 76.4 mg/L for 96 hours. Loss of color (chlorophyll) and general fading of cells (representing disintegration of the cell wall and cell death) was noted only at 37.64 mg/L. No viable cell material was found at 74.6 mg/L.
96-h EC_{50} (biomass) = 26.6 mg/L

Conclusion: The acute toxicity of methallyloxyphenol to fish and aquatic invertebrates is high and to aquatic plants is low.

3. Human Health Effects

Acute Oral Toxicity

Sprague-Dawley rats (10/sex/dose) were administered single doses of methallyloxyphenol via gavage at 2000, 2500, 3000, 4000 or 4500 mg/kg-bw (males) or 2500, 2700, 3000 or 4500 mg/kg-bw (females) and observed for 14 days. Predominant clinical signs included decreased locomotion, ataxia, recumbency, exophthalmos, hematuria, lacrimation, oral discharge, and abdominogenital staining. Most signs of toxicity subsided by the 5th day of the study. Gross necropsy findings among decedents included red fluid in the intestines and bladder of several rats. The necropsy of survivals did not reveal any abnormalities.
LD_{50} = 2943 mg/kg-bw

Repeated-Dose Toxicity

The requirement for repeated-dose toxicity endpoint was waived for the purposes of the HPV Challenge Program because methallyloxyphenol is a closed system intermediate.

Reproductive Toxicity

The requirement for reproductive toxicity endpoint was waived for the purposes of the HPV Challenge Program because methallyloxyphenol is a closed system intermediate. However, the sponsor submitted a combined reproductive/developmental toxicity test which is described below in the Developmental Toxicity section.

Developmental Toxicity

In a combined reproductive/developmental toxicity study, Sprague-Dawley rats (group size not indicated) were administered methallyloxypehnol via gavage at 0, 60, 240 or 720 mg/kg-bw/day. Males were exposed from 2 weeks before mating to end of mating (28 days) and females were exposed from 2 weeks before mating through gestation to day 3 post partum (54 days). There was a high incidence of salivation in both sexes at 240 and 720 mg/kg-bw doses. There were no treatment-related changes in body weight, food consumption, necropsy findings, and male reproductive organ weights or histopathological findings. There were no treatment-related changes in precoital time, mating index, fertility index, pregnancy index and reproductive and litter findings such as gestation length, number of live and dead pups at birth, sex ratio, and body weights of live pups.
NOAEL for systemic/reproductive/developmental toxicity = 720 mg/kg-bw/day (based on no effects at the highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
(1) In two separate assays, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to methallyloxyphenol at concentrations from 20 – 5000 ug/plate in the presence and absence of metabolic activation. Mthallyloxyphenol was not mutagenic in any strain in the presence of metabolic activation, but caused an increase in revertants/plate in TA1535 in the absence of metabolic activation. An increase in mutant frequency in TA100 was observed in the absence of metabolic activation; however this increase did not meet the criterion for a positive response due to the high background incidence in this strain. The positive and negative (DMSO) controls were included in the assay and gave appropriate response.
Methallyloxyphenol was mutagenic in these assays.

(2) *Salmonella typhimurium* strain TA1535 was exposed to methallyoxyphenol at concentrations of 2.5, 12.5, 62.5, 312.5, 625, 1250, 2500, 5000 or 10,000 μg/plate in the absence of metabolic activation in a modified Ames assay. No positive controls were used. All concentrations induced an increase in the revertants per plate.
Methallyloxyphenol was mutagenic in this assay.

(3) Mouse lymphoma L5178Y cells were exposed to methallyloxyphenol (64% purity) in the presence and absence of metabolic activation. Concentrations were 0.0006 − 0.0084 μL/mL in the presence of metabolic activation and 0.0013 − 0.0075 μL/mL in the absence of metabolic activation. In the absence of metabolic activation, methallyloxyphenol induced an increase in mutant frequency. In the presence of metabolic activation, there was no increase in mutant frequency.
Methallyloxyphenol was mutagenic in this assay.

(4) Mouse lymphoma L5178Y cells were exposed to methallyloxyphenol (64% purity) in the presence and absence of metabolic activation. Concentrations tested were 0.2 − 3.3 μg/mL in the presence of metabolic activation and 20.0 − 330 μg/mL in the absence of metabolic activation. The test material induced significant increases in the mutant frequency in both the presence and absence of metabolic activation in this assay at concentrations in which cell survival was greater than 10%. The positive and negative (DMSO) controls were included in the assay and gave appropriate response.
Methallyloxyphenol was mutagenic in this assay.

Genetic Toxicity – Chromosomal aberrations

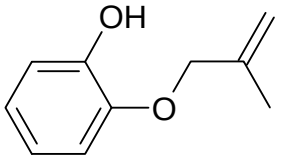
In vivo
Sprague-Dawley rats (5 males/dose) were administered methallyloxyphenol via gavage at 0 (corn oil), 100, 300 or 1000 mg/kg-bw and were sacrificed 6, 24, and 48 hours later. A positive control group of 5 rats received 40 mg/kg-bw cyclophosphamide and were sacrificed after 24 hours. Two hours prior to sacrifice, animals were given a single intraperitoneal injection of 2.0 mg/kg colchicine to arrest cells in metaphase. Bone marrow was collected from both femurs, cells were prepared and analyzed. The test material did not induce an increase in chromosomal aberrations relative to the solvent control.
Methallyloxyphenol did not induce chromosomal aberrations in this assay.

Genetic Toxicity – Other

In an unscheduled DNA synthesis assay, rat primary hepatocytes were exposed to methallyloxyphenol at 0.1, 0.5, 1.0, 5.0, 10, 50, 100 or 500 µg/mL for 24 hours. There was no net increase in the mean net nuclear grain count in cells treated with the test article compared to the solvent control (100 cells counted). The positive controls showed the expected increase in net nuclear grain counts (50 cells counted). Higher doses (not specified) were cytotoxic. **Methallyloxyphenol did not induce unscheduled DNA synthesis in this assay.**

Conclusion: The acute oral toxicity of methallyloxphenol to rats is low. Repeat-dose and reproductive toxicity studies are not required for the HPV Challenge Program because methallyloxphenol is a closed-system intermediate (CSI). A combined reproductive/developmental toxicity study in rats showed no reproductive, developmental, or parental systemic toxicity. Methallyloxphenol was mutagenic *in vitro*, but did not induce chromosomal aberrations *in vivo*.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL Methallyloxyphenol (4790-71-0)**
Structure	
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC_{50} (mg/L)	0.71 mg/L (Marine spot) 4.6 (Atlantic silverslide) 9.8 (Sheepshead minnow)
Aquatic Invertebrates 48-h EC_{50} (mg/L)	0.201 − 1.3 mg/L (*Mysidopsis bahia*)
Aquatic Plants 72-h EC_{50} (mg/L) (biomass)	26.6
Summary of Human Health Data	
Acute Oral Toxicity LD_{50} (mg/kg-bw)	2943
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Data not required based on CSI.
Reproductive/Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day) Systemic/Reproductive/Developmental Toxicity	NOAEL = 720 (highest dose tested)
Genetic Toxicity – Gene Mutation *In vitro*	Positive
Genetic Toxicity – Chromosomal Aberrations *In vitro*	Negative
Genetic Toxicity – Other Unscheduled DNA Synthesis	Negative

Screening Level Exposure Characterization for HPV Challenge Chemical

Phenol, 2-[(2-methyl-2-propenyl)oxy]-

CAS # 4790-71-0

September 2008

Prepared by

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Chemical Engineering Branch
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Screening Level Exposure Characterization

Phenol, 6-tert-butyl-3-(chloromethyl)-2,4-dimethyl (CAS # 4790-71-0)

Non-CBI Executive Summary

There are no 2002 or 2006 Inventory Update Rule (IUR) submissions for phenol, 6-tert-butyl-3-(chloromethyl)-2,4-dimethyl (CAS # 4790-71-0). A pre-manufacture notification for this chemical was submitted to EPA, and this notification contains data and information that are claimed confidential.

Potential for Exposures to Human and the Environment:

Based on the information considered and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a low relative ranking for each of the potentially exposed groups (including workers, general population, consumers and children) and the environment. In 2003, EPA reviewed the information in the HPV submission and test plan and determined that the HPV chemical satisfied the guidance to demonstrate that the chemical is a closed system intermediate.[12] The use of this chemical solely as an intermediate to produce other chemicals in enclosed vessels is expected to reduce the potential for worker exposures. Wastewater containing the chemical is treated on-site before discharge to a publicly-owned wastewater facility for further treatment. There are no 2002 or 2006 IUR submissions for this chemical. No information on commercial/consumer uses is available in the IUR or any other sources.

[12] USEPA, 2003. EPA Comments on Chemical RTK HPV Challenge Submission. Letter dated July 24, 2002. http://www.epa.gov/chemrtk/pubs/summaries/methyall/c13458ct.pdf. Accessed June 20, 2008.