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

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol (CASRN 23500-79-0) (CA Index Name: Phenol, 3-(chloromethyl)-6-(1,1-dimethylethyl)-2,4-dimethyl-)

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

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0)
[9th CI Name: 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol]

September 2008

Prepared by

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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0)

1. Physical-Chemical Properties and Environmental Fate

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is a solid at room temperature and has a moderate vapor pressure. The water solubility of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol cannot be accurately measured because the compound is unstable in water. It is expected to be minimally mobile in soil. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is considered to have low-to-moderate volatility from moist soil and water given its Henry's Law constant; however, the rapid rate of hydrolysis suggests volatilization is not an important environmental fate process. Its rate of hydrolysis is considered rapid under environmental conditions (pH 5-9). The rate of vapor-phase photooxidation in the ambient atmosphere is moderate. Its rate of biodegradation was low based on the results of a ready biodegradation test; however, this study likely measured the rate of biodegradation of the hydrolysis products not 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol. Due to the rapid rate of hydrolysis, 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is judged to have low persistence potential (P1) and low bioaccumulation potential (B1).

2. Hazard Characterization

Aquatic Organism Toxicity. The acute toxicity of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol to fish and aquatic invertebrates is low and to aquatic plants is moderate.

Human Health Toxicity. Acute oral and dermal toxicity of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is low in rats and rabbits, respectively. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is highly irritating to rabbit skin and eyes. A combined oral repeated-dose/reproductive/developmental toxicity study in rats showed high systemic and reproductive toxicity in the parental females. There was no developmental toxicity. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol did not induce gene mutation in bacteria. Chromosomal aberrations were observed *in vitro*, but not *in vivo*.

3. Exposure Characterization

Phenol, 6-*tert*-butyl-3-(chloromethyl)-2, 4-dimethyl-, also known as 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol, has an aggregated production and/or import volume in the United States of > 1 million to 10 million pounds. Non-confidential Inventory Update Rule (IUR) information for this chemical indicates that it is used as an intermediate. No commercial/ consumer uses were reported in the IUR submissions or in the Hazardous Substances Data Bank. Information submitted as part of the High Production Volume (HPV) Challenge Program indicates that phenol, 6-*tert*-butyl-3-(chloromethyl)-2, 4-dimethyl- is used in the chemical industry for synthesis.

Potential for Exposures to Human and the Environment:
Based on the information considered, including IUR data and information from the HPV Challenge Program information cited above, 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. The Agency has reviewed the information in the HPV submission or test plan and determined that the information satisfies the guidance to demonstrate that the chemical is a closed system intermediate. The chemical is manufactured and processed in systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting this chemical in accordance with IUR requirements.

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 Challenge Program submission or test plan and determined that the HPV chemical satisfies the guidance to demonstrate that the chemical is a closed-system intermediate (CSI). 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is manufactured and processed in closed systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting this chemical in accordance with IUR requirements. 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

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0)
[9th CI Name: Phenol, 3-(chloromethyl)-6-(1,1-dimethylethyl)-2,4-dimethyl-]

September 2008

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SCREENING-LEVEL HAZARD CHARACTERIZATION
6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0)

Introduction

The sponsor, Cytec Industries Inc., submitted a Test Plan and Robust Summaries to EPA for 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol (CAS No. 23500-79-0; 9th CI name: phenol, 3-(chloromethyl)-6-(1,1-dimethylethyl)-2,4-dimethyl-) on May 30, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on July 8, 2003 (http://www.epa.gov/chemrtk/pubs/summaries/6tbutyl3/c14526tc.htm). EPA comments on the original submission were posted to the website on November 14, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on November 25, 2003 and February 28, 2005, which were posted to the ChemRTK website on January 13, 2004 and May 10, 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 2003 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 stated that 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is a commercially-isolated material that contains 11 – 13% methyl isobutyl ketone and 5.5% 6-*tert*-butyl-2,4-dimethyl phenol. The sponsor also claimed 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol to be a closed system intermediate (CSI) chemical and submitted adequate information to support this claim in its revised submissions. EPA considered that the submitter's information is adequate to meet the guidance for claiming 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol as a closed-system intermediate. Based on the CSI status for this chemical (the commercial product), the requirement for repeated-dose toxicity and reproductive toxicity endpoints have been waived under the HPV Challenge Program. However, the sponsor provided data for a combined repeated-dose/reproductive/developmental toxicity screening test to address the developmental toxicity endpoint and this information has been summarized in this hazard assessment.

Hazard Characterization

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is a solid at room temperature and has a moderate vapor pressure. The water solubility of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol cannot be accurately measured because the compound is unstable in water. It is expected to be minimally mobile in soil. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is considered to have low-to-moderate volatility from moist soil and water given its Henry's Law constant; however the rapid rate of hydrolysis suggests volatilization is not an important environmental fate process. Its rate of hydrolysis is considered rapid under environmental conditions (pH 5-9). The rate of vapor-phase photooxidation in the ambient atmosphere is moderate. Its rate of biodegradation was low based on the results of a ready biodegradation test; however, this study likely measured the rate of biodegradation of the hydrolysis products not 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol. Due to the rapid rate of hydrolysis, 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is judged to have low persistence potential (P1) and low bioaccumulation potential (B1).

The acute toxicity of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol to fish and aquatic invertebrates is low and to aquatic plants is moderate.

Acute oral and dermal toxicity of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is low in rats and rabbits, respectively. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is highly irritating to rabbit skin and eyes. Repeated-dose and reproductive toxicity data were not required for the HPV Challenge Program because 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is a closed system intermediate. However a combined oral repeated-dose/reproductive/developmental

toxicity study in rats was submitted and showed high systemic and reproductive toxicity in the parental females. There was no developmental toxicity. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol did not induce gene mutations in bacteria. Chromosomal aberrations were observed *in vitro* but not *in vivo*.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol 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

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is a solid at room temperature. It has moderate vapor pressure. Water solubility cannot be accurately measured because this chemical substance is unstable in water.

Table 1a. Physical-Chemical Properties of 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol[1]

Property	Value
CAS No.	23500-79-0
Molecular Weight	226.75
Physical State	Solid
Melting Point	45°C (measured)
Boiling Point	ca. 320°C at 1013 hPa (estimated)
Vapor Pressure	0.00042 hPa at 25°C (measured)
Henry's Law Constant	3.43×10^{-6} (estimated)[2]
Water Solubility	3.46 mg/L at 20°C, pH 1.8-1.9 (measured; lower limit) 10.19 mg/L at 25°C (estimated)[2]
Log K_{ow}	5.32 (estimated)[2]

[1] Cytec Industries Inc. 2005. Revised Robust Summary and Test Plan for 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol. http://www.epa.gov/chemrtk/pubs/summaries/6tbutyl3/c14526tc.htm.

[2] US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

Environmental Fate Characterization

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is expected to partition primarily to soil and sediment, according to the results of a Level III fugacity model. It is minimally mobile in soil. The Henry's Law constant indicates that it has low-to-moderate volatility from moist soil and water; however, the rapid rate of hydrolysis suggests that volatilization is not an important environmental fate process. Its rate of hydrolysis is considered rapid under environmental conditions (pH 5-9). The rate of vapor-phase photooxidation in the ambient atmosphere is moderate. Its rate of biodegradation was low based on the results of a ready biodegradation test; however, this study likely measured the rate of biodegradation of the hydrolysis products, not 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol. Due to the rapid rate of hydrolysis, 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is judged to have low persistence potential (P1) and low bioaccumulation potential (B1).

Table 1b. Environmental Fate Characteristics of 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol[1]	
Property	**Value**
Photodegradation Half-life	8.9 hours (estimated)[2]
Biodegradation	7 % after 28 days (measured; not readily biodegradable)
Hydrolysis Half-life	< 9.8 min at pH 4 and 2 °C < 6.4 min at pH 7 and 25°C Spontaneous at pH 1.2 and 37°C Spontaneous at pH 9 and 25°C
Bioconcentration	BCF = 795 (estimated)[2]
K_{oc}	15,850 (estimated)[2]
Fugacity (Level III Model)[2]	Air = 0.283 % Water = 10.4 % Soil = 52.6 % Sediment = 36.7 %
Persistence[3]	P1 (low)
Bioaccumulation[3]	B1 (low)

[1] Cytec Industries Inc. 2005. Revised Robust Summary and Test Plan for 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol. http://www.epa.gov/chemrtk/pubs/summaries/6tbutyl3/c14526tc.htm.

[2] US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. 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: 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is a solid at room temperature and has a moderate vapor pressure. The water solubility of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol cannot be accurately measured because the compound is unstable in water. It is expected to be minimally mobile in soil. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is considered to have low-to-moderate volatility from moist soil and water given its Henry's Law constant; however the rapid rate of hydrolysis suggests volatilization is not an important environmental fate process. Its rate of hydrolysis is considered rapid under environmental conditions (pH 5-9). The rate of vapor-phase photooxidation in the ambient atmosphere is moderate. Its rate of biodegradation was low based on the results of a ready biodegradation test; however, this study likely measured the rate of biodegradation of the hydrolysis products not 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol. Due to the rapid rate of hydrolysis, 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is judged to have low persistence potential (P1) and low bioaccumulation potential (B1).

2. Environmental Effects – Aquatic Toxicity

The test substance is not stable in the aquatic environment (hydrolysis half-life < 6.4 minutes at 25°C). During the aquatic toxicity testing, the aquatic organisms were actually exposed to (6-*tert*-butyl-3-(hydroxymethyl)-2,4-xylenol, the hydrolysis product of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol.

Acute Toxicity to Fish

Rainbow trout (*Oncorhynchus mykiss,* 20/concentration) were exposed to 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol at measured concentrations of 8.2, 10, 19, 28, or 47 mg/L under semi-static conditions (daily renewal) for 96 hours. Mortality was 100% at 47 mg/L within 3 hours of exposure and at 28 mg/L after 6 hours of exposure. At 19 mg/L all fish died after 48 hours of exposure. Mortality was 50% at 10 mg/L after 96 hours. None of the fish died in control and 8.2 mg/L groups. Loss of equilibrium was noted at 10, 19 and 28 mg/L and moribund condition at 47 mg/L.

96-h LC_{50} = 11 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*, 10/replicate) were exposed to 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol at measured concentrations of 0.56, 1.0, 1.8, 3.2, 5.8, 10, 18, 30 or 51 mg/L under static conditions for 48 hours. No immobilization was seen at concentrations $\leq$ 3.2 mg/L. At 48 hours, 25, 45, 60 and 90% immobilization was seen at 5.8, 10, 30, and 51 mg/L, respectively.
48-h EC_{50} = 19 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol at measured concentrations of 5.1, 10.4, 21, 39, and 70 mg/L under static conditions for 72 hours. Significant effects on area under growth were seen at and above 10.4 mg/L. No effect was seen at 5.1 mg/L.
72-h EC_{50} (growth) = 6.6 mg/L

Conclusion: The acute toxicity of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol to fish and aquatic invertebrates is low and to aquatic plants is moderate.

3. Human Health Effects

Acute Oral Toxicity

(1) Wistar rats (5 males/dose) were administered 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol via gavage at 5.0 or 10.0 mL/kg-bw (approximately 5220 or 10,440 mg/kg-bw) and observed for up to 14 days. Mortality occurred in the high-dose group within 3 days of dosing. All animals had a sluggish, unsteady gait 1 hour after treatment. All animals in the low-dose group recovered within 2 days. Animals that died exhibited distended, gas-filled and injected stomachs with glandular portions mottled pink and yellow, red kidney medullae, distended, liquid, blood-filled and injected intestines that were yellow and red in areas, and red adrenals. Survivors exhibited stomachs adhered to abdominal walls and livers.
LD_{50} ~ 8050 mg/kg-bw

(2) Sprague-Dawley rats (3/sex) were administered 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol via gavage at 2000 mg/kg-bw and observed for 14 days. No mortality occurred. Hunched posture and diarrhea were observed in all animals. Lethargy and piloerection were observed in males. All animals recovered within 2 – 4 days of dosing. No abnormal findings were observed at necropsy.
LD_{50} > 2000 mg/kg-bw

Acute Dermal Toxicity

New Zealand White rabbits (2-4 males/dose) were administered 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol dermally on to clipped skin under occluded conditions for 24 hours and observed for 14 days. Three groups of four rabbits were administered 3.2, 6.4 or 10.0 mL/kg-bw (approximately 3341, 6682 or 10,440 mg/kg-bw) and two rabbits were administered 0.8 mL/kg-bw (approximately 835 mg/kg-bw). Mortality occurred at 3.2 and 10.0 mL/kg-bw. Erythema, edema, ecchymosis, areas of necrosis and scabs were observed at the application site. Animals that died exhibited red kidneys.
LD_{50} ~ 10,420 mg/kg-bw

Repeated-Dose Toxicity

In a combined repeated-dose/reproductive/developmental toxicity screening test, Sprague-Dawley rats (10/sex/dose) were administered 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol (in polyethylene glycol 400) via gavage at 0, 15, 50 or 200 mg/kg-bw/day. Males were administered the test substance daily for a total of 34 days during the pre-mating and mating periods. Females were dosed daily from 43 to 57 days during pre-mating, mating, gestation, and up until lactation day 3. Dose-related mortality included one, two and five female deaths in the 15, 50 and 200 mg/kg-bw/day, respectively. The deaths of one male and one female at the high dose were noted as dosing accidents.

High-dose males exhibited a 45 – 65% decrease in body-weight gain and an 8 – 10% decrease in weekly mean body weight throughout the study. Reductions in female body weight gains were noted at the high dose during the pre-mating period and at all doses during the gestation period. Decreased food consumption and efficiency were noted in high-dose males and females during the pre-mating period. Throughout gestation, reduced food consumption was noted in females at 50 and 200 mg/kg-bw/day. Clinical observations included lung noise, diarrhea, hunched over posture and stained fur in males at the high-dose. During the pre-mating period, stained fur, diarrhea, hunched over posture and irregular respiration was observed in high-dose females. During the gestation period, females at all doses exhibited clinical signs associated with dystocia, which included dehydration, diarrhea, immobility/lethargy, pallor, ptosis and stained/wet fur. Irregular respiration and lung noise were noted in high-dose females during the gestation and lactation periods. Test substance-related decreases in hindlimb grip strengths (males only) and motor activity (males and females) were observed at the high-dose level. No other treatment-related effects were noted. A treatment-related increase in cholesterol concentration was noted in some males of all treatment groups, some females at 15 or 50 mg/kg-bw/day and in all high-dose females. There was an increase in liver weights in males and females treated at and above 50 mg/kg-bw/day. Mean relative liver weights were increased 7, 16 and 45% in males and 3, 11 and 21% in females at 15, 50 and 200 mg/kg-bw/day, respectively. The absolute and relative liver weights were markedly increased at the high-dose. Minimal hypertrophy of centrilobular hepatocytes were observed in the livers of high-dose females and mid- and high-dose males. Minimal hypertrophy of thyroid follicular cells characterized by an increase in the height of the columnar epithelium was noted in high-dose males and females. Follicles were decreased in size, irregular in shape and contained a decreased amount of normal pink colloid.
LOAEL = 15 mg/kg-bw/day (based on mortality and reduced body weight of females during gestation)
NOAEL = Not established

Reproductive/Developmental Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test described previously, maternal toxicity was noted as reduction in body weight gain during gestation at all doses. A total of eight female rats died, six of which were dystocia-related deaths and occurred at all doses. There were no effects on the mating and fertility indices at any dose. No reproductive effects were observed in males. There were no adverse developmental effects, embryo lethality or gross abnormalities at any dose.
LOAEL (systemic toxicity) = 15 mg/kg-bw/day (based on mortality and reduced body weight of females during gestation)
NOAEL (systemic toxicity) = Not established
LOAEL (reproductive toxicity) = 15 mg/kg-bw/day (based on clinical observations associated with dystocia)
NOAEL (reproductive toxicity) = Not established
NOAEL (developmental toxicity) = 200 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 were exposed to 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol at concentrations of 0, 5, 15, 50, 150, 500 or 1500 µg/plate and *Escherichia coli* strain WP2*uvr*A was exposed at concentrations of 0, 50, 150, 500, 1500 or 5000 µg/plate in the absence and presence of metabolic activation. Positive controls were tested concurrently and responded appropriately. Cytotoxicity was observed at 500 µg/plate in *S. typhimurium* strains in the absence of metabolic activation and at 5000 µg/plate for *E. coli* in both the absence and presence of activation.
6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Human peripheral lymphocytes were exposed to 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol at concentrations of 0, 17.5, 35, 70, 105, 140 or 280 µg/mL in the absence of metabolic activation and 0, 35, 70, 140, 210, 280 or 420 µg/mL in the presence of metabolic activation. Positive controls were tested concurrently and responded appropriately. The cytotoxic concentration was 140µg/mL. There was an increase in the number of cells with

aberrations at 105 and 140µg/mL in the absence of metabolic activation and at 140µg/mL in the presence of metabolic activation.
6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol induced chromosomal aberrations in this assay.

In vivo
Male CD-1 mice (seven/dose) were administered 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol via gavage at 0, 250, 500 or 1000 mg/kg-bw. An additional high-dose, negative-control and positive-control groups (five mice) were included in the study. No mortality occurred. Clinical signs included hunched posture, lethargy and ptosis at doses of ≥ 250 mg/kg-bw. One group of mice from each of the doses, the two vehicle-control groups and the positive-control group were all sacrificed 24 hours after dosing. The additional high-dose group was sacrificed 48 hours after dosing. There were no changes in the number of micronucleated PCEs.
6-*tert*-Butyl-3-(chloromethyl)-2, 4-xylenol did not induce chromosomal aberrations in this assay.

Additional Information

Skin Irritation

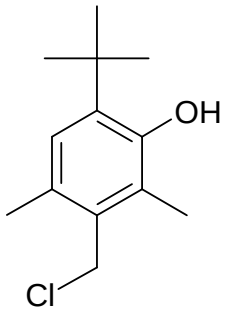
Rabbits (6, sex not specified) were administered undiluted 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol (0.5 mL) dermally on to the intact and abraded skin under semi-occluded conditions for an unspecified period of time. Dermal reactions were evaluated 24 and 72 hours after application and were scored according to the Draize method. The structure of the tissue at the site of contact was destroyed or changed irreversibly in ≤ 24 hours. The mean values for erythema and edema at both intact and abraded sites at 72 hours were at the maximum possible value of 4.00.
6-*tert*-Butyl-3-(chloromethyl)-2, 4-xylenol was highly irritating to rabbit skin in this study.

Eye Irritation

Rabbits (6, sex not specified) were instilled undiluted 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol (0.1 mL) into the conjunctival sac of one eye of each rabbit. Ocular reactions were evaluated for up to 72 hours and were scored according to the Draize method. Irreversible changes/tissue destruction was observed within 24 hours of treatment. Observations at all intervals included discernable opacity or ulceration of the cornea, inflammation of the iris, slight circumcorneal injection, red appearance of the conjunctivae with individual vessels not easily discernable, swelling of the conjunctivae (excluding cornea and iris) and partial eversion of the lids.
6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol was highly irritating to rabbit eyes in this study.

Conclusion: Acute oral and dermal toxicity of 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is low in rats and rabbits, respectively. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol is highly irritating to rabbit skin and eyes. Repeated-dose and reproductive toxicity data were not required for the HPV Challenge Program because 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol is a closed system intermediate. However, a combined oral repeated-dose/ reproductive/ developmental toxicity study in rats was submitted and showed high systemic and reproductive toxicity in the parental females. There was no developmental toxicity. 6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol did not induce gene mutations in bacteria. Chromosomal aberrations were observed *in vitro* but not *in vivo*.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL** **6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol** **(23500-79-0)**
Structure	
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish **96-h LC_{50} (mg/L)**	11
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	19
Aquatic Plants **72-h EC_{50} (mg/L)**	6.6
Summary of Human Health Data	
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	> 2000
Acute Dermal Toxicity **LD_{50} (mg/kg-bw)**	~ 10,420
Repeated-Dose/Reproductive/Developmental Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)** **Systemic Toxicity** **Reproductive Toxicity** **Developmental Toxicity**	 NOAEL = Not established (57-d) LOAEL = 15 (57-d) NOAEL = Not established LOAEL = 15 NOAEL = 200
Genetic Toxicity – Gene Mutation ***In vitro***	Negative
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Positive
Genetic Toxicity – Chromosomal Aberrations ***In vivo***	Negative
Additional Information **Skin Irritation** **Eye Irritation**	 Highly irritating Highly irritating

Screening Level Exposure Characterization for HPV Challenge Chemical

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol

CAS # 23500-79-0

September 2008

Prepared by

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Screening Level Exposure Characterization

6-*tert*-Butyl-3-(chloromethyl)-2,4-xylenol (CAS # 23500-79-0)

Non-CBI Executive Summary

Phenol, 6-*tert*-butyl-3-(chloromethyl)-2, 4-dimethyl- (CAS # 23500-79-0), also known as 6-*tert*-butyl-3-(chloromethyl)-2,4-xylenol, has an aggregated production and/or import volume in the United States of > 1 million to 10 million pounds.[12] Non-confidential Inventory Update Rule (IUR) information for this chemical indicates that it is used as an intermediate. No commercial/ consumer uses were reported in the IUR submissions or in the Hazardous Substances Data Bank.[13] Information submitted as part of the High Production Volume (HPV) Challenge Program indicates that phenol, 6-*tert*-butyl-3-(chloromethyl)-2, 4-dimethyl- is used in the chemical industry for synthesis.[14]

Potential for Exposures to Human and the Environment:

Based on the information considered (including IUR data and information from the HPV Challenge Program information cited above) and in combination with 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. The Agency has reviewed the information in the HPV Challenge Program submission or test plan and determined that the information satisfies the guidance to demonstrate that the chemical is a closed system intermediate.[15] Due to the rapid rate of hydrolysis, the chemical is judged to have low persistence potential (P1) and low bioaccumulation potential (B1).[16] The chemical is manufactured and processed in systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting this chemical in accordance with IUR requirements.

[12] USEPA, 2006. Partial Updating of TSCA Chemical Inventory.
[13] HSDB, 2008. Hazardous Substances Data Bank. Accessed June 04, 2008. http://toxnet.nlm.nih.gov/
[14] USEPA, 2008. High Production Volume Information System (HPVIS) and Screening Information Data Sets (SIDS). Accessed May 22, 2008.
[15] USEPA, 2003. EPA Comments on Chemical RTK HPV Challenge Submission. Letter dated November 11, 2003. Accessed June 13, 2008. http://www.epa.gov/chemrtk/pubs/summaries/6tbutyl3/c14526tc.htm
[16] USEPA, 2008. Screening-Level Hazard Characterization for Phenol, 6-tert-butyl-3-(chloromethyl)-2, 4-dimethyl- (CAS # 23500-79-0).

Non Confidential IUR Data Summary: Phenol, 6-*tert*-butyl-3-(chloromethyl)-2, 4-dimethyl- (CAS # 23500-79-0)

Manufacturing/Import Information

Production and import volume:	> 1 million to 10 million pounds
List of non-CBI companies/ sites:*	Cytec Industries Inc. / Willow Island, WV
Maximum number of exposed workers:**	less than 100 (including those of manufacturing, industrial processing and use)
Highest non-CBI maximum concentration:	confidential
Non-CBI physical forms:*	liquid

* Note: There may be other companies/sites and physical forms that are claimed as confidential business information (CBI).
** There may be additional potentially exposed industrial workers that are not included in this estimate since not all submitters were required to report on industrial processing and use and/or there may be at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions.

Table 1
Industrial Processing and Use Information
Reported in 2006 IUR

Processing Activity	Industrial Sector	Functional Use
Processing as a reactant	Other Clothing Stores***	Intermediates

Table 2
Commercial/ Consumer Uses
Reported in 2006 IUR

Commercial/ Consumer Product Category Description	Highest maximum concentration range	Use in Children's Products
None reported		

*** Erroneous numerical code contained in submission.