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

2,4,6-Trimethylphenol (CAS No. 527-60-6)
[9th CI Name: Phenol, 2,4,6-trimethyl-]

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

2,4,6-Trimethylphenol (CAS No. 527-60-6)
[9th CI Name: Phenol, 2,4,6-trimethyl-]

July 2008

Prepared by

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Economics, Exposure and Technology Division
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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR
2,4,6-Trimethylphenol (CAS No. 527-6--6)

1. Physical-Chemical Properties and Environmental Fate

2,4,6-Trimethylphenol is a solid in the form of a powder. It has high water solubility and moderate vapor pressure. It has moderate mobility in soil, the rate of hydrolysis is negligible and bioconcentration is low. 2,4,6-Trimethylphenol did not pass a ready biodegradation test; however the rates of photodegradation and biodegradation in the environment are estimated to be moderate. 2,4,6-Trimethylphenol is expected to have low persistence (P1) and low bioaccumulation potential (B1).

2. Hazard Characterization

Aquatic Organism Toxicity. The evaluation of the available aquatic toxicity data indicates the acute hazard to fish, aquatic invertebrates and aquatic plants is moderate.

Human Health Toxicity. Acute oral and dermal toxicity of 2,4,6-trimethylphenol is low. The acute dermal toxicity test noted 2,4,6-trimethylphenol is irritating to skin. Repeated exposures of rats via the oral route in a 10-day range finding study affected body weight and body weight gains at high doses. In a combined repeated-dose/reproductive/developmental toxicity screening test in rats, there was no evidence of toxicity at the highest dose tested. 2,4,6-Trimethylphenol was negative in an *in vivo* mouse micronucleus test and bacterial mutagenicity tests, but results from an *in vitro* mammalian cell gene mutation test were equivocal. *In vitro*, 2,4,6-trimethylphenol was positive in a test for structural chromosomal aberrations in mammalian cells in the presence of metabolic activation.

The potential health hazard of 2,4,6-trimethylphenol is low.

3. Exposure Characterization

2, 4, 6-Trimethylphenol has an aggregated production and/or import volume in the United States of 1 to 10 million pounds. Non-confidential information in the IUR indicated that the chemical is primarily used as a solvent in paints and coatings. The HPV Challenge submission for 2, 4, 6-trimethylphenol states that the chemical is used as a component in solvent formulation for either polyamide or polyurethane based resin to coat wire. There were no consumer uses reported under the IUR.

Exposure to the General Population and the Environment. It is likely that there would be some releases to water and/or air during manufacturing, processing, and industrial use. 2, 4, 6-Trimethylphenol was found in quantifiable amounts in air, ground water, and in the effluent of a petroleum refinery and publicly owned treatment works. Based on the information considered – reported uses and the Agency's expert judgment - EPA identifies, for purposes of risk-based prioritization, a medium potential that the general population and the environment might be exposed to this chemical.

Exposure to Workers. Based on the information considered (including IUR data and information from the HPV submission) and in combination with Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a high relative ranking for the potential worker exposure. Although 2, 4, 6-trimethylphenol is a solid at room temperature, it is manufactured in liquid form. The vapor pressure is 0.05 mm Hg and therefore workers could be exposed to vapors. In addition, workers could be exposed to mists based on uses in spray paints and coatings.

Exposure to Consumers. There were no consumer uses reported under the IUR. Therefore, EPA identifies, for the purposes of risk-based prioritization, a low potential that consumers might be exposed to this chemical.

Exposure to Children. There were no consumer uses in children's products reported under the IUR. Therefore, EPA identifies, for the purposes of risk-based prioritization, a low potential that children might be exposed to this chemical.

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 Summary and Rationale

Potential Risk to Aquatic Organisms from Environmental Releases (MEDIUM CONCERN). EPA identifies a medium potential for exposure to aquatic organisms from environmental releases. In addition, 2,4,6-trimethylphenol was found in quantifiable amounts in air, ground water, and other environmental samples. A moderate acute aquatic hazard considered in combination with the environmental fate characteristics of low persistence and bioaccumulation suggests a medium concern for potential risk to aquatic organisms from environmental releases.

Potential Risk to the General Population from Environmental Releases (LOW CONCERN). EPA identifies a medium potential for exposure to the general population from environmental releases. In addition, 2,4,6-trimethylphenol was found in quantifiable amounts in air, ground water, and other environmental samples. The potential human health hazard is expected to be low due to the lack of specific toxicity to animals following exposure to high doses. The low hazard and the environmental fate characteristics of low persistence and bioaccumulation considered together suggest a low concern for potential risk to the general population from environmental releases.

Potential Risk to Workers (LOW CONCERN). EPA identifies a high potential for worker exposure. The potential human health hazard is expected to be low due to the lack of specific toxicity to animals following exposure to high doses. However, there is the potential for skin irritation at high concentrations. Adherence to standard good industrial hygiene practices (gloves, respirators, goggles and other protective clothing) to prevent irritation will limit the

exposure of workers. Therefore, taken together, the available information suggests a low concern for potential risks to workers.

Potential Risk to Consumers from Known Uses (LOW CONCERN). EPA identifies a low potential that consumers may be exposed. The potential human health hazard is expected to be low due to the lack of specific toxicity to animals following exposure to high doses. Therefore, taken together, the available information suggests a low concern for potential risks to consumers.

Potential Risk to Children (LOW CONCERN). EPA identifies a low potential that children may be exposed. The potential human health hazard is expected to be low due to the lack of specific toxicity to developing animals following exposure to high doses. Therefore, taken together, the available information suggests a low concern for potential risks to children.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

2,4,6-Trimethylphenol (CAS No. 527-60-6)
[9th CI Name: Phenol, 2,4,6-trimethyl-]

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS SCREENING-LEVEL HAZARD CHARACTERIZATION 2,4,6-Trimethylphenol (CAS No. 527-60-6)

Introduction

The sponsor, General Electric Company, submitted a Test Plan and Robust Summaries to EPA for 2,4,6-trimethylphenol (CAS No 527-60-6; 9th CI name: Phenol, 2,4,6-trimethyl-) on December 30, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on January 30, 2003 (http://www.epa.gov/chemrtk/pubs/summaries/246trime/c14218tc.htm). EPA comments on the original submission were posted to the website on June 16, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 5, 2003 and December 29, 2005, which were posted to the ChemRTK website on September 5, 2003 and March 16, 2006, 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 April 2008: the NLM databases (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, ATSDR, 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 toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Hazard Characterization

2,4,6-Trimethylphenol is a solid in the form of a powder. It has high water solubility and moderate vapor pressure. It has moderate mobility in soil, the rate of hydrolysis is negligible and bioconcentration is low. 2,4,6-Trimethylphenol did not pass a ready biodegradation test; however the rates of photodegradation and biodegradation in the environment are estimated to be moderate. 2,4,6-Trimethylphenol is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of 2,4,6-trimethylphenol to aquatic organisms is moderate.

Acute oral and dermal toxicity of 2,4,6-trimethylphenol is low. The acute dermal toxicity test noted 2,4,6-trimethylphenol is irritating to skin. Repeated exposures of rats via the oral route in a 10-day range finding study affected body weight and body weight gains at high doses. In a combined repeated-dose/reproductive/developmental toxicity screening test in rats, there was no evidence of toxicity at the highest dose tested. 2,4,6-Trimethylphenol was negative in an *in vivo* mouse micronucleus test and bacterial mutagenicity tests, but results from an *in vitro* mammalian cell gene mutation test were equivocal. *In vitro*, 2,4,6-trimethylphenol was positive in a test for structural chromosomal aberrations in mammalian cells in the presence of metabolic activation.

The potential health hazard of 2,4,6-trimethylphenol is low.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of 2,4,6-trimethylphenol are summarized in Table 1a, while its environmental fate properties are provided in Table 1b. The structure of the compound is provided in the Appendix.

Physical-Chemical Properties Characterization

2,4,6-Trimethylphenol is a solid at room temperature, with high water solubility and moderate vapor pressure.

Table 1a. Physical-Chemical Properties of 2,4,6-Trimethylphenol[1]

Property	Value
CAS No.	527-60-6
Molecular Weight	136.19
Physical State	Solid (powder)
Melting Point	72°C (measured); 73°C (measured)
Boiling Point	221°C (measured); 220°C (measured)
Vapor Pressure	0.05 mm Hg @ 25°C (measured); 3.86 Pa at 25.2°C (measured)
Water Solubility	1.01×10^3 mg/L (measured); 1.2 g/L (measured)
Henry's Law Constant	3.1×10^{-6} atm-m^3/mole (estimated)[2]
Log K_{ow}	2.73 (measured)

[1] General Electric Company. 2005. U.S. High Production Volume (HPV) Chemical Challenge Program. Robust Summary for 2,4,6-Trimethylphenol. http://www.epa.gov/chemrtk/pubs/summaries/246trime/c14218tc.htm

[2] USEPA. 2008. EPI Suite™ (version 3.20), PC-Computer software developed by EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.

Environmental Fate Characterization

Based on its vapor pressure, 2,4,6-trimethylphenol will exist in the vapor phase in the atmosphere. In the atmosphere, 2,4,6-trimethylphenol has an estimated half-life of 8 hours due to photooxidation with hydroxyl radicals. Volatilization of 2,4,6-trimethylphenol is considered slow to moderate based on its Henry's Law constant. It has moderate mobility in soil, does not bioaccumulate, and hydrolysis is negligible at environmental pH. 2,4,6-Trimethylphenol was not readily biodegradable in an aerobic screening test, but the rate of biodegradation in the environment is judged to be moderate. 2,4,6-Trimethylphenol is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 1b. Environmental Fate Characteristics of 2,4,6-trimethylphenol [1]	
Property	**Value**
Photodegradation Half-life	8 hours (estimated)
Direct Photolysis	Not significant
Hydrolysis Half-life	Not susceptible under environmental conditions
Biodegradation	11.3% at 28 days (not readily biodegradable)
Bioconcentration	BCF = 3 – 10 (measured)[2]
Log K_{oc}	700 (estimated)[2]
Fugacity (Level III Model)[3]	Air = 0.773% Water = 31.7% Soil = 67.2% Sediment = 0.336%
Persistence	P1 (low)[4]
Bioaccumulation	B1 (low)[4]

[1]General Electric Company. 2005. U.S. High Production Volume (HPV) Chemical Challenge Program. Robust Summary for 2,4,6-Trimethylphenol. http://www.epa.gov/chemrtk/pubs/summaries/246trime/c14218tc.htm
[2]HSDB. 2008. Hazard Substances Data Base. Accessed March 6, 2008. http://toxnet.nlm.nih.gov/.
[3] USEPA. 2008. EPI Suite™ (version 3.20), PC-Computer software developed by EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.
[4] FR 1999, Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) Page 60194-60204.

Conclusion: 2,4,6-Trimethylphenol is a solid in the form of a powder. It has high water solubility and moderate vapor pressure. It has moderate mobility in soil, the rate of hydrolysis is negligible and bioconcentration is low. 2,4,6-Trimethylphenol did not pass a ready biodegradation test; however the rates of photodegradation and biodegradation in the environment are estimated to be moderate. 2,4,6-Trimethylphenol is expected to have low persistence (P1) and low bioaccumulation potential (B1).

2. Environmental Effects - Aquatic Toxicity

Acute Toxicity to Fish

Rainbow trout *(Oncorhynchus mykiss)* were exposed to 2,4,6-trimethylphenol at nominal concentrations of 0, 0.8, 1.7, 3.8, 8.3, 18.2 or 40 mg/L under static conditions for 96 hours. Analysis of the 0.8, 8.3 and 40 mg/L treatment solutions showed the measured concentrations were within 20% of the nominal concentrations. All fish at 18.2 and 40 mg/L died within 3 hours of exposure.
96-h LC_{50} = 9.7 mg/L

Acute Toxicity to Aquatic Invertebrates

(1) *Daphnia magna* were exposed to 2,4,6-trimethylphenol at measured concentrations of 0, 0.8, 1.7, 3.8, 8.3, 18.2 or 40 mg/L under static conditions for 24 hours. A subset of test solutions were measured at the start and end of the experiment.
24-h EC_{50} = 3.5 mg/L

(2) *Daphnia magna* were exposed to 2,4,6-trimethylphenol at measured concentrations of 0, 0.1, 0.35, 1.0, 3.5, 100 or 350 mg/L under static conditions for 24 hours. Acetone was used as a solvent dispersant. Test solution concentrations were not measured.
24-h EC_{50} = 28.95 mg/L

(3) In response to the original submission that included 24-hour daphnid test data, but not the normally required 48-hour daphnid test data, EPA requested that the submitter support the 24-hour data with structure-activity estimates or measured data for an analogous chemical. In the revised submission, neither was provided. Therefore, EPA estimated a 48-hour LC_{50} for *Daphnia magna* using the EPA's ECOSAR Program

(http://www.epa.gov/oppt/newchems/tools/21ecosar.htm) in order to confirm the robustness of the 24-hour data. The modeled results for the 48-hour test were in good agreement with the 24-hour results for the test conducted without a solvent and with analytical confirmation of the water concentrations. Therefore, the 24-hour data from that test were accepted for the purpose of the HPV Challenge Program.
48-h EC_{50} = 2.48 mg/L (estimated)

Toxicity to Aquatic Plants

Pseudokirchneriella subcapitata were exposed to 2,4,6-trimethylphenol at concentrations of 0, 0.82, 2.05, 5.12, 12.8, 32.0 or 80.0 mg/L under static conditions for 96 hours.
72-h EC_{50} (biomass) = 2.54 mg/L
72-h EC_{50} (growth) = 5.59 mg/L

Conclusion: The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of 2,4,6-trimethylphenol to aquatic organisms is moderate.

3. Human Health Effects

Acute Oral Toxicity

Albino rats (3/sex) were administered 2,4,6-trimethylphenol as a single oral dose of 2000 mg/kg-bw. No mortality was observed. Piloerection was the major clinical sign, which resolved by day 4 of the study.
LD_{50} > 2000 mg/kg-bw

Acute Dermal Toxicity

New Zealand White rabbits were administered 2,4,6-trimethylphenol as a single, occlusive dermal application of 2000 mg/kg-bw for 24 hours. After removal of the test substance 24 hours later, necrosis was observed at the site of application in 6 out of 10 animals. The necrotic areas remained visible for the duration of the study (14 days). Slight to moderate erythema and edema was observed in the remaining four animals without necrosis. No mortality or overt signs of systemic toxicity were evident during the study.
LD_{50} > 2000 mg/kg-bw

Repeated-Dose Toxicity

In a combined repeated-dose/reproductive/developmental toxicity screening test, extended with longer duration of the F1 generation exposures from weaning to adulthood and additional neurotoxicity, immunotoxicity and reproductive toxicity endpoints, Sprague-Dawley rats (10/sex/dose) were administered 2,4,6-trimethylphenol in corn oil via gavage at doses of 0, 10, 100 or 200 mg/kg-bw/day for 2 weeks prior to mating and during a 2-week mating period through 3 weeks of gestation and lactation (F0 parents). A 2-week recovery group of five additional males and females per group (at 0 and 200 mg/kg-bw/day) was also included. Maximum dose was determined by a 10-day ranging finding study of 0, 100, 300 or 1000 mg/kg-bw/day. Treatment with 2,4,6-trimethylphenol affected body weight over the 10-day period with loss for males at 1000 mg/kg-bw/day and females at both 300 and 1000 mg/kg-bw/day. Furthermore, weight gain in males was reduced by 43% at the 300 mg/kg-bw/day dose. The authors concluded 300 mg/kg-bw/day would be too toxic for the longer OECD 422 protocol.

Five additional females (not mated) were dosed at 0 and 200 mg/kg-bw/day for 28 days and subsequently sacrificed (28-day females). Selected F1 offspring (10/sex/treatment) were dosed from weaning through scheduled sacrifice approximately 7 weeks post-weaning (F1 adults). The study summary concluded that except for signs of a taste aversion response (dose-related incidences of rooting); no systemic toxicity was noted. The study authors reported a NOAEL of $\geq$ 200 mg/kg-bw/day, the highest dose tested.
NOAEL = 200 mg/kg-bw/day

Reproductive Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test described previously, there was no adult F0 or F1 reproductive toxicity. The study reported a NOAEL of ≥ 200 mg/kg-bw/day, the highest dose tested.
NOAEL = 200 mg/kg-bw/day

Developmental Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test described previously, there was no evidence of F0 parental toxicity in pregnant females and no systemic, neurobehavioral, developmental, or reproductive toxicity in the F1 offspring, exposed *in utero* and directly treated from weaning to adulthood. For both maternal and developmental toxicity, the study reported a NOAEL of ≥ 200 mg/kg-bw/day, the highest dose tested.
NOAEL (maternal toxicity) = 200 mg/kg-bw/day
NOAEL (developmental toxicity) = 200 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
(1) In an Ames assay, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to 2,4,6-trimethylphenol at concentrations of 0, 0.03, 0.3, 3 and 30 µmol/plate; with and without metabolic activation. The publication concludes that the number of revertants/plate at all concentrations in all tester strains was less than the number reported in the negative control group, with and without metabolic activation. The publication did not provide actual test data.
2,4,6-Trimethylphenol was not mutatgenic in this assay.

(2) Mouse lymphoma L5178Y cells were exposed to 2,4,6-trimethylphenol at test concentrations of 0, 10, 30, 40, 50 or 100 µg/mL with metabolic activation and 0, 50, 75, 100, 125 or 150 µg/mL without metabolic activation. Mutations were equivocal in the absence of metabolic activation at 4- and 24-hour exposures and negative in the presence of metabolic activation. No dose/response trend was observed in either the activated or non-activated test systems.
2,4,6-Trimethylphenol gave equivocal results in this assay.

Genetic Toxicity – Chromosomal Aberrations

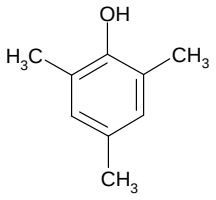
In vitro
Chinese hamster ovary (CHO) cells were exposed for 4 hours to 2,4,6-trimethylphenol at concentrations of 0, 25, 50, 100, 150, 200, or 300 µg/mL without metabolic activation and at concentrations of 0, 12.5, 25, 50, 100, 150 or 200 µg/ with metabolic activation. In addition, cells were exposed for 20 hours to concentrations of 0, 25, 50, 100, 150, 200 300 or 400 µg/mL without metabolic activation for the 20 hours. Mitomycin C and cyclophosphamide were used as the positive controls and DMSO was used as the solvent control. Cytotoxic concentrations were greater than 136 and 408 µg/mL with and without metabolic activation, respectively. 2,4,6-Trimethylphenol did not induce structural and numerical chromosome aberrations without metabolic activation system. In the presence of metabolic activation, 2,4,6-trimethylphenol was negative for numerical chromosomal aberrations but induced statistically significant ($p \leq 0.01$ at 100 µg/mL and $p \leq 0.05$ at 200 µg/mL) structural chromosomal aberrations.
2,4,6-Trimethylphenol was positive and induced structural chromosomal aberrations in this assay.

In vivo
Male and female mice were administered 2,4,6-trimethylphenol at concentrations of 0, 500, 1000, 1200, 1400 and 1600 mg/kg-bw via intraperitoneal injection. The vehicle was corn oil and the positive control was cyclyphosphamide. The number of micronucleated polychromatic erythrocytes (MPCEs) per 1000 PCEs in treated groups was not statistically increased relative to the respective vehicle controls in either male or female mice, regardless of dose level or bone marrow collection time. Positive and negative (vehicle) control results indicated appropriate responses.
2,4,6-Trimethylphenol did not induce MPCEs in this assay.

Conclusion: Acute oral and dermal toxicity of 2,4,6-trimethylphenol is low. At high dose, 2,4,6-trimethylphenol causes skin irritation in rabbit testing. Repeated exposures of rats via the oral route in a 10-day range finding study affected body weight and body weight gains at high doses. In a combined repeated-dose/reproductive/developmental toxicity screening test in rats, there was no evidence of toxicity at the highest dose tested. An *in vivo* mouse bone marrow micronucleus test was negative for chromosomal aberrations, but an *in vitro* test of 2,4,6-trimethylphenol was positive for structural chromosomal aberrations in CHO cells with metabolic activation. Bacterial mutagenesis tests of 2,4,6-trimethylphenol were negative, but an *in vitro* test of mammalian cell gene mutation gave equivocal results without metabolic activation and negative with metabolic activation.

The potential health hazard of 2,4,6-trimethylphenol is low.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL 2,4,6-Trimethylphenol (527-60-6)**
Structure	
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish **96-h LC_{50} (mg/L)**	9.7
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	3.5 (24-h) 28.95 (24-h) 2.48 (estimated)
Aquatic Plants **72-h EC_{50} (mg/L)** **(growth)** **(biomass)**	 5.59 2.54
Summary of Human Health Data	
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	> 2000
Acute Dermal Toxicity **LD_{50} (mg/kg-bw)**	> 2000
Repeated-Dose Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)**	NOAEL = 200 (54-d)
Reproductive Toxicity **NOAEL/LOAEL** **(mg/kg-bw/day)**	NOAEL = 200
Developmental Toxicity **NOAEL/LOAEL** **(mg/kg-bw/day)** **Maternal Toxicity** **Developmental Toxicity**	 NOAEL = 200 NOAEL = 200
Genetic Toxicity – Gene Mutation-Bacterial cells ***In vitro***	Negative
Genetic Toxicity – Gene Mutation-Mammalian cells ***In vitro***	Equivocal
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Positive
Genetic Toxicity – Chromosomal Aberrations ***In vivo***	Negative

Screening Level Exposure Characterization for HPV Challenge Chemical

2, 4, 6-Trimethylphenol

CAS # 527-60-6

July 2008

Prepared by

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Screening Level Exposure Characterization

2, 4, 6-Trimethylphenol (CAS # 527-60-6)

Non-CBI Executive Summary

This exposure characterization was completed using both public, non-confidential sources, and one or more IUR submissions. 2, 4, 6-Trimethylphenol has an aggregated production and/or import volume in the United States of 1 million to 10 million pounds. Non-confidential information in the IUR indicated that the chemical is primarily used as a solvent in paints and coatings. The HPV submission for 2, 4, 6-trimethylphenol states that the chemical is used as a component in solvent formulation for either polyamide or polyurethane based resin to coat wire. There were no consumer uses reported under the IUR.

Exposure to the General Population and the Environment. It is likely that there would be some releases to water and/or air during manufacturing, processing, and industrial use. 2, 4, 6-Trimethylphenol was found in quantifiable amounts in air, ground water, and in the effluent of a petroleum refinery and publicly owned treatment works.[12] 2, 4, 6-Trimethylphenol is not expected to be persistent in the environment (P1) and the bioaccumulation potential is low (B1). Based on the information considered – reported uses and the Agency's expert judgment - EPA identifies, for purposes of risk-based prioritization, a medium potential that the general population and the environment might be exposed to this chemical.

Exposure to Workers. Based on the information considered (including IUR data and information from the HPV submission) and in combination with Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a high relative ranking for the potential worker exposure. Although 2, 4, 6-trimethylphenol is a solid at room temperature, it is manufactured in liquid form. The vapor pressure is 0.05 mm Hg and therefore workers could be exposed to vapors. In addition, workers could be exposed to mists based on uses in spray paints and coatings.

Exposure to Consumers. There were no consumer uses reported under the IUR. Therefore, EPA identifies, for the purposes of risk-based prioritization, a low potential that consumers might be exposed to this chemical.

Exposure to Children. There were no consumer uses in children's products reported under the IUR. Therefore, EPA identifies, for the purposes of risk-based prioritization, a low potential that children might be exposed to this chemical.

[12] USEPA, 2008. Screening-Level Hazard Characterization for High Production Chemical, 2, 4, 6-Trimethylphenol CAS: 527-60-6 USEPA, 2008.

Volume and Use Information

2, 4, 6-Trimethylphenol (CAS # 527-60-6) has an aggregated production and/or import volume in the United States of 1 million to 10 million pounds.[13] Non-confidential information in the Inventory Update Rule (IUR) indicates that this chemical was manufactured and/or imported at the following companies and sites: Merisol USA LLC / Houston, TX and General Electric Company / Selkirk, NY. There may be other companies and sites that are claimed as confidential. Persons submitting IUR information for 2005 asserted that some or all of the information was confidential. Data and information that are confidential have been excluded from this summary.

The IUR submissions indicated that the chemical is primarily used as a solvent in paints and coatings. There may be other uses that are claimed as confidential business information (CBI). Table 1 at the end of this summary provides additional details.

There was no commercial/consumer use reported under IUR.

The High Production Volume (HPV) Challenge Program submission for this chemical states that the chemical is used as a component in solvent formulation for either polyamide or polyurethane based resin to coat wire. The coating provides ease of use, insulation, and durability to the wire surface[14].

Hazardous Substances Data Bank (HSDB) indicates that a major use of 2, 4, 6-Trimethylphenol is as a chemical intermediate for poly (2, 6-Dimethyl-1, 4-Phenylene oxide) and its phosphate ester, for polyamide/cellulosic blends and half wool. Other uses include petroleum processing and wood treatment operations.[15]

Exposures to Workers

Based on the information considered including IUR data and information from HSDB, HPV submission and in combination with Agency's professional judgment, EPA identifies, for the purpose of risk-based prioritization, a high relative ranking for the potential worker exposure. This relative ranking is based on the potential for vapor inhalation exposure to industrial workers during the manufacturing and use of the chemical as a solvent in resins and coatings and possible mist exposure during spray painting and/or wood treatment operations.

[13] USEPA, 2006 Partial Updating of TSCA Chemical Inventory.
[14] USEPA, 2007a. High Volume Production Submission. Accessed, 3/20/08. http://www.epa.gov/chemrtk/pubs/summaries/246trime/c14218rr2.pdf.
[15] HSDB, 2008. Hazardous Substances Data Bank. Accessed, 3/20/08, 2, 4, 6-Trimethylphenol. http://toxnet.nlm.nih.gov/.

Summary of Parameters affecting Worker Exposure

Parameter	
Volume*	1 million to 10 million lbs
Physical Form(s)*	Liquid
Vapor Pressure	0.05 torr
Concentration*	Up to 100% by weight
Number of Industrial Workers*	100 to 999
Uses *	Chemical intermediate, solvent in resins, paints and coatings, petroleum processing, wood treatment operations
Key MSDS Info	Causes burns

* Only non-confidential IUR data are reported in this summary.

Based on IUR data, the maximum total number of workers reasonably likely to be exposed to this chemical during manufacturing and industrial processing and use is between 100 and 999. 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. This estimate does not include potentially exposed commercial workers. The National Occupational Exposure Survey (NOES), conducted from 1981 to 1983, estimated a total of 93 workers potentially exposed to this chemical[16]. Differences between numbers of workers estimated by IUR submitters and by the NOES are attributable to many factors, including time, scope, and method of the estimates. For example, NOES estimates are for all workplaces while IUR are for industrial workplaces only, and NOES used a survey and extrapolation method while IUR submitters simply provide their best estimates based on available information for the specific reporting year.

Based on IUR data, the chemical is manufactured in liquid form, and worker exposures are possible for this chemical in this form. Also, the non-confidential maximum concentration is up to 100%. There may be other physical forms and concentrations that are claimed as confidential business information (CBI). This chemical has a vapor pressure of 0.05 torr[17]. This chemical's vapor pressure could result in significant worker exposures to vapors. Additional information on worker exposure is available in Hazardous Substances Data Bank[18].

Based on the use information, workers may also be potentially exposed to mist during activities such as spray painting or in wood treatment operations.

This chemical does not have OSHA Permissible Exposure Limits (PELs)[19].

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[16] NIOSH, 1983. National Occupational Exposure Survey (NOES, 1981-1983). Accessed, 3/20/08. http://www.cdc.gov/noes/srch-noes.html.
[17] USEPA, 2008. Screening-Level Hazard Characterization for High Production Chemical, 2, 4, 6-Trimethylphenol CAS: 527-60-6 USEPA, 2008.
[18] HSDB, 2008. Hazardous Substances Data Bank. Accessed, 3/20/08, 2, 4, 6-Trimethylphenol. http://toxnet.nlm.nih.gov/.
[19] NIOSH, 1988. OSHA PEL Project Documentation. http://www.cdc.gov/niosh/pel88/npelcas.html. Accessed, 4/4/08.

Environmental Releases

Environmental releases may impact general population and environmental exposures. Factors affecting releases include quantities produced, processed and used; numbers of sites; and, processes of manufacture, processing, and use.

The following release statements are made based on inferences regarding the non-confidential use information reported in IUR and summarized in Tables 1 and 2.

Many chemicals processed into a formulation, mixture, or reaction product have industrial releases that are a relatively low percentage of the volume. Many chemicals designated by IUR to have industrial use as solvents in product formulations or mixtures have industrial and/ or end use releases that are a relatively high percentage of the volume associated with this use. Higher percentage releases occur when the chemical's intended use is as a solvent that may evaporate into the atmosphere or may be collected and disposed to aqueous media. In some cases, some engineering controls or capture for recycle or reclamation may reduce these losses. The actual percentage and quantity of release of the reported chemical associated with this use are not known but could be high.

The chemical is not on the Toxics Release Inventory[20]. Emission data is not available on the National Emission Inventory (NEI) Database[21].

This chemical has a vapor pressure of 0.05 torr[22]. Experience has shown that air releases due to volatilization have not been an issue for chemicals with vapor pressures below 0.01 torr. Based on the vapor pressure, air releases are possible.

Exposures to the General Population and the Environment

Based on the information under the release section above, it is likely that there would be some releases to water and/or air during manufacturing, processing, and use. A search of additional relevant databases provided further information on releases of this chemical. This chemical was found in measurable amounts in air, ground water and in the effluent of a petroleum refinery and publicly owned treatment works[23]. EPA identifies, for the purposes of risk-based prioritization, a moderate potential that the general population and the environment might be exposed to this chemical. Based on IUR alone potential exposure to general population and the environment is medium. It is unlikely that there will be exposure to this chemical based on the use codes in the IUR data, but this chemical was found in measurable amounts in air, ground water and in the effluent of a petroleum refinery and publicly owned treatment works. In addition, public data

[20] USEPA, 2006. Toxic Release Inventory. Accessed, 4/4/08. http://www.epa.gov/tri/.
[21] USEPA, 2002. National Emission Inventory. Accessed, 4/4/08. http://www.epa.gov/ttn/chief/net/.
[22] USEPA, 2008. Screening-Level Hazard Characterization for High Production Chemical, 2, 4, 6-Trimethylphenol CAS: 527-60-6 USEPA, 2008.
[23] USEPA, 2008. Screening-Level Hazard Characterization for High Production Chemical, 2, 4, 6-Trimethylphenol CAS: 527-60-6 USEPA, 2008.

sources indicate that potential exposure to the general population, environment and children is likely from this chemical found in ground water[24].

Persistence and bioaccumulation ratings for this chemical are P1 and B1. These ratings suggest that this chemical is not very persistent in the environment; and is not very bioaccumulative.

Based on the information considered, known uses, and the Agency's expert judgment, EPA identifies, for purposes of risk-based prioritization, a moderate potential that the general population and the environment might be exposed to this chemical.

Exposures to Consumers

No uses in products intended to be used by consumers were reported in the IUR, nor were any found in other data sources.

EPA identifies, for the purposes of risk-based prioritization, a low potential that consumers might be exposed to this chemical.

Information from public data sources did not indicate potential exposure to consumers.

Exposures to Children

No uses in products intended to be used by children were reported in the IUR, nor were any found in other data sources. Therefore, EPA identifies, for the purposes of risk-based prioritization, a low potential that children might be exposed to this chemical.

[24] NAWQA, 2008. National Water Quality Assessment Program. Accessed, 4/4/08. http://infotrek.er.usgs.gov/traverse/f?p=NAWQA:23:0.

Non Confidential IUR Data Summary

Manufacturing/ Import Information

Production and import volume:	1 million to 10 million lbs
List of non-CBI companies/ sites:	Merisol USA LLC / Houston, TX General Electric Company / Selkirk, NY
Highest non-CBI maximum concentration:	up to 100%
Non-CBI physical forms:	liquid

Table 1
Industrial Processing and Use
Information Reported in 2006 IUR

Processing Activity	**Industrial Sector**	**Function in Ind. Sector**
Processing—incorporation into formulation, mixture, or reaction product	Paint and Coating Manufacturing	Solvents
CBI Use		

Table 2
Commercial/ Consumer Uses
Information Reported in 2006 IUR

Commercial/ Consumer Product Category Description	Highest maximum concentration range	Use in Children's Products
Not reported		