SCREENING-LEVEL HAZARD CHARACTERIZATION

Phosphoric acid tris(methylphenyl) ester
(Tricresyl phosphate; CASRN 1330-78-5)

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

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

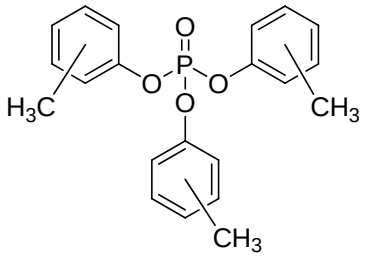
The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments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

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental

[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.

authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

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

Chemical Abstract Service Registry Number (CASRN)	**1330-78-5**
Chemical Abstract Index Name	**Phosphoric acid, tris(methylphenyl) ester**
Structural Formula	 Representative Structure

Summary

The isomeric composition of the sponsored substance was not stated in the submission. CASRN 1330-78-5 is a mixture of three isomers; CASRN 78-30-8 (*ortho* isomer), CASRN 563-04-2 (*meta* isomer) and CASRN 78-32-0 (*para* isomer). The ratio of isomers is not specified but is known to be predominantly a mixture of the *meta* and *para* isomers with very small amounts of the *ortho* isomer present (<1%).

CASRN 1330-78-5 is a liquid with low water solubility and low vapor pressure at room temperature. It is expected to have low mobility in soil. Volatilization is considered low based on the Henry's Law constant of this substance. The rate of hydrolysis is considered negligible under environmental conditions. The rate of atmospheric photooxidation is considered moderate. CASRN 1330-78-5 is expected to have low persistence (P1) and moderate bioaccumulation potential (B2).

The acute toxicity of CASRN 1330-78-5 is low via the oral (rats, mice and rabbits) and inhalation routes (rats). The acute dermal toxicity is low in rabbits. In a 28-day repeated-dose dietary toxicity study in rats, at 250 mg/kg-bw/day there was mortality and decreased body weights; the NOAEL for systemic toxicity is 50 mg/kg-bw/day. In a 3-month repeated-dose oral gavage toxicity study in rats, changes in body weight and hypertrophy of the adrenal cortex were observed at 1000 mg/kg-day; the NOAEL for systemic toxicity is 300 mg/kg-day. In 13-week repeated-dose oral gavage and dietary toxicity studies in rats and mice, cytoplasmic vacuolization of the adrenal cortex was observed in the gavage studies in both species at 50 mg/kg-day (lowest dose tested); the NOAEL for systemic toxicity is not established in rats or mice. In the dietary studies, cytoplasmic vacuolization of the adrenal cortex was observed at 55 (male) and 65 (female) mg/kg-bw/day in rats and 65 (female) and 110 (male) mg/kg-bw/day in mice. The NOAEL for systemic toxicity is not established in rats and female mice; for male mice, it is 45 mg/kg-bw/day. The reason for the range of NOAELs is not clear, but it may be related to variations in isomeric composition of CASRN 1330-78-5. In two-year feeding studies in rats and mice, cytoplasmic vacuolization of the adrenal cortex was observed in rats at 7 (female) and 26 (male) mg/kg-bw/day; the NOAEL for systemic toxicity is 4 (female) to 13

(male) mg/kg-bw/day. In mice, ceroid pigmentation of the adrenal cortex was observed at 7 (male) and 37 (female) mg/kg-bw/day; the NOAEL for systemic toxicity is not established in male mice and is 18 mg/kg-bw/day for females. Repeated oral exposures to rats and mice showed atrophy of the seminiferous tubules in male rats (≥430 mg/kg-bw/day) and ovarian interstitial cell hypertrophy in the female rats (15 mg/kg-bw/day) and mice (≥50 mg/kg-bw/day). In a one-generation oral gavage reproductive toxicity study in rats, fetotoxicity, abnormal sperm morphology and histopathological changes in testes, epididymides and ovaries were observed at 100 mg/kg-day (lowest dose tested). In a continuous breeding oral gavage toxicity study in rats, there was a decrease in the number of litters and fertility index, and decreased testicular and epididymal weights at 400 mg/kg-day (only dose tested). The NOAEL for reproductive toxicity in rats is not established. In a continuous breeding study in mice, there was a decrease in the number of litters at 62.5 mg/kg-bw/day (lowest concentration tested); the NOAEL for reproductive toxicity in mice is not established. In a prenatal oral developmental toxicity study in rats, alopecia and unkempt appearance were observed in dams at 400 mg/kg-day; the NOAEL for maternal toxicity is 100 mg/kg-day. Fetal body weights were lower than controls at 20 mg/kg-day (lowest dose tested) and above; the NOAEL for developmental toxicity is not established. CASRN 1330-78-5 was not mutagenic in bacteria or mammalian cells *in vitro* and did not induce chromosomal aberrations *in vitro*. CASRN 1330-78-5 is not irritating to rabbit eyes or skin. CASRN 1330-78-5 did not increase the incidence of tumors in rats and mice. CASRN 1330-78-5 exhibited neurotoxicity in mice.

The acute 96-hour LC_{50} for fish to CASRN 1330-78-5 is 0.75 mg/L. The 48-hour LC_{50} value for aquatic invertebrates to CASRN 1330-78-5 is 0.27 mg/L. The estimated 96-hour LC_{50} value for aquatic plants to CASRN 1330-78-5 is 0.56 mg/L. The 21-day chronic toxicity to aquatic invertebrates ranges from 0.1 - 0.3 mg/L.

No data gaps were identified under the HPV Challenge Program.

The sponsor, Great Lakes Chemical Corporation, submitted a Test Plan and Robust Summaries to EPA for phosphoric acid tris(methylphenyl) ester (CAS No. 1330-78-5; CA Index name: Phosphoric acid, tris(methylphenyl) ester) on November 28, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on December 19, 2001 (http://www.epa.gov/hpv/pubs/summaries/tricphos/c13318tc.htm). EPA comments on the original submission were posted to the website on July 19, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on May 15, 2002, which were posted to the ChemRTK website on June 6, 2002.

1. Chemical Identity

The test plan does not state the composition of the sponsored substance, tricresyl phosphate (TCP; CASRN 1330-78-5). However, this CASRN corresponds to the mixed isomers of tricresyl phosphate comprising tri-*o*-cresyl phosphate (TOCP; CASRN 78-30-8), tri-*m*-cresyl phosphate (CASRN 563-04-2) and tri-*p*-cresyl phosphate (CASRN 78-32-0) (http://www.inchem.org/documents/ehc/ehc/ehc110.htm). For studies identified through literature search, the composition of the test substance is included in the summaries.

The isomeric composition of the manufactured product or the test substances in the submitted robust summaries was not stated.

1.1 Identification and Purity

The physical-chemical properties of phosphoric acid, tris(methylphenyl) ester are summarized in Table 1. Commercial phosphoric acid, tris(methylphenyl) ester is not a single chemical. It is a mixture of three isomers; phosphoric acid, tris(2-methylphenyl) ester (CASRN 78-30-8, *ortho* isomer), phosphoric acid, tris(3-methylphenyl) ester (CASRN 563-04-2, *meta* isomer) and phosphoric acid, tris(4-methylphenyl) ester (CASRN 78-32-0, *para* isomer). The ratio of isomers is not specified but is known to be predominately a mixture of the *meta* and *para* isomers with very small amounts of the *ortho* isomer present (<1%).

1.2 Physical-Chemical Properties

Phosphoric acid, tris(methylphenyl) ester is a liquid with low water solubility and low vapor pressure at room temperature.

Table 1. Physical-Chemical Properties of Phosphoric Acid, Tris(methylphenyl) Ester[1]	
Property	**Value**
CASRN	1330-78-5
Molecular Weight	368.37
Physical State	Liquid
Melting Point	-33°C (measured)[2]
Boiling Point	241–255°C at 0.4 mm Hg (measured), 485–502°C at 760 mm Hg (extrapolated)[3]; 266–272°C at 9.8 mm Hg (measured)[4], 423–430°C at 760 mm Hg (extrapolated)[3]
Vapor Pressure	0.003 mm Hg at 150°C; 1.4×10^{-6} mm Hg at 30°C (measured), 6.0×10^{-7} mm Hg at 25°C (extrapolated)[5]
Water Solubility	0.36 mg/L at 25°C (measured)[6]; 0.34 mg/L at 25°C (measured)[7]
Dissociation Constant (pK_a)	Not applicable
Henry's Law Constant	5.4×10^{-8} atm-m^3/mole (estimated)[8]; 8.3×10^{-5} atm-m^3/mole (*meta*-TCP, measured)[9]
Log K_{ow}	5.93 (measured); 5.11 (measured)[10]; 5.1–5.3 (measured)[11]; 6.34 (estimated)[8]

[1] Great Lakes Chemical Corporation. July 27, 2001. Revised Roust Summary and Test Plan for Phosphoric Acid Tris(methylphenyl) Ester (Tricresyl Phosphate). Available online from: http://www.epa.gov/chemrtk/pubs/summaries/tricphos/c13318tc.htm as of May 05, 2010.
[2] Midwest Research Institute. 1977. Assessment of the Need for the Character of and the Impact Resulting from Limitations on Aryl Phosphates, MRI 4309-L. Midwest Research Institute, Kansas City, Mo., 279 p.
[3] NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.
[4] Ashford, R.D. 1994. Ashford's Dictionary of Industrial Chemicals. Wavelength Publications Ltd., London, England. p. 908. Melting points of individual isomers reported as 11°C (*ortho*-TCP, measured); 25.5°C (*meta*-TCP, measured); 77.5°C (*para*-TCP, measured).
[5] Boethling, R.S.; Cooper, J.C. 1985. Environmental Fate and Effects of Triaryl and Tri-Alkyl/Aryl Phosphate Esters. Residue Reviews 94:49–99.
[6] Saeger, V.W.; Hicks, O.; Kaley, R.G.; Michael, P.R.; Mieure, J.P.; Tucker, E.S. 1979. Environmental fate of selected phosphate esters. Environ. Sci. Technol. 13:840–844.
[7] Ofstad, E.B.; Sletten, T. 1985. Composition and water solubility determination of a commercial tricresylphosphate. Sci. Total Environ. 43:233–241.
[8] U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of May 05, 2010. Estimations were performed using the structure of the *para* isomer, tris(4-methylphenyl) ester (CASRN 78-32-0).
[9] Muir, D.C.G.; Lint, D.; Grift, N.P. 1985. Fate of three phosphate ester flame retardants in small ponds. Environ. Toxicol. Chem. 4:663–675.
[10] Hansch, C.; Leo, A.; Hoekman, D. 1995. Exploring QSAR: Hydrophobic, Electronic, and Steric Constants. American Chemical Society, Washington, DC.
[11] Bengtsson, B.E.; Tarkpea, M.; Sletten, T.; Carlberg, G.E.; Kringstad, A.; Renberg, L. 1986. Bioaccumulation and effects of some technical triaryl phosphate products in fish and *Nitocra Spinipes*. Environ. Toxicol. Chem. 5:853–861.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

According to the 2006 IUR submissions, CASRN 1330-78-5 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds.

Industrial processing and uses as well as commercial and consumer uses for the chemical were claimed confidential.

2.2 Environmental Exposure and Fate

The environmental fate properties of phosphoric acid, tris(methylphenyl) ester are provided in Table 2.

Phosphoric acid, tris(methylphenyl) ester is expected to have low mobility in soil. Phosphoric acid, tris(2-methylphenyl) ester (CASRN 78-30-8, *ortho* isomer) was inherently biodegradable (65.7% in 28 days) using a MITI-II test (OECD TG 302C), while phosphoric acid, tris(3-methylphenyl) ester (CASRN 563-04-2, *meta* isomer) was not readily biodegradable (30.8 and 43.1% in 28 days) by a modified MITI-I test (OECD TG 301C). Phosphoric acid, tris(4-methylphenyl) ester (CASRN 78-32-0, *para* isomer) was inherently biodegradable (100% in 28 days) using a modified MITI-II test (OECD TG 302C). The biodegradation of commercial grade, phosphoric acid, tris(methylphenyl) ester in an inherent screening test using an acclimated bacterial inoculum (14-day acclimation period) indicated CO_2 evolution was followed over 48 days. On day 7, 28, and 48, 78.6, 82.1, and 86.3% theoretical CO_2 evolution was reported, respectively. This test indicates that commercial grade, phosphoric acid, tris(methylphenyl) ester is inherently biodegradable. In a river die-away test using 200 mL settled Mississippi River water from St. Louis, primary degradation of commercial grade, phosphoric acid, tris(methylphenyl) ester was measured using gas chromatography; the percent remaining was 100, 92, and 0% at day 0, 2, and 4, respectively. In a 28-day semi-continuous activated sludge system (SCAS) test, commercial grade, phosphoric acid, tris(methylphenyl) ester was 97 and 99+% biodegraded (primary biodegradation) at 3 and 13 mg/L/day, respectively. Volatilization of phosphoric acid, tris(methylphenyl) ester is considered low based on the Henry's Law constant. A die-away study using Lake Ontario water from Oswego, NY found that the individual isomers of tris(methylphenyl) ester exhibited a two-day lag period before degrading rapidly; the *ortho*- and *meta*-isomers were completely degraded within 4 days while about half of the *para*-isomer was degraded in 5 days. The rate of hydrolysis is considered negligible under environmental conditions; but may increase at higher pH levels. Phosphoric acid, tris(methylphenyl) ester is expected to have low persistence (P1) and moderate bioaccumulation potential (B2).

Table 2. Environmental Fate Characteristics of Phosphoric Acid, Tris(methylphenyl) Ester[1]	
Property	**Value**
Photodegradation Half-life	9.4 hours at 25°C (estimated)[2]

Hydrolysis Half-life	pH 7 = 319 days;
	pH 8 = 31.9 days;
	pH 9 = 3.19 days;
	0.25 /M-sec (base-catalyzed hydrolysis rate constant; *para*-TCP (estimated)[3]

Biodegradation	82.1% $ThCO_2$ in 28 days (inherently biodegradable)[4]; 65.7% in 28 days (*ortho*-TCP, inherently biodegradable)[5]; 30.8 and 43.1% in 28 days (*meta*-TCP, not readily biodegradable)[5]; 100% in 28 days (*para*-TCP, inherently biodegradable)[5]
Bioaccumulation Factor	BAF = 1,382 (estimated)[2]
Log K_{oc}	4.7 (estimated)[2]
Fugacity (Level III Model)[2] Air (%) Water (%) Soil (%) Sediment (%)	 0.4 8.3 70.9 20.4
Persistence[6]	P1 (low)
Bioaccumulation[6]	B2 (moderate)

[1] Great Lakes Chemical Corporation. July 27, 2001. Revised Roust Summary and Test Plan for Phosphoric Acid Tris(methylphenyl) Ester (Tricresyl Phosphate). Available online from: http://www.epa.gov/chemrtk/pubs/summaries/tricphos/c13318tc.htm as of May 05, 2010.
[2] U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of May 05, 2010. Estimations were performed using the structure of the *para* isomer, tris(4-methylphenyl) ester (CASRN 78-32-0).
[3] Wolfe, N.L. 1980. Organophosphate and organophosphorothionate esters: Application of linear free energy relationships to estimate hydrolysis rate constants for use in environmental fate assessment. Chemosphere 9:571–579.
[4] Saeger, V.W.; Hicks, O.; Kaley, R.G.; Michael, P.R.; Mieure, J.P.; Tucker, S.E. 1979. Environmental fate of selected phosphate esters. Environ. Sci. Technol. 13: 840–844.
[5] National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from: http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of May 05, 2010.
[6] Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3. Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

(1) Wistar rats (5/sex/dose) were administered tricresyl phosphate via gavage at 20,000 mg/kg-bw and observed for 14 days. Two males and two females died on days 3 and 7, respectively, during the observation period.
LD_{50} > 20,000 mg/kg-bw

(2) The acute oral toxicity of tricresyl phosphate to several species is reported in a document published by the International Programme on Chemical Safety (IPCS; http://www.inchem.org/documents/ehc/ehc/ehc110.htm).
LD_{50} (rat) > 4640 - >15,800 mg/kg-bw
LD_{50} (mouse) > 3900 mg/kg-bw
LD_{50} (chicken) > 10,000 mg/kg-bw

(3) In a study with New Zealand White rabbits of both sexes, the minimum lethal oral dose of tricresyl phosphate (25% dilution in corn oil) was in the range of 220 – 300 mg/kg-bw. Survival time was 1-3 days. In several other studies comparing different samples of tricresyl phosphate, six New Zealand White rabbits (males and females)/sample were given undiluted tricresyl phosphate by gavage at concentrations up to 3.00 g/kg-bw. The range of the minimum lethal dose was 2.23-2.50 g/kg-bw. The animals survived for two-four days. (http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384: OTS 0206227).

(4) Rabbits (1-3/dose, sex not stated) were treated with either (A) at 0.1, 1.0 or 3.2 or 10 g/kg or (B) at 0.1, 3.2 or 1.0 g/kg commercial tricresyl phosphate [commercial samples A and B comprising the three cresol (methyl phenol) isomers, six xylenol (dimethyl phenol) isomers, ethyl phenol and other alkylated phenols] by gavage in a 10% (w/w in water) gum acacia vehicle. Mortalities occurred within 1 (B) to 2 (A) days of treatment. For Sample A, mortalities for increasing doses were 0/1, 0/3, 1/2 and 2/2. For Sample B, mortalities for increasing doses were 0/3, 0/2 and 2/2. (http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384: OTS 0206104).
LD_{50} (A) = 3000 mg/kg-bw
LD_{50} (B) = 600 mg/kg-bw

Acute Inhalation Toxicity

(1) Sprague-Dawley rats (10/sex/concentration) were exposed whole-body to tricresyl phosphate as an aerosol at 5.2 mg/L for 4 hours and observed for 14 days. No mortalities were observed.
LC_{50} > 5.2 mg/L

(2) Sprague-Dawley rats (5/sex/concentration) were exposed whole-body to tricresyl phosphate as an aerosol at 11.1 mg/L for 1 hour and observed for 14 days. No mortalities were observed. (http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384: OTS0519262).
LC_{50} > 11.1 mg/L

Acute Dermal Toxicity

(1) Albino rabbits (10/dose, sex not stated) were administered tricresyl phosphate via the dermal route at 10,000 mg/kg-bw to intact and abraded skin and observed for 14 days. No mortalities were observed.
LD_{50} > 10,000 mg/kg-bw

(2) The acute dermal toxicity of tricresyl phosphate is reported in a document published by the International Programme on Chemical Safety (IPCS; http://www.inchem.org/documents/ehc/ehc/ehc110.htm).
LD_{50} (rabbit) > 7900 mg/kg-bw

Repeated-Dose Toxicity

(1) In a 28-day study, Sprague-Dawley rats (10/sex/concentration) were administered tricresyl phosphate at 0, 0.1, 0.5 or 1.0% (~ 0, 50, 250 or 500 mg/kg-bw/day) in the diet. Mortalities occurred at 1% (10 males and 9 females), 0.5% (4 males and 5 females) and 0.1% (1 male) exposure concentrations. Surviving animals at 0.5% had significantly lower body weights and food consumption. These effects were not observed at 0.1%. No significant treatment-related effects on hematological and urinalysis parameters were observed. No treatment-related histopathological effects were observed. The liver to body weight ratio was increased at 0.5% (significance not stated).
LOAEL ~ 250 mg/kg-bw/day (based on mortality and decreased body weights)
NOAEL ~ 50 mg/kg-bw/day

(2) In a three month study, Sprague-Dawley rats (5/sex/dose) were administered tricresyl phosphate in 5% gum arabic solution via gavage at 30, 100, 300 and 1000 mg/kg-day for six days/week. Excessive salivation was observed in some animals at all doses. A significant decrease in body weights was observed in males at 1000 mg/kg-day. The significance of an increase in adrenal weight (females) at 1000 mg/kg-day was not stated. No treatment-related effects on hematological and urinalysis parameters were observed. No significant changes were seen in serum enzyme activities. At 300 mg/kg-day, there was a decrease in albumin levels and an increase in potassium levels (significance not stated) in both sexes. Hypertrophy of the adrenal cortex was observed at 1000 mg/kg-day in both sexes.
LOAEL = 1000 mg/kg-day (based on decreased body weight in males and hypertrophy of the adrenal cortex)
NOAEL = 300 mg/kg-day

(3) In a 13-week National Toxicology Program (NTP) study, Fischer 344/N rats (10/sex/dose) received tricresyl phosphate [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)] in corn oil by gavage at 0, 50, 100, 200, 400 or 800 mg/kg-day. No mortalities were observed. Final mean body weights of males receiving ≥ 200 mg/kg-day were significantly lower than controls. Cytoplasmic vacuolization of the adrenal cortex was observed in both sexes at all dose groups with severity increasing with dose. Ovarian interstitial cell hypertrophy was observed in all treated females. Atrophy of seminiferous tubules was observed in male rats at ≥ 400 mg/kg-day. There were no biologically significant changes in neurobehavioral parameters (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).
LOAEL = 50 mg/kg-day (lowest dose tested; based on cytoplasmic vacuolization of the adrenal cortex)
NOAEL = Not established

(4) In a 13-week NTP study, B6C3F1 mice (10/sex/dose) received tricresyl phosphate [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)] in corn oil via gavage at 0, 50, 100, 200, 400 or 800 mg/kg-day. No mortalities were observed. Final mean body weights were significantly decreased in males at ≥ 200 mg/kg-day and females at ≥ 400 mg/kg-day. Cytoplasmic vacuolization of the adrenal cortex was observed in both sexes of all treated groups and the severity increased with dose. Ovarian interstitial cell hypertrophy was observed in all treated females. Multifocal degeneration of the spinal cord was observed at ≥ 100 mg/kg-day (both sexes) and multifocal degeneration of the sciatic nerve was observed at ≥ 200 (males) and at ≥ 100 mg/kg-day (females). Significantly decreased forelimb grip strength was observed at ≥ 200 and ≥ 400 mg/kg-day in females and males, respectively. Significantly decreased hindlimb grip strength was observed at ≥ 200 mg/kg-day in both sexes (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).
LOAEL = 50 mg/kg-day (lowest dose tested; based on cytoplasmic vacuolization of the adrenal cortex and ovarian interstitial cell hypertrophy)
NOAEL = Not established

(5) In a 13-week NTP feeding study, Fischer 344/N rats (10/sex/concentration) received diets containing 0, 900, 1700, 3300, 6600 or 13,000 ppm tricresyl phosphate (0 and approximately 55, 120, 220, 430 or 750 mg/kg-bw/day for males and 65, 120, 230, 430 or 770 mg/kg-bw/day for females) [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)]. No mortalities were observed. Final mean body weights were significantly decreased at ≥ 430 mg/kg-bw/day (males) and at ≥ 230 mg/kg-bw/day (females). There were no biologically significant changes in neurobehavioral parameters. Cytoplasmic vacuolization of the adrenal cortex was observed in all exposed groups. Ovarian interstitial cell hypertrophy and inflammation of the ovarian interstitium were observed in all exposed groups of females. Renal papillary edema and renal papillary necrosis were observed at 750 mg/kg-bw/day (males) and at ≥ 430 mg/kg-bw/day (females). Basophilic hypertrophy of the pituitary gland *pars distalis* and atrophy of the seminiferous tubules occurred at ≥ 430 mg/kg-bw/day in males

(http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).
LOAEL (males-females) ~ 55-65 mg/kg-bw/day (based on cytoplasmic vacuolization of the adrenal cortex and hyperplasia of ovarian interstitial cells)
NOAEL (males-females) ~ Not established

(6) In a 13-week NTP study, B6C3F1 mice (10/sex/concentration) received diets containing 0, 250, 500, 1000, 2100 or 4200 ppm tricresyl phosphate (approximately 0, 45, 110, 180, 380 or 900 mg/kg-bw/day for males and 0, 65, 130, 230, 530 or 1050 mg/kg-bw/day for females) [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)]. No mortalities occurred. Mean body weights of 900 mg/kg-bw/day males and ≥ 530 mg/kg-bw/day females were decreased (significance not stated). Cytoplasmic vacuolization of the adrenal cortex was observed in all exposed groups except for the 45 mg/kg-bw/day males. Papillary hyperplasia of the gallbladder mucosa was observed at ≥ 110 mg/kg-bw/day (males) and at ≥ 230 mg/kg-bw/day (females). Renal tubule degeneration was observed in all males at 900 mg/kg-bw/day. Axonal degeneration was observed at ≥ 380 mg/kg-bw/day (males) and at ≥ 230 mg/kg-bw/day (females). Significant decreases in forelimb grip strength were observed at 380 and 530 mg/kg-bw/day in males and females, respectively ($p \leq 0.05$) and at 900 and 1050 mg/kg-bw/day in males and females, respectively ($p \leq 0.01$). Significant decreases in hindlimb grip strength were observed at 900 and ≥530 mg/kg-bw/day in males and females, respectively ($p \leq 0.01$). (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).
LOAEL (males) ~ 110 mg/kg-bw/day (based on cytoplasmic vacuolization of the adrenal cortex)
NOAEL (males) ~ 45 mg/kg-bw/day
LOAEL (females) ~ 65 mg/kg-bw/day (lowest concentration tested; based on cytoplasmic vacuolization of the adrenal cortex)
NOAEL (females) ~ Not established

(7) In a 2-year NTP feeding study, Fischer 344/N rats (95/sex/concentration) received diets containing 0, 75, 150 or 300 ppm tricresyl phosphate (approximately 0, 3, 6 or 13 mg/kg-bw/day for males and 0, 4, 7 or 15 mg/kg-bw/day for females) [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)]. An additional group of rats (95/sex/concentration) received diets containing 600 ppm tricresyl phosphate for 22 weeks and then received only control feed (approximately 26 mg/kg-bw/day for males and 30 mg/kg-bw/day for females). At 3, 9 and 15 months of exposure, up to 15 rats/sex/concentration were necropsied and evaluated for histopathologic lesions. No mortalities occurred. No effect on the final mean body weights was observed. Cytoplasmic vacuolization of the adrenal cortex was observed in 26 mg/kg-bw/day males and at ≥ 7 mg/kg-bw/day females at 3 months. At 9 and 15 months, cytoplasmic vacuolization was observed primarily in 15 mg/kg-bw/day females, the incidence and severity significantly increased at the end of the study. Ovarian interstitial cell hyperplasia was observed in female rats at 15 mg/kg-bw/day and the incidence and severity were increased at the end of the study (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).

LOAEL (females) ~ 7 mg/kg-bw/day (based on cytoplasmic vacuolization of the adrenal cortex)
NOAEL (females) ~ 4 mg/kg-bw/day
LOAEL (males) ~ 26 mg/kg-bw/day (based on cytoplasmic vacuolization of the adrenal cortex)
NOAEL (males) ~ 13 mg/kg-bw/day

(8) In a 2-year NTP feeding study, B6C3F1 mice (95/sex/concentration) received diets containing 0, 60, 125 or 250 ppm tricresyl phosphate (approximately 0, 7, 13 or 27 mg/kg-bw/day for males and 0, 8, 18 or 37 mg/kg-bw/day for females) [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-m-cresyl phosphate (21%), tri-p-cresyl phosphate (4%), tri-o-cresyl phosphate (undetectable)]. At 3, 9 and 15 months of exposure, up to15 mice/sex/concentration were necropsied and evaluated for histopathologic lesions. Body weights, survival and feed consumption of exposed groups were similar to that of controls. Ceroid pigmentation of the adrenal cortex was observed in all exposed groups throughout most of the 2-year study, except in 8 and 18 mg/kg-bw/day females at the 3-month necropsy. The severity was markedly increased in females at 37 mg/kg-bw/day. Increased incidence in clear cell foci, fatty change and ceroid pigmentation of the liver were observed in males at ≥ 13 mg/kg-bw/day.
(http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).
LOAEL (females) ~ 37 mg/kg-bw/day (based on ceroid pigmentation of the adrenal cortex)
NOAEL (females) ~ 18 mg/kg-bw/day
LOAEL (males) ~ 7 mg/kg-bw/day (lowest concentration tested; based on ceroid pigmentation of the adrenal cortex)
NOAEL (males) ~ Not established

Reproductive Toxicity

(1) In a one-generation reproductive toxicity study, Long-Evans rats (12 males/dose) were administered tricresyl phosphate in corn oil via gavage at 100 or 200 mg/kg-day for 56 days prior to breeding. Female rats (24/dose) were administered tricresyl phosphate in corn oil via gavage at 200 or 400 mg/kg-day for 14 days prior to breeding. Both sexes continued to receive respective doses for 10 days during the breeding period. The 100 mg/kg-day males were mated with the 200 mg/kg-day females and the 200 mg/kg-day males were mated with the 400 mg/kg-day females. A dose-dependent abnormal sperm morphology was observed at all doses. Sperm concentration, motility and progressive movement were decreased at 200 mg/kg-day. In females, the number delivering live pups was decreased at all doses. Decreased litter size and pup viability were observed at 400 mg/kg-day. Histopathological changes were observed in the testes, epididymides and ovaries.
LOAEL (reproductive toxicity) = 100 mg/kg-day (lowest dose tested; based on fetotoxicity, abnormal sperm morphology, histopathological changes in testes, epididymides and ovaries)
NOAEL (reproductive toxicity) = Not established

(2) In a modified continuous breeding protocol, Fischer 344 rats (20 – 40 pairs/dose) were administered tricresyl phosphate in sesame oil via gavage at 400 mg/kg-day for 135 days. Rats were dosed for 7 days prior to mating and then for a 63-day breeding period and 28 days post

breeding. A crossover mating occurred between treated and control rats just after the postbreeding phase to determine which sex was affected by treatment. There was a significant decrease in fertility index and number of litters per fertile pair. The number of live pups per litter was decreased (significance not stated) when compared to controls. In males there was a significant decrease in testicular and epididymal weights. In the crossover phase, there were no reproductive effects with the treated females; treated male rats produced no litters.
LOAEL/NOAEL (reproductive toxicity) = Not established (one dose tested)

(3) In a continuous breeding protocol, CD-1 mice (20/sex/concentration for test groups, 40/sex/control group) were administered tricresyl phosphate via the diet at 0, 0.05, 0.1 or 0.2% of the diet (approximately 0, 62.5, 124 or 250 mg/kg-bw/day) for 7 days prior to breeding and 98 days during breeding. A significant (p<0.01) dose-dependent decrease in the number of litters/pair was observed. The proportion of pups born live was significantly decreased at 260 mg/kg-bw/day. At completion of the initial study, control males were mated with treated females and control females were mated with treated males in a crossover study. Impaired fertility, as well as decreased body weight and changes in adrenal morphology were observed at 250 mg/kg-bw/day. A significant (p<0.05) decrease in sperm motility was observed at 62.5 and 124 mg/kg-bw/day (250 mg/kg-bw/day not examined).
LOAEL (reproductive toxicity) ~ 62.5 mg/kg-bw/day (lowest concentration tested; based on decreased number of litters/pair)
NOAEL (reproductive toxicity) = Not established

(3) In the repeated-dose studies described previously, rats and mice showed atrophy of the seminiferous tubules in male rats (≥430 mg/kg-bw/day) and ovarian interstitial cell hypertrophy in the female rats (15 mg/kg-bw/day) and mice (≥50 mg/kg-bw/day).

Developmental Toxicity

In a prenatal developmental toxicity study, pregnant rats were treated via gavage with 0, 20, 100, 400 or 750 mg/kg-day Durad 125 (>99.9% CASRN 1330-78-5) during gestation days 0-19. Clinical observations included increased salivation at ≥ 100 mg/kg-day and alopecia and unkempt appearance at ≥ 400 mg/kg-day. Fetal body weights were reduced (significance not stated) compared to control groups at all dose levels. Incomplete ossification was observed at 750 mg/kg-day. (Durad 125 MSDS: www.chemtura.com)
LOAEL (maternal toxicity) = 400 mg/kg-day (based on alopecia and unkempt appearance)
NOAEL (maternal toxicity) = 100 mg/kg-day

LOAEL (developmental toxicity) = 20 mg/kg-day (lowest dose tested; based on reduced fetal body weights)
NOAEL (developmental toxicity) = Not established

Genetic Toxicity – Gene Mutation

In vitro

In an NTP study, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA 1537 were treated with 0, 100, 333, 1000, 3333 and 10,000 µg/plate tricresyl phosphate [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)] with and without metabolic activation. The positive and negative controls gave expected responses. Precipitate was observed at ≥ 3333 µg/plate. The compound was negative for mutagenicity both with and without metabolic activation (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).

CASRN 1330-78-5 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

In an NTP study, Chinese hamster ovary (CHO) cells were exposed to tricresyl phosphate [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)] at concentrations of 0, 50, 160, 500, 1600 or 5000 µg/mL for 12 hours with metabolic activation and 2 hours without metabolic activation. Positive controls were assessed concurrently and responded appropriately. Negative tests results were obtained (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).

CASRN 1330-78-5 did not cause chromosomal aberrations in this assay.

Genetic Toxicity – Other

In an NTP study, CHO cells were exposed to tricresyl phosphate [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)] at concentrations of 0.05, 0.16, 0.5, 1.6, 5 and 16 µg/mL with and without metabolic activation and were assessed for sister chromatid exchange. Positive and negative controls were assessed concurrently and responded appropriately. Negative test results were obtained (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=1330-78-5&fuseaction=ntpsearch.searchresults).

CASRN 1330-78-5 did not induce sister chromatid exchange in this assay.

Additional Information

Skin Irritation

Six albino rabbits were administered undiluted tricresyl phosphate to shaved and intact, or abraded skin, under semi-occlusive conditions for 24 hours and observed for 72 hours. Transient

erythema was observed in one rabbit. No edema was observed at either the abraded or unabraded site.
CASRN 1330-78-5 was not irritating to rabbit skin in this study.

Eye Irritation

Nine rabbits were administered 0.1 mL of undiluted tricresyl phosphate in the right eyes. The eyes of six rabbits remained unwashed. The eyes of the three remaining rabbits were washed 4 seconds after application. The rabbits were observed for 48 hours. Transient conjunctival effects were observed in two rabbits (unwashed eyes). No effects were observed in the rabbits with the washed eyes.
CASRN 1330-78-5 was not irritating to rabbit eyes in this study.

Carcinogenicity

(1) In the 2-year NTP feeding study previously described, Fischer 344 rats (95/sex/concentration) received tricresyl phosphate [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)] in the diet at doses of approximately 75, 150 or 300 mg/kg-bw/day. Ingestion for up to 2 years did not increase the incidence of tumors in any tissue.
CASRN 1330-78-5 did not increase the incidence of tumors in rats in this study.

(2) In the 2-year NTP feeding study previously described, B6C3F1 mice (95/sex/concentration) received tricresyl phosphate [commercial product comprising 18% dicresyl phosphate esters and 79% tricresyl phosphate esters; tri-*m*-cresyl phosphate (21%), tri-*p*-cresyl phosphate (4%), tri-*o*-cresyl phosphate (undetectable)] in the diet at doses of approximately 0, 60, 125 or 250 mg/kg-bw/day. Ingestion for up to 2 years did not increase the incidence of tumors in any tissue.
CASRN 1330-78-5 did not increase the incidence of tumors in mice in this study.

Neurotoxicity

Of the three isomers comprising tricresyl phosphate, tri-*o*-cresyl phosphate (TOCP) is the only isomer that produces delayed neurotoxicity. The delayed neuropathy associated with TOCP is organophosphate induced delayed neuropathy (OPIDN) (http://www.inchem.org/documents/ehc/ehc/ehc110.htm).

(1) In the 13-week NTP gavage study in B6C3F1 mice described previously, multifocal degeneration of the spinal cord was observed at ≥ 100 mg/kg-bw/day and multifocal degeneration of the sciatic nerve was observed in males at ≥ 200 and females at ≥ 100 mg/kg-bw/day. Decreased hindlimb grip strength was observed at ≥ 200 mg/kg-bw/day. Decreased forelimb grip strength was observed at ≥ 200 and ≥ 400 mg/kg-bw/day in females and males, respectively. Decreased hindlimb grip strength was observed at ≥ 200 mg/kg-bw/day in both sexes.

(2) In the 13-week NTP feeding study in B6C3F1 mice described previously, axonal degeneration was observed in males at ≥ 380 mg/kg-bw/day and in females at ≥ 230 mg/kg-bw/day. Significant decreases in forelimb grip strength at ≥ 380 and 530 mg/kg-bw/day and in hindlimb grip strength at 900 and 1050 mg/kg-bw/day in males and females, respectively, were observed.

(3) In the 2-year NTP feeding study in B6C3F1 mice described previously, a decrease was observed in hindlimb grip strength in females at 37 mg/kg-bw/day at the 3-month interim evaluation.

Conclusion: The acute toxicity of CASRN 1330-78-5 is low via the oral (rats, mice and rabbits) and inhalation routes (rats). The acute dermal toxicity is low in rabbits. In a 28-day repeated-dose dietary toxicity study in rats, at 250 mg/kg-bw/day there was mortality and decreased body weights; the NOAEL for systemic toxicity is 50 mg/kg-bw/day. In a 3-month repeated-dose oral gavage toxicity study in rats, changes in body weight and hypertrophy of the adrenal cortex were observed at 1000 mg/kg-day; the NOAEL for systemic toxicity is 300 mg/kg-day. In 13-week repeated-dose oral gavage and dietary toxicity studies in rats and mice, cytoplasmic vacuolization of the adrenal cortex was observed in the gavage studies in both species at 50 mg/kg-day (lowest dose tested); the NOAEL for systemic toxicity is not established in rats or mice. In the dietary studies, cytoplasmic vacuolization of the adrenal cortex was observed at 55 (male) and 65 (female) mg/kg-bw/day in rats and 65 (female) and 110 (male) mg/kg-bw/day in mice. The NOAEL for systemic toxicity is not established in rats and female mice; for male mice, it is 45 mg/kg-bw/day. The reason for the range of NOAELs is not clear, but it may be related to variations in isomeric composition of CASRN 1330-78-5. In two-year feeding studies in rats and mice, cytoplasmic vacuolization of the adrenal cortex was observed in rats at 7 (female) and 26 (male) mg/kg-bw/day; the NOAEL for systemic toxicity is 4 (female) to 13 (male) mg/kg-bw/day. In mice, ceroid pigmentation of the adrenal cortex was observed at 7 (male) and 37 (female) mg/kg-bw/day; the NOAEL for systemic toxicity is not established in male mice and is 18 mg/kg-bw/day for females. Repeated oral exposures to rats and mice showed atrophy of the seminiferous tubules in male rats (≥430 mg/kg-bw/day) and ovarian interstitial cell hypertrophy in the female rats (15 mg/kg-bw/day) and mice (≥50 mg/kg-bw/day). In a one-generation oral gavage reproductive toxicity study in rats, fetotoxicity, abnormal sperm morphology and histopathological changes in testes, epididymides and ovaries were observed at 100 mg/kg-day (lowest dose tested). In a continuous breeding oral gavage toxicity study in rats, there was a decrease in the number of litters and fertility index, and decreased testicular and epididymal weights at 400 mg/kg-day (only dose tested). The NOAEL for reproductive toxicity in rats is not established. In a continuous breeding study in mice, there was a decrease in the number of litters at 62.5 mg/kg-bw/day (lowest concentration tested); the NOAEL for reproductive toxicity in mice is not established. In a prenatal oral developmental toxicity study in rats, alopecia and unkempt appearance were observed in dams at 400 mg/kg-day; the NOAEL for maternal toxicity is 100 mg/kg-day. Fetal body weights were lower than controls at 20 mg/kg-day (lowest dose tested) and above; the NOAEL for developmental toxicity is not established. CASRN 1330-78-5 was not mutagenic in bacteria or mammalian cells *in vitro* and did not induce chromosomal aberrations *in vitro*. CASRN 1330-78-5 is not irritating to rabbit eyes or skin. CASRN 1330-78-5 did not increase the incidence of tumors in rats and mice. CASRN 1330-78-5 exhibited neurotoxicity in mice.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data	
Endpoints	**SPONSORED CHEMICAL Phosphoric acid tris(methylphenyl) ester (1330-78-5)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**> 20,000 (rat) > 3900 (mouse) > 10,000 (chicken) 600-3000 (rabbit)**
Acute Inhalation Toxicity LC_{50} (mg/L)	**> 5.2 (4h; rat) > 11.1 (1h; rat)**
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	**10,000 (rabbit)**
Repeated-Dose Toxicity NOAEL/LOAEL Oral gavage (mg/kg-day)	**(90-day, rat) NOAEL = 300 LOAEL = 1000 (13-week, rat) NOAEL = NE LOAEL = 50 (lowest dose tested) (13-week, mouse) NOAEL = NE LOAEL = 50 (lowest dose tested)**

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data	
Endpoints	**SPONSORED CHEMICAL** **Phosphoric acid tris(methylphenyl) ester** **(1330-78-5)**
Repeated-Dose Toxicity **NOAEL/LOAEL** **Oral diet (mg/kg-bw/day)**	**(28-day, rat)** **NOAEL ~ 50** **LOAEL ~ 250** **(13-week, rat)** **NOAEL ~ NE** **LOAEL ~ 55-65 (lowest concentrations tested)** **(13-week, mouse)** **$NOAEL_m$ ~ 45** **$NOAEL_f$ ~ NE** **$LOAEL_m$ ~ 110** **$LOAEL_f$ ~ 65** **(2 year, rat)** **$NOAEL_m$ ~ 13** **$NOAEL_f$ ~ 4** **$LOAEL_m$ ~ 26** **$LOAEL_f$ ~ 7** **(2 year, mouse)** **$NOAEL_m$ ~ NE** **$NOAEL_f$ ~ 18** **$LOAEL_m$ ~ 7** **$LOAEL_f$ ~ 37**
Reproductive Toxicity **NOAEL/LOAEL** **Oral gavage (mg/kg-day)** **Reproductive Toxicity**	**(rat)** **NOAEL = NE** **LOAEL = 100 (lowest dose tested)**
Reproductive Toxicity **NOAEL/LOAEL** **Oral diet (mg/kg-bw/day)** **Reproductive Toxicity**	**(mouse)** **NOAEL ~ NE** **LOAEL ~ 62.5 (lowest concentration tested)**

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data	
Endpoints	**SPONSORED CHEMICAL Phosphoric acid tris(methylphenyl) ester (1330-78-5)**
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day) maternal toxicity developmental toxicity	** (rat) NOAEL = 100 LOAEL = 400 NOAEL = NE LOAEL = 20 (lowest dose tested)**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vitro*	**Negative**
Additional Information Skin irritation Eye irritation Carcinogenicity Neurotoxicity	** Not irritating Not irritating Negative (rats and mice) Positive**

f=female; m= male: NE = not established

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

Rainbow trout (*Salmo gairdneri*) were exposed to CASRN 1330-78-5 at nominal concentrations of 0.56, 1.0, 1.8, 3.2 or 5.6 mg/L under static conditions for 96 hours. Mortalities were observed at all concentrations.
96-h LC_{50} = 0.75 mg/L

Acute Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to CASRN 1330-78-5 at nominal concentrations of 0.06, 0.10, 0.18, 0.32 or 0.56 mg/L under static conditions for 96 hours. Mortalities were observed at ≥ 0.18 mg/L in a concentration-dependant manner.
48-h LC_{50} = 0.27 mg/L

Toxicity to Aquatic Plants

Scenedesmus pannonicus were exposed to CASRN 1330-78-5. Temperature was 23 ºC and hardness as $CaCO_3$ was 54.3 mg/L (Adema *et al*., 1981).
96-h EC_{50} = 0.56 mg/L (growth rate)

Chronic Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to CASRN 1330-78-5 for 21 days at temperature 19 ºC, pH 8.2, hardness 209.43 mg/L CaCO3, and > 6.5 mg/L DO (dissolved oxygen). No other information was provided (Adema *et al*., 1981).
21-d LC_{50} = 0.1 - 0.3 mg/L

Conclusion: The acute 96-hour LC_{50} for fish to CASRN 1330-78-5 is 0.75 mg/L. The 48-hour LC_{50} value for aquatic invertebrates to CASRN 1330-78-5 is 0.27 mg/L. The estimated 96-hour LC_{50} value for aquatic plants to CASRN 1330-78-5 is 0.56 mg/L. The 21-day chronic toxicity to aquatic invertebrates ranges from 0.1 - 0.3 mg/L.

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data

Endpoints	SPONSORED CHEMICAL Phosphoric acid tris(methylphenyl) ester (1330-78-5)
Fish 96-h LC_{50} (mg/L)	**0.75**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**0.27**
Aquatic Plants 96-h EC_{50} (mg/L) (growth rate)	**0.56**
Chronic Toxicity to Invertebrates 21-day EC_{50} (mg/L)	**0.1 – 0.3**

Bold = measured data

5. References

Adema, D.M.M., Canton, J.H., Slooff, W., Hanstveir, A.O. 1981. Research for a useful combination of test methods to determine the aquatic toxicity to environmentally dangerous chemicals. Rep.No.CL81/100, Natl.Inst.Public Health Environ.Hyg. :107