

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### SPONSORED CHEMICALS Category Phosphoric Acid Derivatives

#### SUB-CATEGORY I

SPONSORED CHEMICAL  
Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)

#### SUB-CATEGORY II

SPONSORED CHEMICALS  
Bis(2-ethylhexyl) phosphate (CASRN 298-07-7)  
Phosphoric acid, 2-ethylhexyl ester (CASRN 12645-31-7)  
(Mixture of CASRN 298-07-7 and CASRN 1070-03-7)

SUPPORTING CHEMICAL  
Mono(2-ethylhexyl) phosphate (CASRN 1070-03-7)

#### SUB-CATEGORY III

SPONSORED CHEMICAL  
Triisobutyl phosphate (CASRN 126-71-6)

SUPPORTING CHEMICAL  
Tributyl phosphate (CASRN 126-73-8)

The High Production Volume (HPV) Challenge Program<sup>1</sup> 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<sup>1,2</sup>) 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

---

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

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

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<sup>2,3</sup> 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 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.

---

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

<p><b>Chemical Abstract Registry Number (CASRN)</b></p>	<p><b>SUB-CATEGORY I</b></p> <p><b>CASRN 78-42-2</b></p> <p><b>SUB-CATEGORY II</b></p> <p><b>SPONSORED CHEMICALS</b> <b>CASRN 298-07-7</b> <b>CASRN 12645-31-7</b></p> <p><b>SUPPORTING CHEMICAL</b> <b>CASRN 1070-03-7</b></p> <p><b>SUB-CATEGORY III</b></p> <p><b>SPONSORED CHEMICAL</b> <b>CASRN 126-71-6</b></p> <p><b>SUPPORTING CHEMICAL</b> <b>CASRN 126-73-8</b></p>
<p><b>Chemical Abstract Index Name</b></p>	<p><b>SUB-CATEGORY I</b> <b>Phosphoric acid, tris(2-ethylhexyl) ester</b></p> <p><b>SUB-CATEGORY II</b></p> <p><b>SPONSORED CHEMICALS</b> <b>Phosphoric acid, bis(2-ethylhexyl) ester</b></p> <p><b>Phosphoric acid, 2-ethylhexyl ester</b></p> <p><b>SUPPORTING CHEMICAL</b> <b>Phosphoric acid, mono(2-ethylhexyl) ester</b></p> <p><b>SUB-CATEGORY III</b></p> <p><b>SPONSORED CHEMICAL</b> <b>Phosphoric acid, tris(2-methylpropyl) ester</b></p> <p><b>SUPPORTING CHEMICAL</b> <b>Phosphoric acid, tributyl ester</b></p>
<p><b>Structural Formula</b></p>	<p>See Table 1, Section 1.1</p>

### Summary

The phosphoric acid derivatives are liquids with moderate water solubility and low vapor pressure, except for the triisobutyl phosphate, which has moderate vapor pressure, and the supporting chemical mono(2-ethylhexyl)phosphate, which has a high water solubility. They are expected to have low to moderate mobility in soil. Volatilization of the phosphoric acid derivatives is considered low to moderate based upon their Henry's Law constants. The  $pK_a$  values of bis(2-ethylhexyl)phosphate and mono(2-ethylhexyl) phosphate indicate that sub-category II members will exist almost entirely in the anionic form and therefore volatilization from water surfaces is not expected. The rate of hydrolysis is considered negligible for the chemicals in this category. The rate of atmospheric photooxidation is considered rapid to moderate. Compounds in the phosphoric acids derivatives category were found to be readily and inherently biodegradable. The phosphoric acid derivatives are expected to have low persistence (P1) and low bioaccumulation potential (B1).

**Sub-Category I:** Acute oral toxicity of CASRN 78-42-2 to rats and rabbits, acute inhalation toxicity to guinea pigs and acute dermal toxicity to rabbits is low. This chemical is irritating to rabbit skin, and not irritating to rabbit eyes. In the oral repeated-dose studies, rats and mice exposed to CASRN 78-42-2 at doses greater than or equal to 1550 mg/kg-day had body weight losses; the NOAEL for systemic toxicity was 430 mg/kg-day. One study of repeated-dose inhalation exposures in guinea pigs showed histological changes in the kidney at 0.0096 mg/L/day; the NOAEL for systemic toxicity was 0.0016 mg/L/day. No data are available for the reproductive/developmental toxicity endpoints. This chemical did not induce gene mutations or chromosomal aberrations *in vitro*. CASRN 78-42-2 showed some evidence of carcinogenicity in rats and mice which is considered equivocal.

**Sub-Category II:** Acute oral toxicity of CASRN 298-07-7 and CASRN 12645-31-7 (mixture) to rats and acute dermal toxicity of CASRN 298-07-7 and supporting chemical CASRN 1070-03-7 to rabbits is low. CASRN 298-07-7 and supporting chemical CASRN 1070-03-7 are irritating to rabbit skin and corrosive to rabbit eyes. No data are available for the repeated-dose, reproductive and developmental toxicity endpoints for this sub-category. CASRN 298-07-7 and CASRN 12645-31-7 did not induce gene mutations *in vitro*. No data are available for the chromosomal aberrations endpoint for this sub-category.

**Sub-Category III:** Acute oral toxicity of CASRN 126-71-6 and CASRN 126-73-8 (supporting chemical) to rats and mice and acute dermal toxicity to rabbits and guinea pigs are low. Acute inhalation toxicity of CASRN 126-71-6 in rats is low in one study. Both chemicals in the sub-category are irritating to rat, rabbit, human and guinea pig skin, are irritating to rabbit eyes and are dermal sensitizers in guinea pigs but not in humans. Oral repeated-dose studies of rats administered CASRN 126-71-6 showed limited hematological and clinical chemistry effects at 346 mg/kg-day; the NOAEL for systemic toxicity was 68 mg/kg-day. Oral repeated-dose studies of rats administered CASRN 126-73-8 (supporting chemical) showed hematology and histopathological changes of the urinary bladder at 68 mg/kg-day; the NOAEL for systemic toxicity was 13.8 mg/kg-day. In a two-generation oral reproductive toxicity study in rats, CASRN 126-73-8 (supporting chemical) showed no reproductive toxicity, and the NOAEL for reproductive toxicity was 225 mg/kg-day. In the same study, there was developmental (pre- and

postnatal) toxicity at 225 mg/kg-day as demonstrated by reduced pup weights; the NOAEL for developmental toxicity was 53mg/kg-day. Both chemicals in this sub-category did not induce gene mutations *in vitro* and did not induce chromosomal aberrations *in vitro* or *in vivo*. No evidence of neurotoxicity was seen for the supporting chemical, CASRN 126-73-8. The supporting chemical showed evidence of carcinogenicity in rats.

**Sub-Category I:** The predicted 96-hour LC<sub>50</sub> of CASRN 78-42-2 to fish is 0.000218 mg/L. The predicted 48-hour EC<sub>50</sub> of CASRN 78-42-2 to aquatic invertebrates 0.009 mg/L. The 96-hour EC<sub>50</sub> of CASRN 78-42-2 to aquatic plants is 0.000798 mg/L.

**Sub-Category II:** The 96-hour LC<sub>50</sub> of CASRN 298-07-7 ranged from 20 – 56 mg/L and CASRN 126-73-8 ranged from greater than 100 to 5018 mg/L to fish.. The 48-hour LC<sub>50</sub> of CASRN 298-07-7 ranged from 42 to 83.7 mg/L to aquatic invertebrates. The 48-hour LC<sub>50</sub> of CASRN 126-73-8 is 110 mg /L to aquatic invertebrates. The 72-hour EC<sub>50</sub> of CASRN 298-07-7 to aquatic plants is greater than 100 mg/L. The 48-hour EC<sub>50</sub> of CASRN 12645-31-7 to aquatic plants is 168 mg/L. The 62-day chronic value of the supporting chemical CASRN 12645-31-7 is 20.6 mg/L to fish.

**Sub-Category III:** The 96-hour LC<sub>50</sub> of CASRN 126-71-6 and CASRN 126-73-8 ranged from 11 to 23 mg/L to fish. The 48-hour EC<sub>50</sub> of CASRN 126-71-6 CASRN 126-73-8 is 11 and 2.6 mg/L respectively to aquatic invertebrates. The 72-hour EC<sub>50</sub> of CASRN 126-71-6 CASRN 126-73-8 ranged from 1.1 to 33 mg/L (biomass) and 2.8 to 34 mg/L (growth) to aquatic plants. The 95-day MATC of CASRN 126-73-8 is 1.2 mg/L to fish. The 21-day MATC of CASRN 126-73-8 is 1.2 mg/L to aquatic invertebrates.

For sub-category I, the reproductive and developmental toxicity endpoints, as well as the acute toxicity to fish, aquatic invertebrates, and aquatic plants remain as data gaps. For sub-category II, the chromosomal aberrations, repeated-dose, reproductive and developmental toxicity endpoints remain as data gaps.

The sponsor, American Chemistry Council (ACC) Phosphoric Acid Derivatives Panel, submitted a Test Plan and Robust Summaries to EPA for phosphoric acid derivatives on December 13, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 15, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/phsacdde/c13356tc.htm>). EPA comments on the original submission were posted to the website on November 19, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on December 22, 2005, which were posted to the ChemRTK website on March 21, 2006.

### **Category Justification**

EPA did not agree with the sponsor's proposed category or the adequacy of several of the proposed supporting chemicals. EPA has divided the four sponsored chemicals and two supporting chemicals into three sub-groups for assessment of data adequacy for endpoints under the HPV Challenge Program. Structures of the chemicals are presented in Table 4. Read-across between the sub-categories I, II and III is not supported.

### **Justification for Supporting Chemicals**

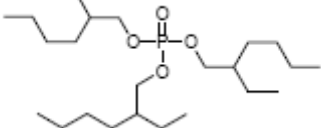
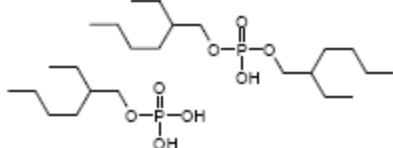
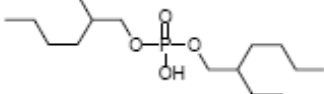
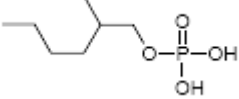
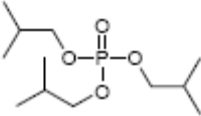
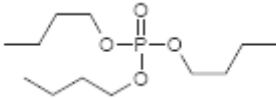
EPA did not agree with the adequacy of several of the sponsor's proposed supporting chemicals. For sub-category II, EPA did agree to the use of supporting chemical CASRN 1070-03-7, since it is a component of the HPV sub-category member CASRN 12645-31-7 (a mixture of CASRN 298-07-7 and CASRN 1070-03-7). Toxicity data for supporting chemical CASRN 1070-03-7 is not used to support the hazard characterization for aquatic organisms.

For sub-category III, EPA used the supporting chemical CASRN 126-73-8. Both CASRN 126-73-8 and CASRN 126-71-6 are tri-esters and the supporting chemical is expected to be metabolized similarly to CASRN 126-71-6 to produce methoxypropanol as the alcohol metabolite.

## 1 Chemical Identity

### 1.1 Identification and Purity

**Table 1. Structures**

Chemical Name	CASRN	Chemical Structure
<b>Sub-Category I</b>		
<b>Sponsored Chemical</b>		
Tris(2-ethylhexyl) phosphate	78-42-2	
<b>Sub-Category II</b>		
<b>Sponsored Chemical</b>		
Phosphoric acid, 2-ethylhexyl ester (mixture)	12645-31-7	
Bis(2-ethylhexyl) phosphate	298-07-7	
<b>Supporting Chemical</b>		
Mono(2-ethylhexyl) phosphate	1070-03-7	
<b>Sub-Category III</b>		
<b>Sponsored Chemical</b>		
Triisobutyl phosphate	126-71-6	
<b>Supporting Chemical</b>		
Tributyl phosphate	126-73-8	

The sponsor did not discuss purity of the chemicals in this category in the Test Plan.

### 1.2 Physical-Chemical Properties

The substances in the phosphoric acid derivatives category are liquids at room temperature. They have moderate water solubility and low vapor pressure, except for the triisobutyl phosphate which has moderate vapor pressure and the supporting chemical mono(2-ethylhexyl)phosphate which has a high water solubility. The physical-chemical properties of the category members are summarized in Table 2.

## **2 General Information on Exposure**

### **2.1 Production Volume and Use Pattern**

The four chemicals in the phosphoric acid derivatives category had a combined production volume, including both manufactured and imported volumes, in the United States of up to 30 million pounds during calendar year 2005.<sup>2</sup> CASRN 78-42-2 had a production and import volume of less than 500,000 pounds. CASRN 12645-31-7, CASRN 298-07-7 and CASRN 126-71-6 each had production and import volumes of 1 million to 10 million pounds.

The HSDB information for CASRN 78-42-2 (Sub-category I) states that the chemical is primarily used in solvents, anti-foaming agents, or plasticizers.<sup>4</sup> The HPV submission states that this chemical is used in catalysts for polypropylene at concentrations of approximately one percent.<sup>5</sup>

The HSDB for CASRN 298-07-7 (Sub-category II) states that the chemical is primarily used as an additive to lubrication oils, corrosion inhibitor and antioxidant, intermediate for wetting agents and detergents, fire retardant in polymeric materials, and extraction fluid for metal salts.<sup>4</sup> The HPV submission states that CASRN 298-07-7 and CASRN 12645-31-7 are used as components in industrial and automotive gear oil additive packages. CASRN 298-07-7 can also be used as an industrial metal extraction agent and in the production of nylon.<sup>5</sup> Non-confidential information in the IUR indicated that the industrial processing and uses of CASRN 12645-31-7 included processing as functional fluids and “other” in all other chemical product and preparation manufacturing.<sup>2</sup> Non-confidential information in the IUR indicated that the commercial and consumer products containing CASRN 12645-31-7 included “other.”

CASRN 126-71-6 (Sub-category III) does not have any 2006 IUR submissions. The HPV submission states that CASRN 126-71-6 is primarily used in solvents, antifoam agents in hydraulic fluids, extraction agents, and the production of plastics.

### **2.2 Environmental Exposure and Fate**

No quantitative information is available on releases of the chemicals in this category to the environment.

The environmental fate properties are provided in Table 3. The substances in the phosphoric acid derivatives category are liquids at room temperature. They have moderate water solubility and low vapor pressure, except for the triisobutyl phosphate which has moderate vapor pressure and the supporting chemical mono(2-ethylhexyl)phosphate which has a high water solubility.

---

<sup>4</sup> HSDB, 2008. Hazardous Substances Data Bank. Accessed, 11/13/08. <http://toxnet.nlm.nih.gov/>

<sup>5</sup> January 19, 2006. Phosphoric Acid Derivatives Category Test Plan and Data Assessment. Accessed, 11/13/2008. <http://www.epa.gov/chemrtk/pubs/summaries/phsacdde/c13356rt2.pdf>

### **Environmental Fate Characterization**

The substances in the phosphoric acid derivatives category are expected to have low to moderate mobility in soil. Compounds in the phosphoric acids derivatives category were found to be readily and inherently biodegradable. If released to air, the phosphoric acid derivatives may exist in the vapor-phase and the rate of atmospheric photooxidation for these substances is considered moderate. The rate of hydrolysis is considered negligible for the chemicals in this category. Direct photolysis experiments resulted in degradation of 80% and 85% upon irradiation in 1 hour for tris(2-ethylhexyl)phosphate and the supporting chemical tributyl phosphate, respectively, but these experiments were performed with low and high pressure Hg lamps which do not simulate sunlight. The phosphoric acid derivatives are expected to have low persistence (P1) and low bioaccumulation potential (B1).

	<b>Sub-Category I</b>	<b>Sub-Category II</b>			<b>Sub-Category III</b>	
<b>Property</b>	<b>Tris(2-ethylhexyl) phosphate</b>	<b>Phosphoric acid, 2-ethylhexyl ester (mixture)</b>	<b>Bis(2-ethylhexyl) phosphate</b>	<b>Mono(2-ethylhexyl) phosphate (supporting chemical)</b>	<b>Triisobutyl phosphate</b>	<b>Tributyl phosphate (supporting chemical)</b>
CASRN	78-42-2	12645-31-7	298-07-7	1070-03-7	126-71-6	126-73-8
Molecular Weight	434.65	210.21	322.43	210.12	266.32	266.32
Physical State	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid
Melting Point	<-70°C	<-20°C	-60°C	No data	<-50°C	<-70°C
Boiling Point	210°C at 5 hPa; Decomposes 215°C at 4 torr <sup>5</sup> 186°C at 1 torr <sup>5</sup>	354.5°C at 1,013 hPa (estimated); Decomposes	240°C (decomposition temperature)	354.5°C at 1,013 hPa (estimated); Decomposes	272°C at 1,013 hPa (measured) 264°C at 760 torr <sup>6</sup> 209°C at 150 torr <sup>6</sup> 196°C at 100 torr <sup>6</sup> 177°C at 50 torr <sup>6</sup> 138°C at 10 torr <sup>6</sup> 117°C at 5.5 torr <sup>6</sup>	130°C at 5 hPa (decomposes) 289°C at 760 torr <sup>7</sup> (begins to decompose) 227°C at 150 torr <sup>7</sup> 211°C at 100 torr <sup>7</sup> 196°C at 50 torr <sup>7</sup> 150°C at 10 torr <sup>7</sup> 138.5°C at 6 torr <sup>7</sup> 98°C at 0.1 torr <sup>7</sup>
Vapor Pressure (mm Hg)	1.54×10 <sup>-7</sup> (estimated)	5.34×10 <sup>-7</sup> (estimated)	1.8×10 <sup>-7</sup> (estimated)	4.0×10 <sup>-7</sup> (estimated)	1 hPa at 92°C 2 hPa at 103°C (which converts to 0.0068 torr at room temperature) 10 hPa at 133°C 50 hPa at 170°C 130 hPa at 200°C 500 hPa at 243°C	2.6×10 <sup>-6</sup> (measured)
Dissociation Constant (pK <sub>a</sub> )	Not Applicable	3.49 (measured); 1.41 (estimated) <sup>2,3</sup> ; 6.09 (estimated) <sup>2,3</sup>	3.49 (measured)	1.41 (estimated) <sup>2</sup> ; 6.09 (estimated) <sup>2</sup>	Not Applicable	Not Applicable

Henry's Law Constant (atm-m <sup>3</sup> /mole)	9.56×10 <sup>-5</sup> (estimated) <sup>4</sup>	1.77×10 <sup>-11</sup> (estimated) <sup>4</sup>	4.1×10 <sup>-8</sup> (estimated) <sup>4</sup>	1.77×10 <sup>-11</sup> (estimated) <sup>4</sup>	3.19×10 <sup>-6</sup> (estimated) <sup>4</sup>	1.41×10 <sup>-6</sup> (estimated) <sup>4</sup>
Water Solubility (mg/L)	2.0 (measured)	211.3 (estimated); 2.19×10 <sup>3</sup> (measured) <sup>3</sup> ; 182 (measured) <sup>3</sup>	182 (measured)	2.19×10 <sup>3</sup> (measured)	265 (measured)	400 (measured) 285 mg/L at 50°C <sup>8</sup> 390 mg/L at 25°C <sup>8</sup> 380 mg/L at 22°C <sup>8</sup> 420 mg/L at 16°C <sup>8</sup> 1075 mg/L at 3.4°C <sup>8</sup>
Log K <sub>ow</sub>	4.1–4.2 (measured)	2.65 (estimated)	2.67 (measured)	2.65 (estimated)	3.72 (measured)	2.5–4.0 (measured)

<sup>1</sup>Rhodia Inc. January 16, 2006. Revised Robust Summary for Phosphoric Acid Derivatives Category.

<http://www.epa.gov/chemrtk/pubs/summaries/phsacdde/c13356tc.htm>.

<sup>2</sup>Sparc On-Line Calculator. Version 4.2. Accessed November 2008. <http://ibmlc2.chem.uga.edu/sparc>.

<sup>3</sup>Phosphoric acid, 2-ethylhexyl ester is a mixture of bis(2-ethylhexyl) phosphate (CASRN 298-07-7) and mono(2-ethylhexyl) phosphate (CASRN 1070-03-7) and therefore, properties for these chemicals are reported.

<sup>4</sup>U.S. EPA. 2008. Estimation Programs Interface Suite™ (version 3.20). United States Environmental Protection Agency, Washington, DC, USA. Available online at: <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

<sup>5</sup>Beilstein, E4, Volume 1, part 3, page 1786

<sup>6</sup>Beilstein, E3, Volume 1, part 2, page 1563

<sup>7</sup>Beilstein, E3, Volume 1, part 2, page 1511

<sup>8</sup>Beilstein, E4, Volume 1, part 3, page 1531

	<b>Sub-Category I</b>	<b>Sub-Category II</b>			<b>Sub-Category III</b>	
<b>Property</b>	<b>Tris(2-ethylhexyl) phosphate</b>	<b>Phosphoric acid, 2-ethylhexyl ester (mixture)</b>	<b>Bis(2-ethylhexyl) phosphate</b>	<b>Mono(2-ethylhexyl) phosphate (supporting chemical)</b>	<b>Triisobutyl phosphate</b>	<b>Tributyl phosphate (supporting chemical)</b>
CASRN	78-42-2	12645-31-7	298-07-7	1070-03-7	126-71-6	126-73-8
Photodegradation Half-life	1.3 hours (estimated)	3.9 hours (estimated)	3.9 hours (estimated)	3.9 hours (estimated)	4.3 hours (estimated)	1.6 hours (estimated)
Direct Photodegradation	80% degradation by UV light after 1 hour (measured) (using mercury lamp; not environmentally relevant)	No Data	No Data	No Data	No Data	85% degradation by UV light after 1 hour (measured) (using mercury lamp; not environmentally relevant)
Biodegradation <sup>2</sup>	0% in 28 days (not readily biodegradable); 55–60% in 2 days following acclimation (inherent, primary biodegradable)	52% in 28 days (not readily biodegradable)	75% in 28 days (readily biodegradable); 0–17% in 28 days (not readily biodegradable)	No Data	97% in 14 days (readily biodegradable); 70% in 35 days (readily biodegradable)	77–92% in 28 days (readily biodegradable)
Hydrolysis Half-life	No Data	>1 year (pH 4, 7, 9) (measured)	No Data	No Data	170 days (pH 4, 50°C); 303 days (pH 7, 50°C) (measured)	Stable after 30 days (pH 3, 7, 11) (measured)
Log K <sub>oc</sub>	3.66 (estimated) <sup>3</sup>	2.11 (estimated) <sup>3</sup>	1.12 pH 7 (estimated); 4.2 (estimated); 2.28 (estimated)	2.11 (estimated) <sup>3</sup>	3.05 (estimated) <sup>3</sup>	3.16 (measured); 3.07 (measured); 2.58 (measured)
Bioconcentration	2.4–22 (measured in carp)	21.92 (estimated)	1.1–6.0 (measured in carp)	21.92 (estimated)	19.51 (estimated)	5.5–49 (measured in carp)

Fugacity (Level III Model)						
Air (%)	0.312	0.000783	0.302	0.000783	0.518	0.0737
Water (%)	10.9	29.0	24.5	29.0	38.8	41.0
Soil (%)	31.2	70.8	75.0	70.8	59.5	56.7
Sediment (%)	57.6	0.188	0.226	0.188	1.14	1.52
	(estimated)	(estimated)	(estimated)	(estimated)	(estimated) <sup>3</sup>	(estimated) <sup>3</sup>
Persistence <sup>4</sup>	P1	P1	P1	P1	P1	P1
Bioaccumulation <sup>4</sup>	B1	B1	B1	B1	B1	B1

<sup>1</sup>Rhodia Inc. January 19, 2006. Revised Robust Summary for Phosphoric Acid Derivatives Category.

<http://www.epa.gov/chemrtk/pubs/summaries/phsacdde/c13356tc.htm>

<sup>2</sup>Conflicting results from two separate modified MITI tests were provided in the robust summary.

<sup>3</sup>U.S. EPA. 2008. Estimation Programs Interface Suite™ (version 3.20). United States Environmental Protection Agency, Washington, DC, USA. Available online at: <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

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

**Conclusion:** The phosphoric acid derivatives are liquids with moderate water solubility and low vapor pressure, except for the triisobutyl phosphate, which has moderate vapor pressure, and the supporting chemical mono(2-ethylhexyl)phosphate, which has a high water solubility. They are expected to have low to moderate mobility in soil. Volatilization of the phosphoric acid derivatives is considered low to moderate based upon their Henry's Law constants. The pK<sub>a</sub> values of bis(2-ethylhexyl)phosphate and mono(2-ethylhexyl) phosphate indicate that sub-category II members will exist almost entirely in the anionic form and therefore volatilization from water surfaces is not expected. The rate of hydrolysis is considered negligible for the chemicals in this category. The rate of atmospheric photooxidation is considered rapid to moderate. Compounds in the phosphoric acids derivatives category were found to be readily and inherently biodegradable. The phosphoric acid derivatives are expected to have low persistence (P1) and low bioaccumulation potential (B1).

### **3 Human Health Hazard**

A summary of health effects data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for tested category members are read-across (RA) to untested members of the category within the subcategories.

#### ***Acute Oral Toxicity***

##### ***Sub-Category I***

###### ***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

(1) In three studies, rats (strain and number not stated) were administered *tris*(2-ethylhexyl) phosphate via the oral route. Mortality and time of death was not reported.  
**LD<sub>50</sub> > 10,000 – 37,080 mg/kg-bw**

(2) In two studies, rabbits (strain and number not stated) were administered *tris*(2-ethylhexyl) phosphate via the oral route. Mortality and time of death was not reported.  
**LD<sub>50</sub> ~ 46,000 mg/kg-bw**

##### ***Sub-Category II***

###### ***Bis (2-ethylhexyl) phosphate (CASRN 298-07-7)***

(1) Wistar rats (5/sex/dose) were administered *bis*(2-ethylhexyl) phosphate via gavage at 500, 880, 1260, 2000 or 3000 mg/kg-bw and observed for 14 days. Mortalities were observed at all dose levels.  
**LD<sub>50</sub> = 1400 mg/kg-bw**

(2) Sprague-Dawley rats (5/sex/dose) were administered *bis*(2-ethylhexyl) phosphate via gavage at 500 or 5000 mg/kg-bw and observed for 14 days. All animals at the high-dose died within 24 hours. None of the low dose animals died within 14 days observation.  
**LD<sub>50</sub> > 500 mg/kg-bw (but < 5000 mg/kg-bw)**

(3) Sprague-Dawley rats (number and doses not specified) were administered liquid *bis*(2-ethylhexyl) phosphate via gavage and observed for 14 days. Study only available in a secondary source and reliability is not assignable.

**LD<sub>50</sub> = 4742 mg/kg-bw**

***Phosphoric acid, 2-ethylhexyl ester (CASRN 12645-31-7)***

Sprague-Dawley rats (3 females/dose) were administered phosphoric acid, 2-ethylhexyl ester via gavage at 300 mg/kg-bw in arachis oil BP (two groups) or 2000 mg/kg-bw, undiluted (1 group) and observed for 14 days. Mortalities were observed at the high-dose (2/3 animals found dead one or 2 days after dosing). No animals died at 300mg/kg.

**LD<sub>50</sub> < 2000 mg/kg-bw**

***Mono(2-ethylhexyl) phosphate (CASRN 1070-03-7, Supporting Chemical)***

(1) Sprague-Dawley rats (5/dose, sex not specified) were administered mono(2-ethylhexyl) phosphate via gavage at 464, 1000, 2150 or 4640 mg/kg-bw and observed for up to 14 days. Mortalities were observed at the 2 higher doses, but not specified by dose or time of death.

**LD<sub>50</sub> = 2710 mg/kg-bw**

(2) Sprague-Dawley rats (2 or 3/sex/dose) were administered mono(2-ethylhexyl)phosphate via gavage at 2000, 3160, 5010 or 7940 mg/kg-bw and observed for up to 7 days. No mortalities were observed at the low-dose. Number and time of deaths are not specified for the higher dose groups.

**LD<sub>50</sub> = 4100 mg/kg-bw**

***Sub-Category III***

***Triisobutyl phosphate (CASRN 126-71-6)***

(1) In four studies, rats (strain, sex and group size not specified) were administered triisobutyl phosphate via the oral route. Mortality and time of death was not reported.

**LD<sub>50</sub> = 3072 – 12,800 mg/kg-bw**

(2) Mice (strain, sex and group size not specified) were administered triisobutyl phosphate via the oral route. Mortality and time of death was not reported.

**LD<sub>50</sub> = 3200 – 6400 mg/kg-bw**

***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

Sprague-Dawley rats (5 males/dose) were administered tributyl phosphate via gavage at 464, 1000, 2150 or 4640 mg/kg-bw and observed for up to 14 days. All of the animals from the high-dose group died during the study by day 4; no mortality occurred at lower doses.

**LD<sub>50</sub> = 3160 mg/kg-bw**

***Acute Inhalation Toxicity***

***Sub-Category I***

***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

Summaries of two acute inhalation toxicity studies in rats (exposure duration was 4 hours in one study and not indicated in the other) and two acute inhalation toxicity studies in guinea pigs (exposure duration was 1 hour in one study and not indicated in the other) were provided by the sponsor, but were missing all other information. Three of these studies noted LC<sub>50</sub> values of > 0.447, > 0.45 and > 0.46 mg/L, but the remaining study in guinea pigs noted an LC<sub>50</sub> of 450 mg/L (exposure duration not indicated).

**LC<sub>50</sub> (duration not indicated) = 450 mg/L**

### ***Sub-Category III***

#### ***Triisobutyl phosphate (CASRN 126-71-6)***

Results of an acute inhalation study in rats (strain, sex, number and concentrations not specified) with an exposure duration of 4 hours were provided by the sponsor. No mention of mortality and no other study details were provided.

**LC<sub>50</sub> (4-hour) > 5.14 mg/L**

#### ***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

Rats (5/sex/concentration, strain not specified) were exposed to tributyl phosphate at unspecified concentrations for 4 hours. Mortality was seen in males (2/5 died), but not in females. No other data was provided.

**LC<sub>50</sub>(4-hour) > 4.24 mg/L**

### ***Acute Dermal Toxicity***

#### ***Sub-Category I***

##### ***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

Rabbits (strain, sex and group size not specified) were administered *tris*(2-ethylhexyl) phosphate by the dermal route. No other study details were provided.

**LD<sub>50</sub> ~ 20,000 mg/kg-bw**

#### ***Sub-Category II***

##### ***Bis(2-ethylhexyl) phosphate (CASRN 298-07-7)***

New Zealand white rabbits (3/sex/dose) were administered *bis*(2-ethylhexyl) phosphate dermally at 2000 mg/kg-bw on to clipped intact or abraded skin under occlusive conditions for 24 hours and observed for 14 days. No mortalities or clinical signs of toxicity were observed. Severe dermal irritation including crusty scabbing and swelling (eschar and edema) were observed in all animals.

**LD<sub>50</sub> > 2000 mg/kg-bw**

##### ***Mono(2-ethylhexyl) phosphate (CASRN 1070-03-7, Supporting Chemical)***

New Zealand White rabbits (4, sex, strain not specified) were administered mono(2-ethylhexyl) phosphate dermally at 4640 mg/kg-bw on to clipped intact skin. No mortalities or clinical signs of toxicity were observed. Severe redness and swelling (erythema and edema) were noted.

**LD<sub>50</sub> > 4640 mg/kg-bw**

### *Sub-Category III*

#### ***Triisobutyl phosphate (CASRN 126-71-6)***

Rabbits and guinea pigs (strain, sex, group size, and doses not specified) were administered triisobutyl phosphate dermally. No study details are provided.

**LD<sub>50</sub> (rabbits) > 5000 mg/kg-bw**

**LD<sub>50</sub> (guinea pigs) > 9600 mg/kg-bw**

#### ***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

In five studies, rabbits and guinea pigs (strain, sex, group size, and doses not specified) were administered tributyl phosphate dermally. No study details are provided.

**LD<sub>50</sub> (rabbits) > 3100 mg/kg-bw**

**LD<sub>50</sub> (guinea pigs) = 9700 – 19,400 mg/kg-bw**

### ***Repeated-Dose Toxicity***

#### ***Sub-Category I***

##### ***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

(1) In an National Toxicology Program (NTP) study, F344/N rats (10/sex/dose) were administered *tris*(2-ethylhexyl) phosphate in corn oil via gavage at 0 (vehicle control), 250, 500, 1000, 2000 or 4000 mg/kg-bw/day 5 days/week for 13 weeks. Slight to moderate decrease in weight gain was noted at the two highest doses (significance and magnitude not quantified in robust summary). No mortality or treatment-related histopathological effects were observed.

**LOAEL = 2000 mg/kg-bw/day** (based on decreased weight gain)

**NOAEL = 1000 mg/kg-bw/day**

(2) In an NTP study, B6C3F1 mice (10/sex/dose) were administered *tris*(2-ethylhexyl) phosphate in corn oil via gavage at 0 (vehicle control), 500, 1000, 2000, 4000 or 8000 mg/kg-bw/day for 13 weeks. Slight to moderate decrease in weight gain was noted at the two highest dose levels (significance and magnitude not quantified in robust summary). Inflammatory lesions in the gastric mucosa were seen at all doses with increased severity at higher doses. Ulceration was seen in the forestomach of 1 male at 2000 mg/kg-bw/day, 1 female at 4000 mg/kg-bw/day and 1 male and 3 females at 8000 mg/kg-bw/day. No mortalities were observed.

**LOAEL = 2000 mg/kg-bw/day** (based on ulceration in the forestomach)

**NOAEL = 1000 mg/kg-bw/day**

(3) Rats (strain, sex and group size not specified) were administered *tris*(2-ethylhexyl) phosphate in the diet at 10 – 1550 mg/kg-bw/day for 30 days. Weight loss was noted at 1550 mg/kg-bw/day. (Only study results were provided.)

**LOAEL = 1550 mg/kg-bw/day** (based on weight loss)

**NOAEL = 430 mg/kg-bw/day**

(4) Guinea pigs (males, group size not specified) were exposed to *tris*(2-ethylhexyl) phosphate via inhalation at 0, 1.6 or 9.6 mg/m<sup>3</sup> (0, 0.0016, 0.0096 mg/L) 6 hours/day, 5 days/week for 3 months. Increased terminal body weight and microscopic changes of kidney tissue were noted at the highest concentration. Sections of the spinal cord and sciatic nerve stained to demonstrate the myelin sheaths showed no pathologic alteration.

**LOAEL = 0.0096 mg/L** (based on histological changes of kidney)

**NOAEL = 0.0016 mg/L**

(5) Rhesus monkeys (number and sex not specified) were exposed to *tris*(2-ethylhexyl) phosphate via inhalation at 0, 10.8, 26.4 or 85 mg/m<sup>3</sup> (0, 0.0108, 0.0264 or 0.085 mg/L) 6 hours/day, 5 days/week for 3 months. No deaths and no effects were noted on weight gain, hematological and biochemical parameters, evaluation of trained behavior (visual discrimination test) and histopathological findings.

**NOAEL = 0.085 mg/L** (based on no effects at the highest dose tested)

### ***Sub-Category II***

Data gap

### ***Sub-Category III***

#### ***Triisobutyl phosphate (CASRN 126-71-6)***

Sprague-Dawley rats (10/sex for low- and mid-dose, 30/sex for control and high-dose) were administered triisobutyl phosphate in the diet at 0 (control), 200, 1000 or 5000 ppm (equivalent to 0, 13.9 – 16.8, 68.4 – 84.3 or 346.1 – 403.9 mg/kg-bw/day) for 13 weeks. Control and the high-dose animals were observed for 8 weeks post-exposure. High-dose animals exhibited reduced food intake, limited hematological effects (slight reduction in neutrophils - significance and magnitude of change not reported) and clinical chemistry changes (elevated cholesterol - significance and magnitude of change not reported). No mortality, changes in body weight or organ weight or hematological effects were observed.

**LOAEL = 346.1 – 403.9 mg/kg-bw/day** (based on limited hematological and clinical chemistry effects)

**NOAEL = 68.4 – 84.3 mg/kg-bw/day**

#### ***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

Sprague-Dawley rats (15/sex/dose) were administered tributyl phosphate via the diet at 0, 8, 40, 200, 1000 or 5000 ppm (equivalent to approximately 0, 0.6, 3, 15, 75 or 375 mg/kg-bw/day) for up to 13 weeks. After 45 days, blood was collected from 5/sex/dose for hematology and clinical chemistry and these animals were then sacrificed for

histologic examinations. Decreased body weights and decreased food consumption in 375 mg/kg-bw/day animals were observed. At interim sacrifice, treatment-related effects included elevated mean serum gamma-glutamyl transferase (SGGT) activity at 375 mg/kg-bw/day males and females and increased mean albumin and calcium values for 375 mg/kg-bw males. At terminal sacrifice, effects included increased mean SGGT values in 75 mg/kg-bw/day males (actual measured concentration 68.2 mg/kg-bw/day) and 375 mg/kg-bw/day males and females. Animals at 375 mg/kg-bw/day also exhibited increased partial thromboplastin time and increased mean serum glutamic pyruvic transaminase (SGPT) activity (males only). Histopathology revealed generalized transitional cell hyperplasia of the urinary bladder in 75 mg/kg-bw/day males and 375 mg/kg-bw/day males and females.

**LOAEL = 68.2 mg/kg-bw/day** (based on hematology and histopathological changes of the urinary bladder)

**NOAEL = 13.8 mg/kg-bw/day**

### ***Reproductive Toxicity***

#### ***Sub-Category I***

Data gap

#### ***Sub-Category II***

Data gap

#### ***Sub-Category III***

##### ***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

In a two-generation study, Sprague-Dawley rats (30/sex/concentration) were administered tributyl phosphate in the diet at 0, 200, 700 or 3000 ppm (approximately 0, 15, 53 and 225 mg/kg-bw/day) for 13 weeks for the F0 generation and 11 weeks for the F1 generation. Systemic effects included reduced body weight gains in high-dose F0 and F1 generation males and females and mid-dose F1 females, reduced food consumption in high-dose F0 and F1 males and females, urinary bladder epithelial hyperplasia in low-dose (generation and sex not specified) and in mid- and high-dose F0 and F1 males and females. Hepatic centrilobular hypertrophy was noted in mid-dose F0 and F1 generation females and high-dose F0 and F1 males and females. Developmental effects included "occasional" reduced pup weights in mid-dose and consistently and significantly reduced bodyweights in the high-dose pups. No mortalities or clinical signs of toxicity were observed. No reproductive effects were noted for mating indices, fertility indices, gestation length, litter size, pup sex ratio and pre- and postnatal loss.

**LOAEL (systemic toxicity) = 15 mg/kg-bw/day** (based on urinary bladder hyperplasia)

**NOAEL (systemic toxicity) = Not established**

**NOAEL (reproductive toxicity) = 225 mg/kg-bw/day** (based on no effects at the highest dose tested)

**LOAEL (developmental toxicity) = 225 mg/kg-bw/day** (based on reduced pup weights)

**NOAEL (developmental toxicity) = 53 mg/kg-bw/day**

*Developmental Toxicity*

*Sub-Category I*

Data gap

*Sub-Category II*

Data gap

*Sub-Category III*

***Triisobutyl phosphate (CASRN 126-71-6)***

In a prenatal developmental toxicity test, pregnant CD(SD) BR VAF/Plus rats (25/dose) were administered triisobutyl phosphate via gavage at 0, 100, 300 or 1000 mg/kg-bw/day on gestation days 6 – 15. Clinical signs of toxicity included an increased salivation at all doses. Increased water consumption was observed during the treatment phase of the high-dose group. Slightly decreased body weight gains were seen at the high dose after day 8 of gestation but returned to control levels by the study's end. No changes in the number of fetal abnormalities were observed. In the robust summary, it is not clear what developmental endpoints were evaluated.

**NOAEL (maternal toxicity) = 1000 mg/kg-bw/day**(based on no effects at the highest dose tested)

**NOAEL (developmental toxicity) = 1000 mg/kg-bw/day** (based on no effects at the highest dose tested)

***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

In a prenatal developmental toxicity test, pregnant Sprague-Dawley rats (24/dose) were administered tributyl phosphate in corn oil via gavage at 0, 188, 375 or 750 mg/kg-bw/day on days 6 – 15 of gestation. Mortality was noted in high-dose dams (7 of 24 died [29.2%]). Decreased mean body weight gain and body weights were noted in low-, mid- and high-dose dams, decreased food consumption was noted in mid- and high-dose dams and increased relative (to body weight) liver weights were noted in high-dose dams. Reported developmental effects are limited to decreased mean fetal body weight in high-dose pups.

**LOAEL (maternal toxicity) = 188 mg/kg-bw/day** (based on decreased body weight and body weight gain)

**NOAEL (maternal toxicity) = Not established**

**LOAEL (developmental toxicity) = 750 mg/kg-bw/day** (based on decreased mean fetal body weights)

**NOAEL (developmental toxicity) = 375 mg/kg-bw/day**

*Genetic Toxicity – Gene Mutation*

*In vitro*

***Sub-Category I***

***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

(1) In four bacterial reverse mutation assays, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to *tris*(2-ethylhexyl) phosphate in the presence or absence of metabolic activation. Negative results are reported but no other information was provided.

**Tris(2-ethylhexyl) phosphate was not mutagenic in these assays.**

(2) In an NTP study, *Salmonella typhimurium* strains TA98, TA100, TA 1535 and TA1537 were exposed to *tris*(2-ethylhexyl) phosphate at 100, 333, 1000, 3333, and 10,000 µg/plate in the presence and absence of metabolic activation. Positive and negative controls were included and responded appropriately. *Tris*(2-ethylhexyl) phosphate was negative.

**Tris(2-ethylhexyl) phosphate was not mutagenic in this assay.**

***Sub-Category II***

***Bis(2-ethylhexyl) phosphate (CASRN 298-07-7)***

(1) In reverse mutation assays, *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and *Saccharomyces cerevisiae* D4 were exposed to *bis*(2-ethylhexyl) phosphate at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 µL/plate in the presence and absence of metabolic activation. Positive controls were tested, but their response was not provided. The cytotoxic concentration was 5 µL/plate. *Bis*(2-ethylhexyl) phosphate was negative for genotoxic effects.

***Bis*(2-ethylhexyl)phosphate was not mutagenic in this assay.**

(2) In bacterial reverse mutation assays, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to *bis*(2-ethylhexyl) phosphate at 0, 4, 20, 100, 500 or 2500 µg/plate in the presence and absence of metabolic activation. Positive controls were used and produced an appropriate response. The cytotoxic concentration was 100 µg/plate. *Bis*(2-ethylhexyl) phosphate was negative for genotoxic effects.

***Bis*(2-ethylhexyl)phosphate was not mutagenic in this assay.**

(3) Mouse lymphoma L5178Y/TK+/- cells were exposed to *bis*(2-ethylhexyl) phosphate at 0, 0.06, 0.065, 0.07, 0.075, 0.08, 0.085 or 0.9 µL/mL in the absence of metabolic activation and 0, 0.05, 0.055, 0.06, 0.065, 0.07, 0.075 or 0.085 µL/mL in the presence of metabolic activation. Positive controls were tested, but responses were not provided. The cytotoxic concentration was 1 µL/mL. *Bis*(2-ethylhexyl) phosphate was negative for genotoxic effects.

***Bis*(2-ethylhexyl)phosphate was not mutagenic in this assay.**

***Phosphoric acid, 2-ethylhexyl ester (CASRN 12645-31-7)***

(1) In bacterial reverse mutation assays, *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2uvrA- were exposed to phosphoric acid, 2-ethylhexyl ester at 0, 15, 50, 150, 500, 1500 or 5000 µg/plate for all *Salmonella* strains and 0, 50, 150, 500, 1500 or 5000 µg/plate for the *Escherichia .coli* strain in the presence and absence of metabolic activation. Vehicle and positive controls were used and produced appropriate responses. The cytotoxic concentration was 5000 µg/plate for TA100 in the presence and absence of metabolic activation. No cytotoxic concentration was noted for Wp2uvrA-. No increase in revertants was evident.

**Phosphoric acid, 2-ethylhexyl ester was not mutagenic in this assay.**

(2) In mutation assays, *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and *Saccharomyces* strain D4 were exposed to phosphoric acid, 2-ethylhexyl ester at 0.001 – 5 µg/plate (solvent control) in the presence and absence of metabolic activation. Positive controls were tested but their responses were not provided. The cytotoxic concentration was 5 µg/plate, in the presence and absence of metabolic activation for the bacterial tester strains. Phosphoric acid, 2-ethylhexyl ester was negative in these assays.

**Phosphoric acid, 2-ethylhexyl ester was not mutagenic in this assay.**

***Sub-Category III***

***Triisobutyl phosphate (CASRN 126-71-6)***

In three bacterial reverse mutation assays, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 (only present in one of the three studies) were exposed to triisobutyl phosphate at 20 – 5000 µg/plate (Standard Plate Assay) and at 15 – 5000 µg/plate (Preincubation Test) in assay one, 10 – 5000 µg/plate in study two and up to 5 mg/plate in assay three, all in the presence and absence of metabolic activation. No other information was provided. Triisobutyl phosphate showed negative results in these assays.

**Triisobutyl phosphate was not mutagenic in these assays.**

***Tributyl phosphate (CASRN 126-73-8, supporting chemical)***

*Salmonella typhimurium* strains TA102 and TA2638 and *Escherichia coli* strains WP2/pKM101 and WP2uvr/pKM101 were exposed to tributyl phosphate at 0, 31.3, 78, 125, 250, 313, 500, 625, 1000, 1250, 2000, 2500 or 5000 µg/plate in the presence and absence of metabolic activation. Positive controls were tested, but their responses were not provided. No cytotoxic concentration was provided. Tributyl phosphate showed negative results in these assay.

**Tributyl phosphate was not mutagenic in this assay.**

*Genetic Toxicity – Chromosomal Aberrations*

*In vitro*

*Sub-Category I*

***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

In NTP studies, Chinese hamster ovary cells were exposed to *tris(2-ethylhexyl) phosphate* at 25.1, 37.5 and 50 µg/mL in the absence of metabolic activation and at 839, 1253 and 1670 µg/mL in the presence of metabolic activation. There was no significant increase in cell with aberrations. Positive and negative controls responded appropriately. No increase in aberrant cells was noted at any concentration.

***Tris(2-ethylhexyl) phosphate did not induce chromosomal aberrations in these assays.***

*Sub-Category II*

Data gap

*Sub-Category III*

***Tributyl phosphate (CASRN 126-73-8, supporting chemical)***

Two cytogenetic assays were conducted, one using CHO-K1 cells and concentrations up to 0.15 µL/mL and the other with mouse embryos at 45 and 144 hours after conception. No other details were provided.

***Tributyl phosphate did not induce chromosomal aberrations in these assays.***

*In vivo*

*Sub-Category I*

***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

(1) In an NTP study, B6C3F1 mice (5 males/dose) were administered *tris(2-ethylhexyl) phosphate* via intraperitoneal injection at 0 (corn oil control), 500, 1000, 2000 or 3000 mg/kg-bw. At 24 and 48 hours, animals were sacrificed, bone marrow samples collected and scored for the occurrence of micronucleated PCE and PCE/erythrocyte ratios. A positive control was tested and produced an appropriate response. No increase in micronuclei was noted at any concentration.

***Tris(2-ethylhexyl) phosphate did not induce chromosomal aberrations in this assay.***

(2) In an NTP study, B6C3F1 mice (8 males/dose) were exposed to *tris(2-ethylhexyl) phosphate* via intraperitoneal injection at 0 (vehicle control), 1250, 2500 or 5000 mg/kg-bw. At 24 and 48 hours, animals were sacrificed, bone marrow samples collected and scored for the occurrence of micronucleated PCE and PCE/erythrocyte ratios. Positive controls were used and produced an appropriate response. *Tris(2-ethylhexyl) phosphate* was negative in this assay.

***Tris(2-ethylhexyl) phosphate did not induce chromosomal aberrations in this assay.***

*Sub-Category III*

***Triisobutyl phosphate (CASRN 126-71-6)***

CD-1 mice (5/sex/dose/sampling time) were administered triisobutyl phosphate by the intraperitoneally at 0, 300, 600 or 1200 mg/kg-bw. At 24, 48 and 72 hours, animals were sacrificed, bone marrow samples collected and scored for the occurrence of micronucleated PCE and PCE/erythrocyte ratios. The high dose did not induce increases in frequency of micronucleated PCEs. Positive controls were tested, but their responses were not provided.

**Triisobutyl phosphate did not induce chromosomal aberrations in this assay.**

### *Additional Information*

#### *Skin Irritation*

##### *Sub-Category I*

###### *Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)*

In two skin irritation studies in rabbits, *tris(2-ethylhexyl) phosphate* was considered irritating. One test, (dose and number of animals unspecified), treated skin on the rabbit's ear. Moderate erythema (redness) that persisted for 1 week was noted in a study where 250 mg was applied to clipped skin on the back study. (Limited study details were provided)

**Tris(2-ethylhexyl) phosphate was irritating to rabbit skin in this study.**

##### *Sub-Category II*

###### *Bis(2-ethylhexyl) phosphate (CASR N 298-07-7)*

(1) Rabbits (6, sex, strain not specified) were administered 0.5 mL of the test substance dermally on to clipped intact and abraded skin under occluded conditions for 24 hours and assessed for up to 14 days after exposure. Effects included erythema and edema (swelling). The study concluded the substance was highly irritating.

**Bis(2-ethylhexyl) phosphate was irritating to rabbit skin in this study.**

(2) Rabbits (6, sex, strain not specified) were administered 0.5 mL of the test substance dermally on to clipped, intact skin under occluded conditions for 48 hours. There was redness and swelling reported. Test sites for all animals were blanched at 4 hours, but had recovered at the 48-hour observation.

**Bis(2-ethylhexyl) phosphate was irritating to rabbit skin in this study.**

(3) Rabbits (6, sex, strain not specified) were administered 0.5 mL of the test substance dermally on to clipped, intact skin under occluded conditions for 24 hours and assessed for up to 72 hours after exposure. There was no irritation observed.

**Bis(2-ethylhexyl) phosphate was not irritating to rabbit skin in this study.**

###### *Mono(2-ethylhexyl) phosphate (CASRN 1070-03-7, Supporting Chemical)*

Albino rabbits (3, sex, strain not specified) were administered mono(2-ethylhexyl) phosphate dermally on to clipped, intact skin under occluded conditions and assessed at 4, 24, 48, 72, 120 and 168 hours according to the Draize method. The compound was classified as corrosive. No change was observed at termination.

**Mono(2-ethylhexyl) phosphate was corrosive to rabbit skin in this study.**

***Sub-Category III***

***Triisobutyl phosphate (CASRN 126-71-6)***

Two skin irritation studies were conducted in rabbits. The test substance was irritating to rabbit skin in one study but not irritating in the second study. (Limited information was provided.)

**Triisobutyl phosphate was irritating to rabbit skin in this study.**

***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

Ten tests were conducted in rabbits, guinea pigs and rats. Values ranged from slightly irritating to highly irritating. (Limited details were available.)

**Tributyl phosphate was irritating to rabbit, guinea pig and rat skin in this study.**

***Eye Irritation***

***Sub-Category I***

***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

Rabbits (number, sex, strain not specified) were instilled 0.01 – 0.5 mL *tris*(2-ethylhexyl) phosphate into the eye. Slight conjunctivitis was seen up to 0.05 mL and moderate conjunctivitis was seen at  $\geq 0.1$  mL which cleared up within 24 hours.

**Tris(2-ethylhexyl) phosphate was not irritating to rabbit eyes in this study.**

***Sub-Category II***

***Bis(2-ethylhexyl) phosphate (CASRN 298-07-7)***

(1) Six rabbits (strain, sex not specified) were instilled *bis*(2-ethylhexyl) phosphate (0.1 mL) into the right eye. The treated eyes remained unwashed. Irritation was scored at 1, 2, 3, 4, 5, 6 and 7 days after instillation. Effects on the cornea, iris and conjunctiva were noted.

**Bis(2-ethylhexyl) phosphate was corrosive to rabbit eyes in this study.**

(2) Six rabbits (strain, sex not specified) were instilled *bis*(2-ethylhexyl) phosphate (0.1 mL) into one eye. Three treated eyes remained unwashed, while the other three were washed for 1 minute with warm water 20 seconds after instillation. The treated eyes were scored for irritation at 1, 24, 48 and 72 hours after treatment. Cornea, iris and conjunctiva effects were noted in washed and unwashed eyes.

**Bis(2-ethylhexyl) phosphate was highly irritating to rabbit eyes in this study.**

***Mono(2-ethylhexyl) phosphate (CASRN 1070-03-7, Supporting Chemical)***

(1) Three rabbits (strain, sex not specified) were instilled mono(2-ethylhexyl) phosphate (0.01 mL) into one eye. Evaluations at 1, 24, 48 and 72 hours after treatment found that the test substance was corrosive. The corneal opacity did not improve within 10 days, suggesting possible irreversible/corrosive effects.

**Mono(2-ethylhexyl) phosphate was corrosive to rabbit eyes in this study.**

(2) Six rabbits (strain, sex not specified) were instilled mono(2-ethylhexyl) phosphate (0.01 mL) into one eye. The eyes remained unwashed. Evaluations were made at 1, 24,

48, 72, 120 and 168 hours according to the Draize method. The test material was corrosive. At 240 hours, opalescent areas of corneal cloudiness were still present with iris hemorrhagic and showing reaction to light.

**Mono(2-ethylhexyl) phosphate was corrosive to rabbit eyes in this study.**

(3) Three rabbits (strain, sex not specified) were instilled mono(2-ethylhexyl) phosphate (0.01 mL) into one eye. Evaluations were made at 24, 48 and 72 hours after treatment. Erythema and edema of the cornea and moderate opacity were observed. The test substance was classified as corrosive. The irritating effects were reversed in 5 – 7 days.

**Mono(2-ethylhexyl) phosphate was corrosive to rabbit eyes in this study.**

### *Sub-Category III*

#### *Triisobutyl phosphate (CASRN 126-71-6)*

Two eye irritation studies of triisobutyl phosphate were conducted in rabbits. Results were not irritating in one study and irritating in a second study. No other information was provided.

**Triisobutyl phosphate was irritating to rabbit eyes in this study.**

#### *Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)*

Four studies were conducted in rabbits. Values ranged from slightly irritating to irritating. No other information was provided.

**Tributyl phosphate was irritating to rabbit eyes in this study.**

### *Sensitization*

### *Sub-Category III*

#### *Triisobutyl phosphate (CASRN 126-71-6)*

Three sensitization studies were conducted in guinea pigs using the Buehler Test, Guinea Pig Maximization Test and an unspecified method. No other information was provided. All three studies classified the test substance as sensitizing.

**Triisobutyl phosphate was a dermal sensitizer in guinea pigs.**

#### *Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)*

(1) Tributyl phosphate was not sensitizing in an open epicutaneous test in guinea pigs. No additional information available. In a second test a “standard sensitization test” was positive in 6 out of 15 guinea pigs. No further data was presented.

**Tributyl phosphate was a dermal sensitizer in guinea pigs in this study.**

(2) In a patch test, 15 applications of tributyl phosphate were applied as less than 25% formulation to 53 volunteers, on alternate days. No volunteer gave local reactions 24 hours after the final patch, therefore no evidence of sensitization. No additional information available.

**Tributyl phosphate was not a dermal sensitizer in humans in this study.**

## *Carcinogenicity*

### *Sub-Category I*

#### ***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

(1) In an NTP study, Fischer 344 rats (50/sex/dose) were administered *tris(2-ethylhexyl) phosphate* via gavage at 0, 2000 or 4000 mg/kg-bw/day (males) and 0, 1000 or 2000 mg/kg-bw/day (females) in corn oil 5 days/week for 2 years. No clinical signs of toxicity, changes in survival or evidence of carcinogenicity in female rats were noted. Treatment-related effects in males included lower mean body weights throughout the study. A dose-related increase in the incidence of pheochromocytoma of adrenal glands and a positive trend for increased incidence of thyroid follicular cell hyperplasia was observed. The NTP study concludes there was equivocal evidence of carcinogenesis (adrenal gland medulla) in male rats but no evidence in female rats. The high dose of corn oil (10 ml/kg) used as a vehicle in gavage may have decreased the background of some age-related tumors in this study and it was not clear the increased neoplasms were related to treatment with CASRN 78-42-2.

***Tris(2-ethylhexyl) phosphate showed equivocal evidence of carcinogenicity in male rats in this study.***

(2) In an NTP study, B6C3F1 mice (50/sex/dose) were administered *tris(2-ethylhexyl) phosphate* via gavage at 0, 500 or 1000 mg/kg-bw/day in corn oil 5 days/week for 2 years. An increased incidence of follicular cell hyperplasia of the thyroid gland was noted in males and females and an increased incidence of hepatocellular carcinoma was noted in females. No clinical signs of toxicity, depression in body weight or changes in survival were noted. The NTP study concludes there was some evidence of carcinogenesis in female mice (hepatocellular carcinoma) but no evidence in male mice. The increased tumor incidence in females was only moderately increased and significant only at the high dose. There is no mode of action analysis available, but this type of liver cancer in rodents may involve the peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ). This mode of action is specific to rodents and would not be relevant to humans.

***Tris(2-ethylhexyl) phosphate showed some evidence of carcinogenicity in female mice in this study.***

## **Conclusion**

***Sub-Category I:*** Acute oral toxicity of CASRN 78-42-2 to rats and rabbits, acute inhalation toxicity to guinea pigs and acute dermal toxicity to rabbits is low. This chemical is irritating to rabbit skin, and not irritating to rabbit eyes. In the oral repeated-dose studies, rats and mice exposed to CASRN 78-42-2 at doses greater than or equal to 1550 mg/kg-day had body weight losses; the NOAEL for systemic toxicity was 430 mg/kg-day. One study of repeated-dose inhalation exposures in guinea pigs showed histological changes in the kidney at 0.0096 mg/L/day; the NOAEL for systemic toxicity was 0.0016 mg/L/day. No data are available for the reproductive/developmental toxicity endpoints. This chemical did not induce gene mutations or chromosomal aberrations *in vitro*. CASRN 78-42-2 showed some evidence of carcinogenicity in rats and mice which is considered equivocal.

The reproductive and developmental toxicity endpoints remain as data gaps for the purposes of the HPV Challenge Program.

**Sub-Category II:** Acute oral toxicity of CASRN 298-07-7 and CASRN 12645-31-7 (mixture) to rats and acute dermal toxicity of CASRN 298-07-7 and supporting chemical CASRN 1070-03-7 to rabbits is low. CASRN 298-07-7 and supporting chemical CASRN 1070-03-7 are irritating to rabbit skin and corrosive to rabbit eyes. No data are available for the repeated-dose, reproductive and developmental toxicity endpoints for this sub-category. CASRN 298-07-7 and CASRN 12645-31-7 did not induce gene mutations *in vitro*. No data are available for the chromosomal aberrations endpoint for this sub-category.

The chromosomal aberrations, repeated-dose, reproductive and developmental toxicity endpoints remain as data gaps for the purposes of the HPV Challenge Program.

**Sub-Category III:** Acute oral toxicity of CASRN 126-71-6 and CASRN 126-73-8 (supporting chemical) to rats and mice and acute dermal toxicity to rabbits and guinea pigs are low. Acute inhalation toxicity of CASRN 126-71-6 in rats is low in one study. Both chemicals in the sub-category are irritating to rat, rabbit, human and guinea pig skin, are irritating to rabbit eyes and are dermal sensitizers in guinea pigs but not in humans. Oral repeated-dose studies of rats administered CASRN 126-71-6 showed limited hematological and clinical chemistry effects at 346 mg/kg-day; the NOAEL for systemic toxicity was 68 mg/kg-day. Oral repeated-dose studies of rats administered CASRN 126-73-8 (supporting chemical) showed hematology and histopathological changes of the urinary bladder at 68 mg/kg-day; the NOAEL for systemic toxicity was 13.8 mg/kg-day. In a two-generation oral reproductive toxicity study in rats, CASRN 126-73-8 (supporting chemical) showed no reproductive toxicity, and the NOAEL for reproductive toxicity was 225 mg/kg-day. In the same study, there was developmental (pre- and postnatal) toxicity at 225 mg/kg-day as demonstrated by reduced pup weights; the NOAEL for developmental toxicity was 53mg/kg-day. Both chemicals in this sub-category did not induce gene mutations *in vitro* and did not induce chromosomal aberrations *in vitro* or *in vivo*. No evidence of neurotoxicity was seen for the supporting chemical, CASRN 126-73-8. The supporting chemical showed evidence of carcinogenicity in rats.

No data gaps were identified for the purposes of the HPV Challenge Program.

Table 4. Summary of Human Health Data						
Endpoints	Sub-Category I	Sub-Category II			Sub-Category III	
	<i>Tris</i> (2-ethylhexyl) phosphate (78-42-2)	<i>Bis</i> (2-ethylhexyl) phosphate (298-07-7)	Phosphoric acid, 2-ethylhexyl ester (12645-31-7)	Mono(2-ethylhexyl) phosphate (1070-03-7, supporting chemical)	Triisobutyl phosphate (126-71-6)	Tributyl phosphate (126-73-8, supporting chemical)
Acute Oral Toxicity LD <sub>50</sub> (mg/kg-bw)	37,080	1400	>300, <2000	2710	3072	3160
Acute Inhalation Toxicity LC <sub>50</sub> (mg/L)	450	–	–	–	> 5.14	> 4.24
Acute Dermal Toxicity LD <sub>50</sub> (mg/kg-bw)	20,000	> 2000	–	> 4640	9600	9700
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 430 LOAEL = 1550	Data Gap	Data Gap	–	NOAEL = 68.4 – 84.3 LOAEL = 346.1 – 403.9	NOAEL = 13.8 LOAEL = 68.2
Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/day)	NOAEL = 0.0016 LOAEL = 0.0096	–	–	–	–	–
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Data Gap	Data Gap	Data Gap	–		
Reproductive Toxicity					NOAEL = 225	NOAEL = 225 (hdt)
Developmental Toxicity					NOAEL = 53 LOAEL = 225 (RA)	NOAEL = 53 LOAEL = 225

Table 4. Summary of Human Health Data						
	Sub-Category I	Sub-Category II			Sub-Category III	
Endpoints	<i>Tris</i> (2-ethylhexyl) phosphate  (78-42-2)	<i>Bis</i> (2-ethylhexyl) phosphate  (298-07-7)	Phosphoric acid, 2-ethylhexyl ester  (12645-31-7)	Mono(2-ethylhexyl) phosphate (1070-03-7, supporting chemical)	Triisobutyl phosphate  (126-71-6)	Tributyl phosphate  (126-73-8, supporting chemical)
Developmental Toxicity NOAEL/LOAL Oral (mg/kg-bw/day) Maternal Toxicity  Developmental Toxicity	Data Gap	Data Gap	Data Gap	—	NOAEL = 1000 (hdt)  NOAEL = 1000(hdt)	NOAEL = Not Established LOAEL = 188  NOAEL = 375 LOAEL = 750
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative	Negative	Negative	—	Negative	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative	Data Gap	Data Gap	—	No Data Negative (RA)	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Negative	—	—	—	Negative	—
Additional Information Skin Irritation Eye Irritation Sensitization  Carcinogenicity  Neurotoxicity	Irritating Not irritating —  Carcinogenic  —	Irritating Corrosive —  —  —	—      —	Corrosive Corrosive —  —  —	Irritating Irritating Sensitizing  —  No Data Negative (RA)	Irritating Irritating Sensitizing  Carcinogenic  Negative

**Bold = measured data;** (RA) = Read Across; — indicates endpoint was not addressed for this chemical; (hdt) = highest dose tested

#### **4 Hazards to the Environment**

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

##### ***Acute Toxicity to Fish***

##### ***Sub-Category I***

##### ***Tris (2-ethylhexyl) phosphate (CASRN 78-42-2)***

Zebrafish (*Brachydanio rerio*) were exposed to *tris* (2-ethylhexyl) phosphate at unspecified nominal concentrations under static conditions for 96 hours with a reported LC<sub>0</sub> of greater than 100 mg/L. The concentration tested was above the water solubility limit; assuming exposure concentration is the water solubility limit (saturation) for *tris* (2-ethylhexyl) phosphate, the no effect concentration would be approximately 2 mg/L.

##### **No effects at saturation**

A 96-hour LC<sub>50</sub> for fish, estimated by ECOSAR, was 0.000218 mg/L.

**96-h LC<sub>50</sub> = 0.000218 mg/L** (estimated)

##### ***Sub-Category II***

##### ***Bis (2-ethylhexyl) phosphate (CASRN 298-07-7)***

(1) Rainbow trout (*Oncorhynchus mykiss*) were exposed to *bis* (2-ethylhexyl) phosphate at unspecified nominal and measured concentrations under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 48 – 54 mg/L**

(2) Rainbow trout (*Oncorhynchus mykiss*) were exposed to *bis* (2-ethylhexyl) phosphate at unspecified nominal concentrations under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 30 mg/L**

(3) Zebra fish (*Brachydanio rerio*) were exposed to *bis* (2-ethylhexyl) phosphate at unspecified nominal concentrations under static conditions for 96 hours.

**96-h LC<sub>50</sub> > 56 mg/L**

Rainbow trout (*Oncorhynchus mykiss*) were exposed to *bis* (2-ethylhexyl) phosphate for 96 hours in six studies reported in the ECOTOX data base (<http://www.epa.gov/ecotox>).

**96-h LC<sub>50</sub> = 20 – 56 mg/L**

##### ***Phosphoric acid, 2-ethylhexyl ester (CASRN 12645-31-7)***

(1) Rainbow trout (*Oncorhynchus mykiss*) were exposed to phosphoric acid, 2-ethylhexyl ester at a measured concentration of 100 mg/L under semi-static conditions for 96 hours. No mortalities were observed.

**96-h LC<sub>50</sub> > 100 mg/L**

(2) Rainbow trout (*Oncorhynchus mykiss*) were exposed to phosphoric acid, 2-ethylhexyl ester at nominal concentrations of 0, 100, 499, 1026, 2026 or 5018 mg/L under static conditions for 96 hours. Measured concentrations were not provided. No test related mortalities were observed. Cloudy water was observed.

**96-h LC<sub>50</sub> > 5018 mg/L**

### ***Sub-Category III***

#### ***Triisobutyl phosphate (CASRN 126-71-6)***

In six studies, rainbow trout (*Oncorhynchus mykiss*), bluegills (*Lepomis macrochirus*), golden orfes (*Leuciscus idus*) or ricefish (*Oryzias latipes*) were exposed to triisobutyl phosphate under flow-through or static conditions for 24, 48 or 96 hours. Although the studies were missing critical data elements, they are acceptable on a weight-of-evidence basis.

**96-h LC<sub>50</sub> = 17.8 – 23 mg/L**

#### ***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

(1) Rainbow trout (*Oncorhynchus mykiss*) were exposed to tributyl phosphate at measured concentrations of 0 (solvent control), 1.2, 2.1, 4.3, 9.3 and 19 mg/L under static conditions for 96 hours. Mortality was 100% at 19 mg/L; no mortality was seen at lower concentrations.

**96-h LC<sub>50</sub> = 11 mg/L**

(2) Summaries of 17 additional acute fish studies were presented by the sponsor. The median lethal concentration values found in these studies ranged from 4.2 to 14.2 mg/L, but because another adequate study was available and because the additional studies were missing critical information and had no reliability indicators, they were not reviewed further.

### ***Acute Toxicity to Aquatic Invertebrates***

#### ***Sub-Category I***

##### ***Tris(2-ethylhexyl) phosphate (CASRN 78-42-2)***

No measured data were available. A 48-hour EC<sub>50</sub> for *Daphnia*, estimated by ECOSAR, was 0.009 mg/L.

**48-h EC<sub>50</sub> = 0.009 mg/L (estimated)**

#### ***Sub-Category II***

##### ***Bis(2-ethylhexyl) phosphate (CASRN 298-07-7)***

(1) Water fleas (*Daphnia magna*) were exposed to *bis* (2-ethylhexyl) phosphate at unspecified nominal concentrations under static conditions for 48 hours.

**48-h EC<sub>50</sub> = 60.7 mg/L**

(2) Water fleas (*Daphnia magna*) were exposed to *bis* (2-ethylhexyl) phosphate at unspecified nominal concentrations under static conditions for 48 hours.

**48-h EC<sub>50</sub> > 42 mg/L**

(3) Water fleas (*Daphnia magna*) were exposed to *bis* (2-ethylhexyl) phosphate in 20 studies reported in the ECOTOX database (<http://www.epa.gov/ecotox>).

**48-h EC<sub>50</sub> = 75 – 83.7 mg/L**

***Phosphoric acid, 2-ethylhexyl ester (CASRN 12645-31-7)***

Water fleas (*Daphnia magna*) were exposed to phosphoric acid, 2-ethylhexyl ester at nominal concentrations of 32, 56, 100, 180 or 320 mg/L under static conditions for 48 hours. Measured concentrations were not provided.

**48-h EC<sub>50</sub> = 110 mg/L**

***Sub-Category III***

***Triisobutyl phosphate (CASRN 126-71-6)***

In four studies, *Daphnia magna* were exposed to triisobutyl phosphate for 24 or 48 hours. Although the studies were missing critical data elements, they are acceptable on a weight-of-evidence basis.

**48-h EC<sub>50</sub> = 11 mg/L**

***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

(1) Water fleas (*Daphnia magna*) were exposed to tributyl phosphate at measured concentrations of 0 (DMF solvent control), 0 (negative control), 0.32, 0.75, 1.8, 3.5 and 7.8 mg/L under flow-through conditions for 48 hours.

**48-h EC<sub>50</sub> = 2.6 mg/L**

(2) Summaries of 15 additional aquatic invertebrate studies were submitted by the sponsor. The median lethal concentration values found in these studies ranged from 1.7 to 68 mg/L, however, the additional studies were missing critical information and had no reliability indicators and as such, they were not reviewed further.

***Toxicity to Aquatic Plants***

***Sub-Category I***

***Tris (2-ethylhexyl) phosphate (CASRN 78-42-2)***

No measured data were available. A 96-hour EC<sub>50</sub> for green algae, estimated by ECOSAR, was 0.000798 mg/L.

**48-h EC<sub>50</sub> = 0.000798 mg/L (estimated)**

***Sub-Category II***

***Bis (2-ethylhexyl) phosphate (CASRN 298-07-7)***

Algae (*Chlorella emersonii*) were exposed to *bis* (2-ethylhexyl) phosphate at nominal concentrations of 0, 50 or 100 mg/L under static conditions for 72 hours. Measured concentrations were not provided.

**72-h EC<sub>50</sub> (growth) > 100 mg/L**

***Phosphoric acid, 2-ethylhexyl ester (CASRN 12645-31-7)***

(1) Algae (*Pseudokirchneriella subcapitata*) were exposed to phosphoric acid, 2-ethylhexyl ester at unspecified nominal and measured concentrations under static conditions for 72 hours.

**72-h EC<sub>50</sub> (growth) = 168 mg/L**

(2) Algae (*Pseudokirchneriella subcapitata*) were exposed to phosphoric acid, 2-ethylhexyl ester at unspecified nominal and measured concentrations under static conditions for 72 hours.

**72-h EC<sub>50</sub> (biomass) = 161 mg/L**

### ***Sub-Category III***

#### ***Triisobutyl phosphate (CASRN 126-71-6)***

In nine studies, algae (*Scenedesmus subspicatus*) were exposed to triisobutyl phosphate for 72 hours. Although the studies were missing critical data elements, they are acceptable on a weight-of-evidence basis.

**72-h EC<sub>50</sub> (biomass) = 33 mg/L**

**72-h EC<sub>50</sub> (growth) = 34 mg/L**

#### ***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

In seven different aquatic plants (*Chlorella vulgaris*, *Microcystis aeruginosa*, *Scenedesmus quadricauda*, *Scenedesmus subspicatus*, *Pseudokirchneriella subcapitata*, *Chlorella emersonii* and phytoplankton) were exposed to tributyl phosphate for (2, 3, 4, 7, 8 or 14 days). Although the studies were missing critical data elements, they are acceptable on a weight-of-evidence basis. Values below are from a study of *Scenedesmus subspicatus*; other EC<sub>50</sub> values ranged from 3.1 to 10 mg/L.

**72-h EC<sub>50</sub> (biomass) = 1.1 mg/L**

**72-h EC<sub>50</sub> (growth) = 2.8 mg/L**

### ***Chronic Toxicity to Fish***

#### ***Sub-Category I***

##### ***Tris (2-ethylhexyl) phosphate (CASRN 78-42-2)***

A chronic fish value, estimated by ECOSAR, was 0.000012 mg/L.

**Chronic = 0.000012 mg/L (estimated)**

#### ***Sub-Category II***

##### ***Bis (2-ethylhexyl) phosphate (CASRN 298-07-7)***

Rainbow trout (*Oncorhynchus mykiss*) were exposed to bis(2-ethylhexyl) phosphate at unspecified nominal and measured concentrations for 62 days.

**EC<sub>50</sub> (early life stage) = 20.6 mg/L**

#### ***Sub-Category III***

##### ***Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)***

(1) Rainbow trout (*Salmo gairdneri*) were exposed to tributyl phosphate at unspecified nominal and measured concentrations for 50 days under semi-static conditions.

**Threshold concentration = 8.3 mg/L**

(2) Rainbow trout (*Oncorhynchus mykiss*) were exposed to tributyl phosphate at unspecified nominal and measured concentrations for 95 days.

**NOEC = 0.82 mg/L**

**LOEC = 1.7 mg/L**

**MATC = 1.2 mg/L**

### *Chronic Toxicity to Invertebrates*

#### *Sub-Category III*

##### *Tributyl phosphate (CASRN 126-73-8, Supporting Chemical)*

(1) Water fleas (*Daphnia magna*) were exposed to tributyl phosphate at unspecified nominal and measured concentrations for 21 days.

**21-d EC<sub>50</sub> (immobilization) > 2.1 mg/L**

**21-d NOEC (length, days to first brood, Y/D/D) = 0.87 mg/L**

**21-d LOEC (length, days to first brood, Y/D/D) = 2.1 mg/L**

**21-d MATC (length, days to first brood, Y/D/D) = 1.35 mg/L**

(2) Water fleas (*Daphnia magna*) were exposed to tributyl phosphate at unspecified nominal and measured concentrations for 21 days.

**21-d NOEC = 1 mg/L**

### **Conclusions:**

**Sub-Category I:** The predicted 96-hour LC<sub>50</sub> of CASRN 78-42-2 to fish is 0.000218 mg/L. The predicted 48-hour EC<sub>50</sub> of CASRN 78-42-2 to aquatic invertebrates 0.009 mg/L. The 96-hour EC<sub>50</sub> of CASRN 78-42-2 to aquatic plants is 0.000798 mg/L.

The acute toxicity to fish, aquatic invertebrates, and aquatic plants remain as data gaps for this sub-category under the HPV Challenge Program.

**Sub-Category II:** The 96-hour LC<sub>50</sub> of CASRN 298-07-7 ranged from 20 – 56 mg/L and CASRN 126-73-8 ranged from greater than 100 to 5018 mg/L to fish.. The 48-hour LC<sub>50</sub> of CASRN 298-07-7 ranged from 42 to 83.7 mg/L to aquatic invertebrates. The 48-hour LC<sub>50</sub> of CASRN 126-73-8 is 110 mg /L to aquatic invertebrates. The 72-hour EC<sub>50</sub> of CASRN 298-07-7 to aquatic plants is greater than 100 mg/L. The 48-hour EC<sub>50</sub> of CASRN 12645-31-7 to aquatic plants is 168 mg/L. The 62-day chronic value of the supporting chemical CASRN 12645-31-7 is 20.6 mg/L to fish.

**Sub-Category III:** The 96-hour LC<sub>50</sub> of CASRN 126-71-6 and CASRN 126-73-8 ranged from 11 to 23 mg/L to fish. The 48-hour EC<sub>50</sub> of CASRN 126-71-6 CASRN 126-73-8 is 11 and 2.6 mg/L respectively to aquatic invertebrates. The 72-hour EC<sub>50</sub> of CASRN 126-71-6 CASRN 126-73-8 ranged from 1.1 to 33 mg/L (biomass) and 2.8 to 34 mg/L (growth) to aquatic plants. The 95-day MATC of CASRN 126-73-8 is 1.2 mg/L to fish. The 21-day MATC of CASRN 126-73-8 is 1.2 mg/L to aquatic invertebrates.

Table 5. Summary of Environmental Effects – Aquatic Toxicity Data					
	Sub-Category I	Sub-Category II		Sub-Category III	
Endpoints	<i>Tris</i> (2-ethylhexyl) phosphate (78-42-2)	<i>Bis</i> (2-ethylhexyl) phosphate (298-07-7)	Phosphoric acid, 2-ethylhexyl ester (12645-31-7)	Triisobutyl phosphate (126-71-6)	Tributyl phosphate (126-73-8, supporting chemical)
<b>Fish</b> 96-h LC <sub>50</sub> (mg/L)	0.000218 (e)	<b>30</b>	<b>&gt; 100</b>	<b>17.8 – 21.5</b>	<b>11</b>
<b>Aquatic Invertebrates</b> 48-h EC <sub>50</sub> (mg/L)	0.002 (e)	<b>60.7</b>	<b>110</b>	<b>11</b>	<b>2.6</b>
<b>Aquatic Plants</b> 72-h EC <sub>50</sub> (mg/L) (growth) (biomass)	0.0005 (e)	<b>&gt; 100</b>	<b>168</b> <b>161</b>	<b>34</b> <b>33</b>	<b>2.8</b> <b>1.1</b>
<b>Chronic Toxicity to Fish</b>	0.000012 (e)	<b>20.6</b> (Threshold concentration, 62-d)	No Data 20.6 (Threshold concentration, 62-d) (RA)	No Data NOEC (95-d) = 0.82 LOEC (95-d) = 1.7 MATC (95-d) = 1.2 (RA)	<b>NOEC (95-d) = 0.82</b> <b>LOEC (95-d) = 1.7</b> <b>MATC (95-d) = 1.2</b>
<b>Chronic Toxicity to Invertebrates</b> 21-day EC <sub>50</sub> (mg/L)	–	–	–	No Data > 2.1 <sup>b</sup> NOEC <sup>c</sup> = 0.87 LOEC <sup>c</sup> = 2.1 MATC <sup>c</sup> = 1.35 (RA)	<b>&gt; 2.1<sup>b</sup></b> <b>NOEC<sup>c</sup> = 0.87</b> <b>LOEC<sup>c</sup> = 2.1</b> <b>MATC<sup>c</sup> = 1.35</b>

<sup>a</sup>NES = No effects at saturation (water solubility limit); <sup>b</sup>Based on immobilization; <sup>c</sup>Based on length, days to first brood, (Y/D/D); (m) = measured data (i.e., derived from testing); (e) = estimated data (i.e., derived from modeling); (RA) = Read Across; Shaded cells = non-sponsored substances (proposed supporting chemicals)