

SCREENING-LEVEL HAZARD CHARACTERIZATION

Isodecyl/Phenyl Phosphite Category

SPONSORED CHEMICALS

Triisodecyl phosphite	CASRN 25448-25-3
Diisodecyl phenyl phosphite	CASRN 25550-98-5
Isodecyl diphenyl phosphite	CASRN 26544-23-0
Triphenyl phosphite	CASRN 101-02-0
Tritolyl phosphite	CASRN 25586-42-9

The High Production Volume (HPV) Challenge Program¹ 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

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>.

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.

Chemical Abstract Registry Number (CASRN)	CASRN 25448-25-3, CASRN 25550-98-5, CASRN 26544-23-0, CASRN 101-02-0, CASRN 25586-42-9
Chemical Abstract Index Name	Phosphorous acid, triisodecyl ester; Phosphorous acid, diisodecyl phenyl ester; Phosphorous acid, isodecyl diphenyl ester; Phosphorous acid, triphenyl ester; Phosphorous acid, tris(methyphenyl)
Structural Formula	(see Section 1, Table 1)
Summary	
<p>The isodecyl/phenyl phosphite category primarily contains liquids or solids that melt at room temperature with negligible to low water solubility and low vapor pressure. All the compounds in this category are expected to have low mobility in soil. Volatilization is considered moderate to high based on their Henry's Law constants. The rate of hydrolysis for two of the compounds (CASRN 25448-25-3 and CASRN 101-02-0) was rapid; however, these experiments were conducted using a co-solvent, due to the lack of water solubility of the compounds in this category. The isodecyl/phenyl phosphite category members are expected to have moderate persistence (P2). The compounds with negligible solubility, CASRN 25448-25-3, CASRN 25550-98-5 and CASRN 26544-23-0 are expected to have low bioaccumulation potential (B1). CASRN 101-02-0 is predicted to have high bioaccumulation potential (B3) and CASRN 25586-42-9 is predicted to have moderate bioaccumulation potential (B2); however, the possibility for these compounds to hydrolyze may attenuate their bioaccumulation potential.</p>	
<p>The acute oral toxicity to rats and acute dermal toxicity to rabbits of isodecyl/phenyl phosphite category members is low. Repeated-dose testing was performed on two category members. Repeated oral gavage exposure of rats to CASRN 25448-25-3 in a combined repeated-dose/reproductive/developmental toxicity screening test results in no treatment-related effects on the systemic, reproductive or developmental parameters evaluated. The NOAEL for systemic, reproductive and developmental toxicity is 1000 mg/kg-day, the highest dose tested. In a combined repeated-dose/reproductive/developmental toxicity screening test, repeated oral gavage exposure of rats to CASRN 101-02-0 results in reduced adult body weights at 40 mg/kg-day; the NOAEL for systemic toxicity is 15 mg/kg-day. None of the reproductive parameters evaluated are affected by treatment at any dose level and the NOAEL for reproductive toxicity is 40 mg/kg-day, the highest dose tested. In the same study, developmental toxicity is apparent at 40 mg/kg-day as demonstrated by an increase in mortality and reduced body weights/litter in pups; the NOAEL for developmental toxicity is 15 mg/kg-day. Members of the isodecyl/phenyl phosphite category (CASRNs 25448-25-3, 25550-98-5, 26544-23-0, and 101-02-0) do not induce genetic mutations in bacteria <i>in vitro</i> or chromosomal aberrations in mice <i>in vivo</i>.</p>	
<p>For aquatic organisms, there are "no effects at saturation" predicted for the members of this category for acute toxicity. However, ECOSAR predicted a chronic toxicity value of 0.005 mg/L to daphnia for CASRN 101-02-0, and there is a concern for chronic toxicity based on its predicted water solubility of 0.07 mg/L and log Kow of 6.62.</p>	

Chronic toxicity for aquatic organisms remains a data gap for CASRN 101-02-0 under the HPV Challenge Program.

The sponsor, General Electric Company, submitted a Test Plan and Robust Summaries to EPA for the isodecyl/phenyl phosphites category on September 11, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on October 11, 2001 (<http://www.epa.gov/oppt/chemrtk/pubs/summaries/ppipcc/c13182tc.htm>). EPA comments on the original submission were posted to the website on March 19, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on January 3, 2006 and November 22, 2006, which were posted to the ChemRTK website on March 15, 2006 and January 30, 2007, respectively.

Category Justification

The sponsor bases support for grouping the sponsored substances in the category on three criteria: “a common functional group,” “common precursors and/or breakdown products” and an “incremental and constant change across the category.” All of the compounds in the category contain the common phosphite ester functional group, and the ester hydrolysis products are phosphorous acid, isodecyl alcohol, phenol and cresol in relative ratios equivalent to their respective starting esters.

The sponsor added a fifth category member, tritolyl phosphite; CASRN 25586-42-9, in a revised submission. The Agency decided based on its chemical similarity to the other members of the category, the inclusion of this compound is justified.

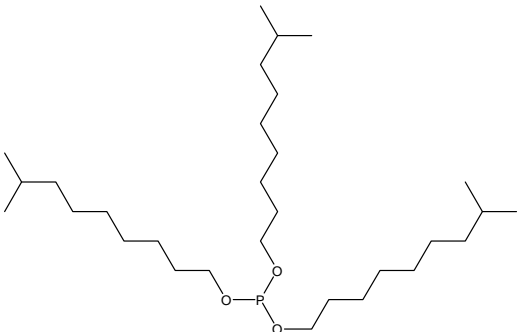
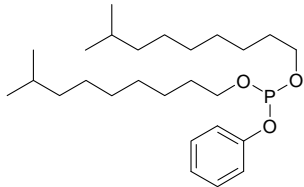
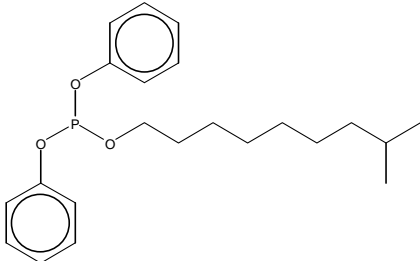
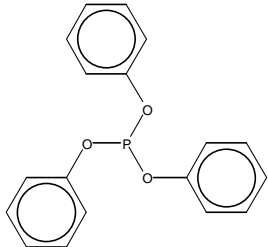
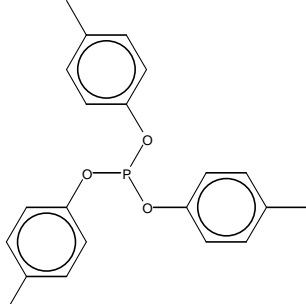
The Agency concluded that the submitter adequately supports the grouping of the category members with the information provided the HPV Challenge Program.

1 Chemical Identity

1.1 Identification and Purity

The sponsor discussed the manufacture and purity of category members in the test plan. Transesterification of phenol with isodecanol to give triisodecyl phosphite (CASRN 25448-25-3) from triphenyl phosphite (CASRN 101-02-0) proceeds cleanly. Commercial triphenyl phosphite (CASRN 101-02-0) and triisodecyl phosphite (CASRN 25448-25-3) are 98+% pure. However, for the partially transesterified products isodecyl diphenyl phosphite (CASRN 26544-23-0) and diisodecyl phenylphosphite (CASRN 25550-98-5), the reaction product obtained is actually a mixture. The ratio of each is controlled by the mole ratio of triphenyl phosphite (CASRN 101-02-0) and isodecanol reacted, and various other manufacturing conditions. It is not practical to produce pure isodecyl diphenyl phosphite (CASRN 26544-23-0) and diisodecyl phenyl phosphite (CASRN 25550-98-5). Isodecyl diphenyl phosphite (CASRN 26544-23-0) and diisodecyl phenyl phosphite (CASRN 2550-98-5) sold in commerce typically range from 50-70% pure.

Table 1.

Sponsored Chemicals		
Chemical Name	CASRN	Chemical Structure
Phosphorous acid, triisodecyl ester	25448-25-3	 <p>Representative structure</p>
Phosphorous acid, diisodecyl phenyl ester	25550-98-5	 <p>Representative structure</p>
Phosphorous acid, isodecyl diphenyl ester	26544-23-0	 <p>Representative structure</p>
Phosphorous acid, triphenyl ester	101-02-0	
Phosphorous acid, tris(methyphenyl) ester	25586-42-9	 <p>Representative structure</p>

1.2 Physical-Chemical Properties

The physical-chemical properties of the compounds included in the isodecyl/phenyl phosphite category are summarized in Table 2. The structures of the compounds composing this category are provided in Table 1.

The isodecyl/phenyl phosphites are liquids or solids that melt at room temperature with negligible to low water solubility and low vapor pressure.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

The isodecyl/phenyl phosphites category chemicals had an aggregated production and/or import volume in the United States between 23 million pounds and 130 million pounds in calendar year 2005.

- CASRN 25448-25-3: 1 to <10 million pounds
- CASRN 25550-98-5: 1 to <10 million pounds
- CASRN 26544-23-0: 1 to <10 million pounds
- CASRN 101-02-0: 10 to <50 million pounds
- CASRN 25586-42-9: 10 to <50 million pounds

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemicals include lubricants, intermediates, and other⁴. Commercial and consumer uses of CASRN 25448-25-3, 26544-23-0, and 101-02-0 are claimed confidential. No commercial and consumer uses were reported in the 2006 IUR for the remaining two chemicals.

2.2 Environmental Exposure and Fate

No quantitative information is available on releases of these chemicals to the environment.

The environmental fate properties are provided in Table 3. The isodecyl/phenyl phosphites are expected to have low mobility in soil. Phosphorous acid, triisodecyl ester and phosphorous acid, triphenyl ester were not readily biodegradable using a closed bottle test (OECD 301D); however the use of these substances as antioxidants in the production of polymers suggests the potential to oxidize which may lower the persistence of these compounds in the environment. The estimated Henry's Law constants suggest volatilization is moderate to high for the isodecyl/phenyl phosphites, but the slow rate of dissolution and the potential to hydrolyze is expected to attenuate the rate of volatilization. The rate of hydrolysis was rapid for two category members (CASRN 25448-25-3 and CASRN 101-02-0); however, these tests were conducted using up to 50% acetonitrile or methanol due to the lack of solubility of these substances. Therefore, the hydrolysis rate under environmental conditions is unknown but may be limited by the rate of

⁴ Reported industrial processing use as lubricants: CASRN 101-02-0; as intermediates: CASRN 25586-42-9; and as "other": CASRN 25448-25-3, 25550-98-5, and 26544-23-0.

dissolution of these substances. The isodecyl/phenyl phosphite category members are expected to have moderate persistence (P2). CASRN 25448-25-3, CASRN 25550-98-5 and CASRN 26544-23-0 are expected to have low bioaccumulation potential (B1) because the solubility of these compounds are negligible. CASRN 101-02-0 is predicted to have high bioaccumulation potential (B3) and CASRN 25586-42-9 is expected to have moderate bioaccumulation potential (B2). Because these two compounds have greater solubility than the other members of this category, hydrolysis may occur more readily which could lower their bioaccumulation potential.

Property	25448-25-3	25550-98-5	26544-23-0	101-02-0	25586-42-9
CASRN	25448-25-3	25550-98-5	26544-23-0	101-02-0	25586-42-9
Molecular Weight	502.8	422.6	374.5	310.3	352.4
Physical State	Liquid	Liquid	Liquid	Water-white to pale yellow solid or oily liquid ²	Liquid
Melting Point	-91 to -64°C (measured)	No data ³	No data ³	25°C (measured)	24–25°C (measured)
Boiling Point	460 °C (estimated) ⁶	448°C (estimated)	436°C (estimated)	360°C (measured)	194°C at 1 torr (measured for 2-methyl and 4-methyl, NOMO5 converts to 400°C)
Vapor Pressure	6.4×10 ⁻⁸ mm Hg at 25°C (estimated)	5.3×10 ⁻⁷ mm Hg at 25°C (estimated)	1.1×10 ⁻⁶ mm Hg at 25°C (estimated)	7.6×10 ⁻⁵ mm Hg at 25°C (estimated)	6.3×10 ⁻⁷ mm Hg at 25°C (estimated)
Water Solubility	5.0×10 ⁻⁷ mg/L at 25°C (estimated) ^{4,5}	3.2×10 ⁻⁵ mg/L at 25°C (estimated)	8.2×10 ⁻⁴ mg/L at 25°C (estimated)	0.07 mg/L at 25°C (estimated)	0.0016 mg/L at 25°C (estimated) ⁴
Dissociation Constant (pK _a)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Henry's Law Constant	0.022 atm-m ³ /mole (estimated) ⁴	5.2×10 ⁻⁶ atm-m ³ /mole (estimated) ⁴	1.9×10 ⁻⁵ atm-m ³ /mole (estimated) ⁴	5.4×10 ⁻⁷ atm-m ³ /mole (estimated) ⁴	7.3×10 ⁻⁷ atm-m ³ /mole (estimated) ⁴
Log K _{ow}	12.31 (estimated) ^{4,5}	9.88 (estimated)	8.52 (estimated)	6.62 (estimated)	8.3 (estimated)

¹The General Electric Company. January 13, 2006 and December 22, 2006. Revised Robust Summary and Test Plan for the Isodecyl/Phenyl Phosphite Category.

<http://www.epa.gov/chemrtk/pubs/summaries/ppipcc/c13182tc.htm>.

²HSDB. 2008. Hazardous Substances Data Bank. Accessed December 20, 2008. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>.

³An estimated melting point was provided in the Robust Summary that is inconsistent with the physical state of the substance at room temperature.

⁴U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA.

<http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

⁵The Robust summary reported a water solubility of 0.1 g/L, and K_{ow} of 12.9 (log K_{ow} = 1.1) for triisodecyl phosphate, which are likely typographical errors.

⁶This boiling point estimated value is based on the NOMO5 conversion of the measured value of 263°C at 2 torr for Phosphorous acid, tridecyl ester given in Beilstein E IV 1/3. The submitter's measured data value of 187°C for this chemical does not agree with this value and is most likely at reduced pressures or is the measurement of some decomposition products.

Property	25448-25-3	25550-98-5	26544-23-0	101-02-0	25586-42-9
CASRN	25448-25-3	25550-98-5	26544-23-0	101-02-0	25586-42-9
Photodegradation Half-life	1.2 hours (estimated)	1.8 hours (estimated)	3.1 hours (estimated)	11.8 hours (estimated)	9.4 hours (estimated)
Hydrolysis Half-life	4.1 hours at pH 5 (measured in 50% acetonitrile); 17 hours at pH 7 (measured in 50% acetonitrile); 20.1 hours at pH 9 (measured in 50% acetonitrile)	No data	No data	0.5 hours at pH 6–7 (estimated in absence of co-solvent); 14 hours at pH 9 (estimated in absence of co-solvent)	No data
Biodegradation	1.31% after 28 days (not readily biodegradable)	No data	No data	0.1% after 28 days (not readily biodegradable)	No data
Bioconcentration	BCF = 3 (estimated) ²	BCF = 3 (estimated) ²	BCF = 17 (estimated) ²	BCF = 25,17018,280 (estimated) ²	BCF = 1189 (estimated) ²
Log K _{oc}	9.4 (estimated) ²	5.4 (estimated) ²	7.4 (estimated) ²	6.4 (estimated) ²	7.0 (estimated) ²
Fugacity (Level III Model)					
Air (%)	0.0216	0.0451	0.0756	0.247	0.0963
Water (%)	1.37	1.86	1.87	2.43	1.31
Soil (%)	31.1	29.8	29.5	31.5	34.1
Sediment (%)	67.4	68.3	68.5	65.8	64.5
Persistence ³	P2 (moderate)	P2 (moderate)	P2 (moderate)	P2 (moderate)	P2 (moderate)
Bioaccumulation ³	B1 (low)	B1 (low)	B1 (low)	B3 (high)	B2 (moderate)

¹The General Electric Company. January 13, 2006 and December 22, 2006. Revised Robust Summary and Test Plan for the Isodecyl/Phenyl Phosphite Category.

<http://www.epa.gov/chemrtk/pubs/summaries/ppipcc/c13182tc.htm>.

²U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA.

<http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

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

Conclusion: The isodecyl/phenyl phosphite category primarily contains liquids or solids that melt at room temperature with negligible to low water solubility and low vapor pressure. All the compounds in this category are expected to have low mobility in soil. Volatilization is considered moderate to high based on their Henry’s Law constants. The rate of hydrolysis for two of the compounds (CASRN 25448-25-3 and CASRN 101-02-0) was rapid; however, these experiments were conducted using a co-solvent, due to the lack of water solubility of the compounds in this category. The isodecyl/phenyl phosphite category members are expected to have moderate persistence (P2). The compounds with negligible solubility, CASRN 25448-25-3, CASRN 25550-98-5 and CASRN 26544-23-0 are expected to have low bioaccumulation potential (B1). CASRN 101-02-0 is predicted to have high bioaccumulation potential (B3) and CASRN 25586-42-9 is predicted to have moderate bioaccumulation potential (B2); however, the possibility for these compounds to hydrolyze may attenuate their bioaccumulation potential.

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.

Acute Oral Toxicity

Triisodecyl phosphite (CASRN 25448-25-3)

Sherman-Wistar rats (5/sex) were administered triisodecyl phosphite via gavage at 5000 mg/kg-bw and observed for the following 21 days. Mortality occurred at this dose level. One male died on day 2. All surviving rats appeared normal by 48 hours. Gross pathological examination revealed no adverse effects.

LD₅₀ > 5000 mg/kg-bw

Diisodecyl phenyl phosphite (CASRN 25550-98-5)

Sherman-Wistar rats (5/sex) were administered diisodecyl phenyl phosphite via gavage at 5000 mg/kg-bw and observed for the following 21 days. No mortalities were noted. Gross pathological examination revealed no adverse effects.

LD₅₀ > 5000 mg/kg-bw

Isodecyl diphenyl phosphite (CASRN 26544-23-0)

Sherman-Wistar rats (5/sex/dose) were administered isodecyl diphenyl phosphite via gavage at 1580, 2000, 2510, 3160, 3550, 3980 or 5010 mg/kg-bw (males) and 1580, 2000, 2510, 3160, 3980, 5010 or 6310 mg/kg-bw (females). Animals were observed for up to 21 days following dose administration. Mortality occurred at doses greater than 3000 mg/kg-bw. All animals died in the group of males treated with 5010 mg/kg-bw and females at 6310 mg/kg-bw. Most animals died in the first 24 hours. Survivors appeared normal after 48 hours and gross pathological examinations revealed no treatment-related effects.

LD₅₀ (males) = 3990 mg/kg-bw

LD₅₀ (females) = 4060 mg/kg-bw

Triphenyl phosphite (CASRN 101-02-0)

Sherman-Wistar rats (5/sex/dose) were administered triphenyl phosphite via gavage at 1000, 1260, 1410 (males only), 1580, 1780 (females only), 2000, 2510, 3160 or 3980 mg/kg-bw. Animals were observed for up to 21 days following dose administration. Complete mortality occurred at ≥ 2000 mg/kg-bw. Gross examination revealed no notable changes.

LD₅₀ (males) = 1590 mg/kg-bw

LD₅₀ (females) = 1630 mg/kg-bw

Acute Inhalation Toxicity

Triisodecyl phosphite (CASRN 25448-25-3)

Sherman-Wistar rats (5/sex) were exposed to triisodecyl phosphite as an aerosol for 1 hour and observed for 21 days following exposure. The mass median diameter of the aerosol was

determined to be 0.48 μm . The average concentration of the aerosol over the 1-hour exposure period was calculated to be 12.6 mg/L (maximum attainable concentration) by differential weighing of the flask from which the aerosol was generated. No adverse effects were observed during the 1-hour exposure or the following 21 days. No mortalities were noted and no adverse effects were revealed during gross pathological examinations.

LC₅₀ (1 hr) > 12.6 mg/L (maximum attainable concentration)

Diisodecyl phenyl phosphite (CASRN 25550-98-5)

Sherman-Wistar rats (5/sex) were exposed to diisodecyl phenyl phosphite as an aerosol at 11.7 mg/L for 1 hour and observed for 21 days following exposure. The mass median diameter of the aerosol was determined to be 0.70 μm . The average concentration of the aerosol over the 1-hour exposure period was calculated to be 11.7 mg/L (maximum attainable concentration) by differential weighing of the flask from which the aerosol was generated. No clinical signs of toxicity were observed during the 1-hour exposure or the following 21 days. No mortalities were noted and no adverse effects were revealed during gross pathological examinations.

LC₅₀ (1 hr) > 11.7 mg/L (maximum attainable concentration)

Isodecyl diphenyl phosphite (CASRN 26544-23-0)

Sherman-Wistar rats (5/sex/group) were exposed to isodecyl diphenyl phosphite as an aerosol at 8.4 mg/L for 1 hour and observed for 21 days following exposure. The mass median diameter of the aerosol was determined to be 0.80 μm . The average concentration of the aerosol over the 1-hour exposure period was calculated to be 8.4 mg/L (maximum attainable concentration) by differential weighing of the flask from which the aerosol was generated. No adverse effects were observed, no mortalities were noted and no adverse effects were revealed during gross pathological examinations.

LC₅₀ (1 hr) > 8.4 mg/L (maximum attainable concentration)

Triphenyl phosphite (CASRN 101-02-0)

Sherman-Wistar rats (5/sex/group) were exposed to triphenyl phosphite as an aerosol at 6.7 mg/L for 1 hour and observed for 21 days following exposure. The mass median diameter of the aerosol was determined to be 0.73 μm . The average concentration of the aerosol over the 1-hour exposure period was calculated to be 6.7 mg/L (maximum attainable concentration) by differential weighing of the flask from which the aerosol was generated. No clinical signs of toxicity were observed. No mortalities were noted and no adverse effects were revealed during gross pathological examinations.

LC₅₀ (1 hr) > 6.7 mg/L (maximum attainable concentration)

Acute Dermal Toxicity

Triisodecyl phosphite (CASRN 25448-25-3)

New Zealand White rabbits (3/sex) were administered triisodecyl phosphite via the dermal route at 5000 mg/kg-bw to clipped and abraded skin under occluded conditions for 24 hours. Excess material was removed following 24 hours and the animals were observed for the following 21 days. No mortalities were noted and the rabbits exhibited no signs of toxicity except skin irritation that lasted for several days.

LD₅₀ > 5000 mg/kg-bw

Diisodecyl phenyl phosphite (CASRN 25550-98-5)

New Zealand White rabbits (3/sex) were administered diisodecyl phenyl phosphite via the dermal route at 5000 mg/kg-bw to clipped and abraded skin under occluded conditions for 24 hours. Excess material was removed following 24 hours and the animals were observed for the following 21 days. No mortalities were noted and the rabbits exhibited no signs of toxicity except skin irritation that lasted for several days. No treatment-related effects were revealed at necropsy.

LD₅₀ > 5000 mg/kg-bw

Isodecyl diphenyl phosphite (CASRN 26544-23-0)

New Zealand White rabbits (3/sex) were administered isodecyl diphenyl phosphite via the dermal route at 5000 mg/kg-bw to clipped and abraded skin under occluded conditions for 24 hours. Excess material was removed following 24 hours and the animals were observed for the following 21 days. No mortalities were noted and the rabbits exhibited no signs of toxicity except skin irritation that lasted for several days.

LD₅₀ > 5000 mg/kg-bw

Triphenyl phosphite (CASRN 101-02-0)

New Zealand White rabbits (3/sex) were administered triphenyl phosphite via the dermal route at 2000 or 5000 mg/kg-bw to clipped and abraded skin under occlusion for 24 hours. Excess material was removed following 24 hours and the animals were observed for the following 21 days. Complete mortality occurred at 5000 mg/kg-bw within the first 24 hours after dosing. At 2000 mg/kg-bw, no mortality occurred and the only clinical sign noted was severe skin irritation lasting several days. No treatment-related findings were revealed at gross necropsy.

2000 ≤ LD₅₀ ≤ 5000 mg/kg-bw

Repeated-Dose Toxicity

Triisodecyl phosphite (CASRN 25448-25-3)

In a combined repeated-dose/reproductive/developmental toxicity screening test (modified OECD 422), Sprague-Dawley rats (10/sex/dose) were administered triisodecyl phosphite via gavage at 0, 50, 250 or 1000 mg/kg-bw/day prior to and during mating (4 weeks). Females were continued on treatment during gestation and lactation (3 weeks each segment). F0 animals were evaluated for auditory function, motor activity and assessment of grip strength. F1 litters were culled on postnatal day 4 and culled pups were necropsied. The study differed from OECD 422 design by following F1 pups to weaning (postnatal day 21). The robust summary reports no systemic toxicity effects were seen at any dose level.

NOAEL (systemic toxicity) = 1000 mg/kg-bw/day (highest dose tested)

Triphenyl phosphite (CASRN 101-02-0)

In a combined repeated-dose/reproductive/developmental toxicity screening test, Sprague-Dawley rats (10/sex/dose) were administered triphenyl phosphite via gavage at 0, 5, 15 or 40 mg/kg-bw/day for 2 weeks prior to mating and during 2 weeks of mating. Females were continued on treatment during gestation and lactation (3 weeks each segment). Selected F1 offspring from the controls and 15 mg/kg-bw group were directly treated from weaning to at

least 7 weeks post-weaning. Additional F0 animals (5/sex/group) from the control and 40 mg/kg-bw groups and F1 males and females (5/sex/group) from the control and 15 mg/kg-bw/day groups were held without dosing for 2 weeks following the dosing periods for evaluation of possible recovery from treatment-related effects. Toxicity, increasing over time, was noted in the high-dose F0 animals and included reduced body weights, ataxia and foot splay. Magnitude and significance of the changes were not provided. During lactation, high-dose F1 offspring exhibited “profound” toxicity with increased mortality and reduced pup body weights/litter during lactation. Because of the toxicity, the high-dose group was terminated earlier than planned on postnatal day 21, but magnitude and significance of the changes were not provided. In the remaining F1 groups, 1/sex/litter/group was selected for continued treatment after weaning until all pups were at least 70 days old.

LOAEL (systemic toxicity) = 40 mg/kg-bw/day (based on reduced body weight)

NOAEL (systemic toxicity) = 15 mg/kg-bw/day

Reproductive/Developmental Toxicity

Triisodecyl phosphite (CASRN 25448-25-3)

In the combined repeated-dose/reproductive/developmental toxicity screening test described above, reproductive performance was assessed through evaluation of gonadal function, mating behavior, conception, development of the embryo and fetus and parturition. Comprehensive external and visceral examinations were conducted on the culled pups, and survival indices were calculated weekly through weaning (postnatal day 21) for the remaining pups. No reproductive or developmental effects were seen at any dose level.

NOAEL (reproductive/developmental toxicity) = 1000 mg/kg-bw/day (highest dose tested)

Triphenyl phosphite (CASRN 101-02-0)

In the combined repeated-dose/reproductive/developmental toxicity screening test described above, treatment did not affect F0 reproductive performance, including gonadal function, mating behavior, conception, development of the embryo and fetus and parturition. No treatment-related effects were seen in histopathologic examinations of reproductive organs of selected control and high-dose rats. Comprehensive external and visceral examinations were conducted on the culled pups, and survival indices were calculated weekly through weaning (postnatal day 21) for the remaining pups. High-dose F1 offspring exhibited increasing mortality and reduced pup body weights/litter during lactation. Toxicity, increasing over time, was noted in the high-dose F0 animals and included reduced body weights, ataxia and foot splay. Magnitude and significance of the changes were not provided. During lactation, high-dose F1 offspring exhibited “profound” toxicity with increased mortality and reduced pup body weights/litter during lactation. Because of the toxicity, the high-dose group was terminated earlier than planned on postnatal day 21, but magnitude and significance of the changes were not provided. In the remaining F1 groups, 1/sex/litter/group was selected for continued treatment after weaning until all pups were at least 70 days old. No reproductive toxicity was observed for the F0 animals. The LOAEL for F1 offspring during lactation was 40 mg/kg-bw/day as was the systemic toxicity in both F0 and F1 post weaning.

NOAEL (reproductive toxicity) = 40 mg/kg-bw/day (no effects in F0 reproductive parameters at highest dose tested)

LOAEL (developmental toxicity) = 40 mg/kg-bw/day (based on increased mortality and reduced body weights/litter in pups)

NOAEL (developmental toxicity) = 15 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

Triisodecyl phosphite (CASRN 25448-25-3)

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to triisodecyl phosphite at concentrations of 0, 10, 100, 500, 1000 or 5000 µg/plate in the presence and absence of metabolic activation. Precipitation was observed at 1000 and 5000 µg/plate. Positive controls appropriate for strain and presence or absence of metabolic activation were tested concurrently. The number of revertants produced at all concentrations of triisodecyl phosphite was comparable to negative control groups, while positive control groups produced expected results.

Triisodecyl phosphite was not mutagenic in this assay.

Diisodecyl phenyl phosphite (CASRN 25550-98-5)

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to diisodecyl phenyl phosphite (in ethanol) at concentrations of 0, 50, 100, 500, 1000 or 5000 µg/plate in the presence and absence of metabolic activation. Precipitation was observed at 1000 and 5000 µg/plate and there was no evidence of cytotoxicity. Positive controls appropriate for strain and presence or absence of metabolic activation were tested concurrently and returned expected results. The number of revertants produced at all concentrations of diisodecyl phenyl phosphite was comparable to negative control groups.

Diisodecyl phenyl phosphite was not mutagenic in this assay.

Isodecyl diphenyl phosphite (CASRN 26544-23-0)

In a bacterial reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to isodecyl diphenyl phosphite (in ethanol) at concentrations of 0, 50, 100, 500, 1000 or 5000 µg/plate in the presence and absence of metabolic activation. Precipitation was observed at 1000 and 5000 µg/plate. Positive controls appropriate for strain and presence or absence of metabolic activation were tested concurrently and returned expected results. The number of revertants produced at all concentrations of isodecyl diphenyl phosphite was comparable to solvent (ethanol) control groups.

Isodecyl diphenyl phosphite was not mutagenic in this assay.

Triphenyl phosphite (CASRN 101-02-0)

(1) In a bacterial reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to triphenyl phosphite (in ethanol) at concentrations of 0, 5, 10, 50, 100 or 500 µg/plate in the presence and absence of metabolic activation. Precipitation of triphenyl phosphite was noted at concentrations of 50, 100 and 500 µg/plate. Cytotoxicity was not observed at any concentration. Positive controls appropriate for strain and presence or absence of metabolic activation were tested concurrently. The number of revertants produced at all concentrations of triphenyl phosphite was comparable to negative control groups.

Triphenyl phosphite was not mutagenic in this assay.

(2) In a bacterial reverse mutation assay, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to triphenyl phosphite at concentrations of 0, 100, 333, 1000, 3333 or 10,000 µg/plate in the presence and absence of metabolic activation. Precipitation was observed at concentrations ≥ 1000 µg/plate. Negative solvent-treated (DMSO) and positive controls appropriate for strain and presence or absence of metabolic activation were tested concurrently. The positive control groups returned appropriate results in all replicate tests, while triphenyl phosphite-treated bacteria produced numbers of revertants/plate comparable to solvent control groups.

Triphenyl phosphite was not mutagenic in this assay.

(3) In a National Toxicology Program (NTP) reverse mutation study, triphenyl phosphite did not induce reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 either in the presence or absence of metabolic activation.

Triphenyl phosphite was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

Triisodecyl phosphite (CASRN 25448-25-3)

In a micronucleus assay, CD-1 mice (5/sex/dose) were administered triisodecyl phosphite via gavage twice in a 24-hour period at total doses of 0, 4450, 9100 or 18,200 mg/kg-bw and observed for 6 hours before bone marrow harvest. A positive control group received mitomycin C with appropriate results provided. All animals in the two highest dose groups displayed piloerection and lethargy. Treatment did not result in increased numbers of micronuclei (per 1000 polychromatic erythrocytes [PCE]). Although the mean polychromatic erythrocytes to normochromatic erythrocytes (PCE/NCE) ratio in the high-dose group was significantly ($p < 0.01$) higher than that of concurrent controls, it was within range of historical controls. Positive and negative controls produced expected results.

Triisodecyl phosphite did not induce micronuclei formation in this assay.

Diisodecyl phenyl phosphite (CASRN 25550-98-5)

In a micronucleus assay, CD-1 mice (5/sex/dose) were administered diisodecyl phenyl phosphite via gavage twice in a 24-hour period at total doses of 0, 2500, 5000 or 10,000 mg/kg-bw and observed for 6 hours before bone marrow harvest. A positive control group received mitomycin C administered by intraperitoneal injection. All diisodecyl phenyl phosphite-treated animals displayed hypopnea and lethargy. Two high-dose males and two high-dose females were found dead after administration of the second dose. Treatment did not result in increased numbers of micronuclei (per 1000 PCE). The PCE/NCE ratio in the 10,000 mg/kg-bw group was comparable to controls; therefore, the ratios of the two lower dose groups were not determined. Positive and negative controls produced expected results.

Diisodecyl phenyl phosphite did not induce micronuclei formation in this assay.

Isodecyl diphenyl phosphite (CASRN 26544-23-0)

In a micronucleus assay, CD-1 mice (5/sex/dose) were administered isodecyl diphenyl phosphite via gavage twice in a 24-hour period at total doses of 0, 2250, 4500 or 9000 mg/kg-bw and observed for 6 hours before bone marrow harvest. A positive control group received mitomycin C administered by intraperitoneal injection. Mice receiving 9000 mg isodecyl diphenyl phosphite/kg-bw displayed hypopnea and lethargy 30 minutes after dosing and one female was found dead. Treatment did not result in increased numbers of micronuclei (per 1000 PCE). The PCE/NCE ratio in the 9000 mg/kg-bw group was comparable to controls; therefore, the ratios of the two lower dose groups were not determined. Positive and negative controls produced expected results.

Isodecyl diphenyl phosphite did not induce micronuclei formation in this assay.

Triphenyl phosphite (CASRN 101-02-0)

In a micronucleus assay, CD-1 mice (5/sex/dose) were administered triphenyl phosphite via gavage twice in a 24-hour period at total doses of 0, 1250, 2500 or 5000 mg/kg-bw and observed for 6 hours before bone marrow harvest. A positive control group received mitomycin C administered by intraperitoneal injection. At the highest dose, three males and two females died after exhibiting tremors, with no notable findings at necropsy. No signs of toxicity were observed in the other dose groups. Treatment did not result in increased numbers of micronuclei (per 1000 PCE). The PCE/NCE ratio in the 5000 mg/kg-bw group was comparable to controls; therefore, the ratios of the two lower dose groups were not determined. Positive and negative controls produced expected results.

Triphenyl phosphite did not induce micronuclei formation in this assay.

Conclusion: The acute oral toxicity to rats and acute dermal toxicity to rabbits of isodecyl/phenyl phosphite category members is low. Repeated-dose testing was performed on two category members. Repeated oral gavage exposure of rats to CASRN 25448-25-3 in a combined repeated-dose/reproductive/developmental toxicity screening test results in no treatment-related effects on the systemic, reproductive or developmental parameters evaluated. The NOAEL for systemic, reproductive and developmental toxicity is 1000 mg/kg-day, the highest dose tested. In a combined repeated-dose/reproductive/developmental toxicity screening test, repeated oral gavage exposure of rats to CASRN 101-02-0 results in reduced adult body weights at 40 mg/kg-day; the NOAEL for systemic toxicity is 15 mg/kg-day. None of the reproductive parameters evaluated are affected by treatment at any dose level and the NOAEL for reproductive toxicity is 40 mg/kg-day, the highest dose tested. In the same study, developmental toxicity is apparent at 40 mg/kg-day as demonstrated by an increase in mortality and reduced body weights/litter in pups; the NOAEL for developmental toxicity is 15 mg/kg-day. Members of the isodecyl/phenyl phosphite category (CASRNs 25448-25-3, 25550-98-5, 26544-23-0, and 101-02-0) do not induce genetic mutations in bacteria *in vitro* or chromosomal aberrations in mice *in vivo*.

Table 4. Summary of Human Health Data

Endpoints	Triisodecyl phosphite (25448-25-3)	Diisodecyl phenyl phosphite (25550-98-5)	Isodecyl diphenyl phosphite (26544-23-0)	Triphenyl phosphite (101-02-0)	Tritolyl phosphite (25586-42-9)
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	> 5000	> 5000	3990	1590	No Data 1590 (RA)
Acute Dermal Toxicity LD ₅₀ (mg/kg-bw)	> 5000	> 5000	> 5000	2000 – 5000	No Data 2000 – 5000 (RA)
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 1000 (highest dose tested)	No Data NOAEL = 15 LOAEL = 40 (RA)	No Data NOAEL = 15 LOAEL = 40 (RA)	NOAEL = 15 LOAEL = 40	No Data NOAEL = 15 LOAEL = 40 (RA)
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 1000 (highest dose tested)	No Data NOAEL = 40 (RA)	No Data NOAEL = 40 (RA)	NOAEL = 40 (highest dose tested)	No Data NOAEL = 40 (RA)
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL 1000 (highest dose tested)	No Data NOAEL = 15 LOAEL = 40 (RA)	No Data NOAEL = 15 LOAEL = 40 (RA)	NOAEL = 15 LOAEL = 40	No Data NOAEL = 15 LOAEL = 40 (RA)
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative	Negative	Negative	Negative	No Data Negative (RA)
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	Negative	Negative	Negative	Negative	No Data Negative (RA)

Measured data in bold text; (RA) = Read Across

4 Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5. The original HPV submission included data on two category members (CASRN 25550-98-5 and 26544-23-0). Although EPA initially accepted the submitted data, based on a more detailed review that included an analysis of the 2007 revised submission documenting the inability to perform aquatic toxicity testing with CASRN 25448-25-3 and 101-02-0, the aquatic toxicity test data for CASRN 25550-98-5 and 26544-23-0 are considered inadequate because the concentrations tested were several orders of magnitude above their predicted water solubility limits (3.2×10^{-5} and 8.2×10^{-4} mg/L) and their log Kow values (both > 8.5). Therefore, the aquatic toxicity of all the chemical category members was evaluated using ECOSAR v1.00a.

Acute Toxicity to Fish, Aquatic Invertebrates, and Toxicity to Aquatic Plants

Isodecyl diphenyl phosphite (CASRN 26544-23-0)

Diisodecyl phenyl phosphite (CASRN 25550-98-5)

Triisodecyl phosphite (CASRN 25448-25-3)

Triphenyl phosphite (CASRN 101-02-0)

Tritolyl phosphate (CASRN 25586-42-9)

Adequate toxicity test data for fish, aquatic invertebrates, and aquatic plants were not available for the category members. The 96-hour EC₅₀ values for fish, 48-hour EC₅₀ for invertebrates, and 96-hour EC₅₀ for aquatic plants, estimated by ECOSAR (v. 1.00a), were provided to evaluate the aquatic toxicity of these chemicals.

Fish 96-h LC₅₀ = NES (e)

Daphnia 48-h EC₅₀ = NES (e)

Algae 96-h EC₅₀ = NES (e)

Chronic Toxicity to Aquatic Invertebrates

Triphenyl phosphite (CASRN 101-02-0)

The chronic toxicity value for aquatic invertebrates, estimated by ECOSAR (v. 1.00a), is provided to evaluate the aquatic toxicity of CASRN 101-02-0.

Chronic Daphnia 21-d EC₅₀ = 0.005 mg/L (e)

Conclusion: For aquatic organisms, there are “no effects at saturation” predicted for the members of this category for acute toxicity. However, there is a concern for chronic toxicity of CASRN 101-02-0 based on the ECOSAR predicted chronic toxicity value of 0.005 mg/L to daphnia and its predicted water solubility of 0.07 mg/L and log Kow of 6.62. Therefore, the chronic toxicity endpoint for CASRN 101-02-0 remains a data gap under the HPV Challenge Program.

Table 5. Summary of Environmental Effects – Aquatic Toxicity Data					
Endpoints	Triisodecyl phosphite (25448-25-3)	Diisodecyl phenyl phosphite (25550-98-5)	Isodecyl diphenyl phosphite (26544-23-0)	Triphenyl phosphite (101-02-0)	Tritolyl phosphite (25586-42-9)
Fish 96-h LC₅₀ (mg/L)	NES(e)	NES(e)	NES(e)	NES(e)	NES(e)
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	NES(e)	NES(e)	NES(e)	NES(e)	NES(e)
Aquatic Plants 72-h EC₅₀ (mg/L)	NES(e)	NES(e)	NES(e)	NES(e)	NES(e)
Chronic endpoint	NES(e)	NES(e)	NES(e)	No data 0.005(e)	NES(e)

(e) = estimated data