

SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL

Isopropylated Triphenyl Phosphate (3:1) (CASRN 68937-41-7)

SUPPORTING CHEMICAL

Trixylyl Phosphate (CASRN 25155-23-1)

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 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

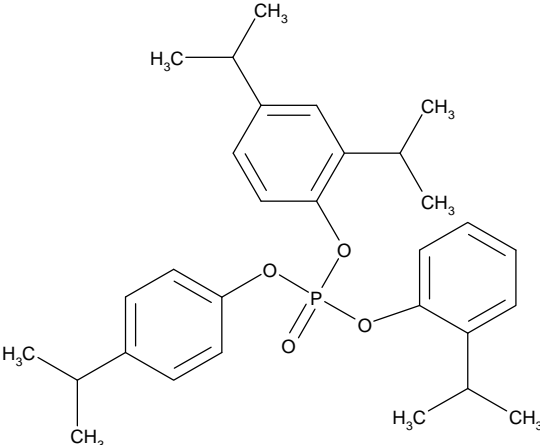
¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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>.

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.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p><u>Sponsored Chemical</u> 68937-41-7</p> <p><u>Supporting Chemical</u> 25155-23-1</p>
<p>Chemical Abstract Index Name</p>	<p><u>Sponsored Chemical</u> Phenol, isopropylated, phosphate (3:1)</p> <p><u>Supporting Chemical</u> Phenol, dimethyl-, phosphate (3:1)</p>
<p>Structural Formula</p>	<div style="text-align: center;">  <p>Representative structure</p> </div>
<p style="text-align: center;">Summary</p> <p>CASRN 68937-41-7 is a liquid with negligible water solubility and low vapor pressure at room temperature. It is expected to have low mobility in soil. Volatilization is considered low based on the Henry's Law constant of this substance. The rate of hydrolysis is considered negligible under environmental conditions. The rate of atmospheric photooxidation is considered moderate. CASRN 68937-41-7 is judged to have moderate persistence (P2) and moderate bioaccumulation potential (B2).</p> <p>The acute oral and dermal toxicity of CASRN 68937-41-7 in rats is low. Submitted data for the repeated-dose and genetic toxicity (gene mutations) endpoints were inadequate. No data were submitted for reproductive, developmental or genetic toxicity (chromosomal aberrations) endpoints. CASRN 68937-41-7 were neurotoxic to hens. CASRN 68937-41-7 was not irritating to rabbit skin but was irritating to rabbit eyes.</p> <p>For CASRN 68937-41-7, the 96-hr LC₅₀ for fish ranges from 1.6 to 50.1 mg/L and the 48-hr EC₅₀ for daphnia ranges from 0.83 to 2.44 mg/L. No data were submitted for toxicity to aquatic plants or chronic toxicity to aquatic invertebrates.</p>	

Repeated-dose/reproductive/developmental toxicity, genetic toxicity (gene mutations and chromosomal aberrations), aquatic plant toxicity and chronic toxicity to aquatic invertebrates are identified as data gaps under the HPV Challenge Program.

The sponsor, the Great Lakes Chemical Corporation, submitted a Test Plan and Robust Summaries to EPA for isopropylated triphenyl phosphate [CASRN 68937-41-7; CA Index name: phenol, isopropylated, phosphate (3:1)] dated November 28, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on December 19, 2001 (<http://www.epa.gov/chemrtk/pubs/summaries/isotriph/c13331tc.htm>). EPA comments on the original submission were posted to the website on July 31, 2002. Public comments were also received and posted to the website.

Justification for Supporting Chemicals

Triphenyl phosphate (CASRN 115-86-6) - Estimation of < 2 mg/L for the *water solubility* for isopropylated triphenyl phosphate is based on the measured value of 2 mg/L for triphenyl phosphate. This value represents the maximum water solubility for the isopropylated triphenyl phosphate, as adding isopropyl groups to the phenyl rings decreases the water solubility of the chemical. Since the isopropylated triphenyl phosphate is a mixture of over 50 different chemicals, measuring water solubility is not possible; therefore using a measured water solubility of an analog (i.e. triphenylphosphate) as the maximum water solubility is the best estimation.

Phenol, dimethyl-, 1,1',1''-phosphate (CASRN 25155-23-1) [commercial mixture of this supporting chemical, identified as Phosflex TXP] was selected as an analog for hydrolysis and biodegradation endpoints. The structural differences (dimethyl versus isopropyl aromatic substitution) are not expected to have a significant impact on rates of biodegradation or hydrolysis based on known structure activity relationships.

1. Chemical Identity

1.1 Identification and Purity

The robust summary describes the test substance as 100% pure. However, this compound is not a single chemical. It is a mixture of over 50 different compounds, many of which are positional isomers, but in addition the phenol group can be mono-, di-, or tri-isopropylated. The number of isomers present in the mixture and their ratios are not reported in the test plan or robust summaries.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 68937-41-7 are summarized in Table 1. This compound is a liquid with negligible water solubility and low vapor pressure at room temperature.

Property	Value
CASRN	68937-41-7
Molecular Weight	452 (typical)
Physical State	Liquid
Melting Point	<25°C (liquid)
Boiling Point	220–270°C at 4 mm Hg (measured); 377–436°C at 760 mm Hg (estimated) ²
Vapor Pressure	1.1×10^{-6} – 1.0×10^{-7} mm Hg at 25°C (estimated) ²
Water Solubility	4.9×10^{-4} mg/L at 25°C (estimated) <2 mg/L (estimated) ³
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	2.9×10^{-7} atm·m ³ /mole (estimated) ⁴
Log K _{ow}	5.44 (measured)

¹Great Lakes Chemical Corporation. November 29, 2001. Robust Summary and Test Plan for Isopropylated Triphenyl Phosphate. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/isotriph/c13331tc.htm> as of May 05, 2010.

²NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.

³This estimated value is based on measured water solubility value of 2 mg/L for triphenyl phosphate (CASRN 115-86-6)

⁴U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of May 05, 2010.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

According to the 2006 IUR submissions, CASRN 68937-41-7 had an aggregated production and/or import volume in the United States between 10 and 50 million pounds.

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

2.2 Environmental Exposure and Fate

CASRN 68937-41-7 is expected to have low mobility in soil. No biodegradation data was provided for this compound; therefore data on a similar mixture, phenol, dimethyl-, 1,1',1''-phosphate (CASRN 25155-23-1) was used. A commercial mixture of this supporting chemical, identified as Phosflex TXP, was not readily biodegradable (0% degradation in 28 days) using a closed bottle test (OECD 301D) and a similar substance was not readily biodegradable using a modified MITI test (OECD 301C); however, it was shown to be inherently biodegradable using mixed microbial populations from activated sludge acclimated to the test substance in a semi-continuous activated sludge system (SCAS) and a die-away test in closed flasks. Volatilization of CASRN 68937-41-7 is considered low based on the Henry's Law

constant. The rate of hydrolysis is considered negligible under environmental conditions based upon measured hydrolysis rates of the supporting chemical CASRN 25155-23-1. CASRN 68937-41-7 is expected to have moderate persistence (P2) and moderate bioaccumulation potential (B2).

Property	Value
Photodegradation Half-life	6.5 hours (estimated) ²
Hydrolysis Half-life	>1 year at pH 4 and 25°C (measured) ^{3,4} ; >1 year at pH 7 and 25°C (measured) ^{3,4} ; 219 days at pH 9 and 25°C (measured) ^{3,4} ; Significant hydrolysis within 5 days at pH 7 and 9 at 50°C (measured) ^{3,4}
Biodegradation	0% after 28 days (not readily biodegradable) ^{3,4} ; 4.7, 43.8, and 65.2% at 7, 28, and 48 days, respectively (not readily biodegradable) ^{4,5} ; 65 and 13% after 24 hours at 3 and 13 mg/L/day addition rates (inherently biodegradable) ^{4,5} ;
Bioaccumulation Factor	BAF = 4,508 (estimated) ²
Log K _{oc}	6.1 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	0.1
Water (%)	1.8
Soil (%)	36.9
Sediment (%)	61.3
Persistence ⁶	P2 (moderate)
Bioaccumulation ⁶	B2 (moderate)

¹ Great Lakes Chemical Corporation. November 29, 2001. Robust Summary and Test Plan for Isopropylated Triphenyl Phosphate. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/isotriph/c13331tc.htm> as of May 05, 2010.

² U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm> as of May 05, 2010.

³ Akzo Nobel Chemicals Inc. July 2, 2007. Revised Robust Summary and Test Plan for Trixylenyl Phosphate. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/trxpp/c13165tc.htm> as of May 05, 2010.

⁴ Tests performed on a similar mixture, phenol, dimethyl-, 1,1',1''-phosphate (CASRN 25155-23-1)

⁵ Saeger, V.W.; Hicks, O.; Kaley, R.G.; Michael, P.R.; Mieux, J.P.; Tucker, S.E. 1979. Environmental fate of selected phosphate esters. *Environ. Sci. Technol.* 13: 840–844.

⁶ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3. Human Health Hazard

The human health data are summarized in Table 3.

Acute Oral Toxicity

Sprague-Dawley rats (3/sex) were administered undiluted test substance at 5000 mg/kg-bw and observed for 14 days. There were no mortalities (TSCATS – OTS0527772-1).

LD₅₀ > 5000 mg/kg-bw

Acute Dermal Toxicity

Sprague-Dawley rats (3/sex) were administered 2000 mg/kg-bw test material for 24 hours using an occlusive wrap and observed for 14 days. There were no mortalities.

LD₅₀ > 2000 mg/kg-bw

Repeated-Dose Toxicity

No adequate data were submitted for this endpoint. EPA commented that the submitted 28-day oral toxicity study in rats was inadequate due to excessive mortality that was apparently not related to treatment.

Reproductive Toxicity

No data were submitted for this endpoint.

Developmental Toxicity

No data were submitted for this endpoint.

Genetic Toxicity – Gene Mutations

In vitro

CASRN 68937-41-7 did not induce mutations in five strains of *Salmonella typhimurium* at five concentrations with or without metabolic activation. No further study details were provided.

CASRN 68937-41-7 was not mutagenic in this assay.

Genetic Toxicity - Chromosomal Aberrations

No data were submitted for this endpoint.

Additional Information

Skin Irritation

(1) Three New Zealand rabbits were administered 0.1 mL undiluted test substance onto shaved backs and exposed for 4 hours under a semi-occlusive wrap. The residual test material was removed after exposure and the application sites evaluated at 4.5, 24, 48 and 72 hrs. No irritation was observed at any of the application sites. The primary irritation score was zero according to the Draize scale.

CASRN 68937-41-7 was not irritating to rabbit skin.

(2) Six rabbits (strain not stated) were administered undiluted test substance onto the skin and exposed for 24 hours under a semi-occlusive wrap. No further details were provided.

CASRN 68937-41-7 was not irritating to rabbit skin.

Eye Irritation

(1) Nine rabbits received a conjunctival instillation of 0.1 mL undiluted test substance. Eyes of six rabbits were unwashed and eyes of the remaining three rabbits were washed 4 seconds after treatment. Treated eyes were examined at 24, 48 and 72 hours and 7 days post-treatment. No irritation was observed at any time point.

CASRN 68937-41-7 was not irritating to rabbit eyes.

(2) Three rabbits received a conjunctival instillation of 0.1 mL undiluted test substance. The primary eye irritation score using the Draize scale was 1.3 at 24 hours (slight conjunctival redness in two eyes) and zero at 48 and 72 hours.

CASRN 68937-41-7 was slightly irritating to rabbit eyes.

Neurotoxicity

(1) Adult White Leghorn hens (20/dose) received CASRN 68937-41-7 in corn oil via oral gavage at 10, 20, 90 or 270 mg/kg-day in 91 daily doses. Twenty additional hens received vehicle only (negative controls), and 20 hens received tri-ortho-cresyl phosphate (TOCP) at 7.5 mg/kg-day (positive controls). Mortality occurred as follows: two negative controls; four positive controls; three hens at 10 mg/kg-day, three hens at 20 mg/kg-day, five hens at 90 mg/kg-day and six hens at 270 mg/kg-day. No clinical signs of neurotoxicity were observed in the negative control or two lowest doses. Four hens at 90 mg/kg-day and nine hens at 270 mg/kg-day exhibited ataxia. Degeneration of the spinal cord was seen in both the negative and positive control hens. Degeneration of the spinal cord as well as the peripheral nerves was also observed in the hens at 90 and 270 mg/kg-day; the severity and incidence was reported to be dose-responsive.

CASRN 68937-41-7 was neurotoxic to hens in this assay.

(2) Groups of 10 adult domestic hens received a single oral dose of 3000, 5000, 7000 or 9000 mg/kg CASRN 68937-41-7 and were observed for 21 days. Eighteen hens each received corn oil (negative controls) or 500 mg/kg TOCP (positive controls). Marked body weight decreases were seen in the positive controls and at the highest dose. No ataxia or neuropathological lesions were

seen in the negative controls. Ataxia was seen in all exposed groups with one animal each at 7000 and 9000 mg/kg still exhibiting effects at the end of the observation period (21 days). Seventeen of 18 positive control hens showed ataxia and serious neuropathological lesions. One bird each at 3000 and 7000 mg/kg and two birds at 9000 mg/kg had distinct neuropathological lesions, some of which were described as relatively severe.

CASRN 68937-41-7 was neurotoxic to hens in this assay.

(3) CASRN 68937-41-7 was administered to two hens once at 1000 mg/kg in gelatine capsules. Negative controls received corn oil and one hen received TOCP at 750 mg/kg (positive control). The test substance inhibited neurotoxic esterase (NTE) activity by 53.1% (TSCATS - OTS O540132).

CASRN 68937-41-7 inhibited NTE activity in this assay.

Conclusion: The acute oral and dermal toxicity of CASRN 68937-41-7 in rats is low. Submitted data for the repeated-dose and genetic toxicity (gene mutations) endpoints were inadequate. No data were submitted for reproductive/developmental toxicity and genetic toxicity (chromosomal aberrations) endpoints. CASRN 68937-41-7 was neurotoxic in hens. CASRN 68937-41-7 was not irritating to rabbit skin but was irritating to rabbit eyes.

Table 3. Summary of the Screening Information Data Set under the U.S. HPV Challenge Program – Human Health Data	
Endpoints	Isopropylated Triphenyl Phosphate (CASRN 68937-41-7)
Acute Dermal Toxicity LD₅₀ (mg/kg-bw)	> 2,000 mg/kg-bw
Repeated-Dose Toxicity NOAEL/LOAEL (mg/kg-day)	No Adequate Data
Reproductive Toxicity	No Data
Developmental Toxicity	No Data
Genetic Toxicity – Gene Mutations <i>in vitro</i>	No Adequate Data
Genetic Toxicity – Chromosomal Aberrations <i>in vitro</i>	No Data
Additional Information Skin Irritation Eye Irritation Neurotoxicity	Not irritating Slightly irritating Positive

4. Hazard to the Environment

The environmental hazard data are summarized in Table 4.

Acute Toxicity to Fish

(1) Fathead minnow (*Pimephales promelas*) were exposed to nominal test concentrations of 0, 1.8, 3.2, 5.6, 10 or 18 mg/L for 96 hours in a static toxicity test. Mortality data for each test concentration were not reported.

96-h LC₅₀ = 10.8 mg/L

(2) Fathead minnow (*P. promelas*) were exposed to nominal test concentrations of 0, 5.6, 10, 18, 32 or 56 mg/L for 96 hours in a static toxicity test. Mortality data for each test concentration were not reported.

96-h LC₅₀ = 50.1 mg/L

(3) Rainbow trout (*Salmo gairdneri*) were exposed to five unspecified nominal test concentrations for 96 hours in a static toxicity test. Mortality data for each test concentration were not reported.

96-h LC₅₀ = 1.6 mg/L

(4) Rainbow trout (*S. gairdneri*) were exposed to nominal test concentrations of 0, 1.0, 1.8, 3.2, 5.6 and 10 mg/L for 96 hours in a static toxicity test. Mortality was observed in all treatment groups.

96-h LC₅₀ = 2.4 mg/L

(5) Rainbow trout (*S. gairdneri*) were exposed to nominal test concentrations of 0, 0.56, 1, 1.9, 3.2 or 5.6 mg/L for 96 hours in a static toxicity test. Mortality was observed in the two highest treatment groups.

96-h LC₅₀ = 4.46 mg/L

Acute Toxicity to Aquatic Invertebrates

(1) A 48-hour static toxicity test was conducted in *Daphnia magna*. Test concentrations were not reported. Mortality/immobilization data for each test concentration were not indicated.

48-h EC₅₀ = 0.83 mg/L

(2) A 48-hour static toxicity test was conducted in *D. magna* using nominal test concentrations of 0, 1, 1.8, 3.2, 5.6, 10 or 18 mg/L. Mortality/immobilization data for each test concentration were not indicated.

48-h LC₅₀ = 1.5 mg/L

(3) A 48-hour static toxicity test was conducted in *D. magna*. Test concentrations were not reported. Mortality/immobilization data for each test concentration were not indicated.

48-h EC₅₀ = 2.44 mg/L

Toxicity to Aquatic Plants

No data were submitted for this endpoint.

Conclusions: For CASRN 68937-41-7, the 96-hr LC₅₀ for fish ranges from 1.6 to 50.1 mg/L and the 48-hr EC₅₀ for daphnia ranges from 0.83 to 2.44 mg/L. No data were submitted for toxicity to aquatic plants and chronic toxicity to aquatic invertebrates.

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data	
Endpoints	Isopropylated Triphenyl Phosphate (CASRN 68937-41-7)
Fish 96-h LC₅₀ (mg/L)	1.6 – 50.1
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	0.83 – 2.44
Aquatic Plants 72-h EC₅₀ (mg/L) (biomass) (growth rate)	No Data
Chronic Toxicity to Invertebrates 21-day EC₅₀ (mg/L)	No Data

Bold = measured data