

SCREENING-LEVEL HAZARD CHARACTERIZATION

Tris(nonylphenyl) Phosphite (CASRN 26523-78-4)

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.

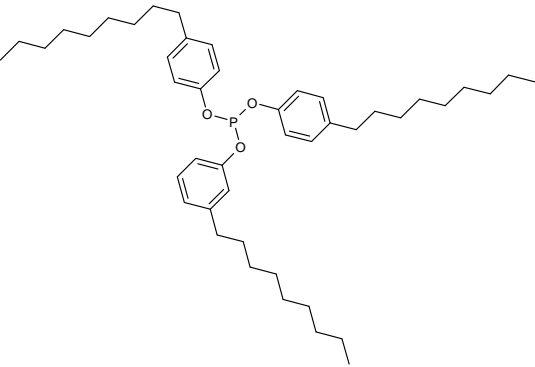
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are 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.

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>.

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>26523-78-4</p>
<p>Chemical Abstract Index Name</p>	<p>Phenol, nonyl-, phosphite (3:1)</p>
<p>Structural Formula</p>	
<p style="text-align: center;">Summary</p> <p>CASRN 26523-78-4 is a liquid with negligible to low water solubility and moderate vapor pressure. It is expected to have low mobility in soil. Volatilization of CASRN 26523-78-4 is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered moderate in acetonitrile/water solution and moderate to slow in water. The rate of atmospheric photooxidation is considered moderate. CASRN 26523-78-4 is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>Acute oral toxicity of CASRN 26523-78-4 to rats and acute dermal toxicity to rats and rabbits is low. In a 90-day repeated-dose toxicity study in rats, dietary administration of CASRN 26523-78-4 resulted in increased mortality at 2500 mg/kg-bw/day; the NOAEL for systemic toxicity is 500 mg/kg-bw/day. Repeated-dose dietary administration of CASRN 26523-78-4 to rats and beagle dogs for two years resulted in decreased body weight gain and increased liver weights in rats at 500 mg/kg-bw/day and altered hematological and clinical chemistry in beagle dogs at 250 mg/kg-bw/day; the NOAELs for systemic toxicity in rats and beagle dogs are 167 and 83 mg/kg-bw/day respectively. In a reproductive/developmental toxicity screening test, administration of CASRN 26523-78-4 via gavage to rats resulted in decreased body weight and kidney effects in males at 1000 mg/kg-day; the NOAEL for systemic toxicity is 200 mg/kg-day. In this study, reproductive effects consisted of reduced ovarian weight and reduced litter size on postnatal day 4 at 1000 mg/kg-day. Developmental effects consisted of decreased relative paired epididymides weights and kidney mineralization in male offspring at 1000 mg/kg-day; the NOAEL for reproductive and developmental toxicity is 200 mg/kg-day. CASRN 26523-78-4 did not induce gene mutations in bacteria or mammalian cells or chromosomal aberrations in mammalian cells <i>in vitro</i>. CASRN 26523-78-4 is irritating to rabbit skin and irritating to the rabbit eye. Based upon the maximization test in guinea pigs, CASRN 26523-78-4 is a skin sensitizer.</p> <p>The estimated acute 96-hour LC₅₀ value for CASRN 26523-78-4 in fish, aquatic invertebrates, and aquatic plants is no effects at saturation.</p>	

Chronic toxicity to aquatic invertebrates from CASRN 26523-78-4 is a data gap under the HPV Challenge Program.

The sponsor, Phosphite Manufacturers Consortium (PMC), submitted a Test Plan and Robust Summaries to EPA for tris(nonylphenyl) phosphite (TNPP) (CASRN 26523-78-4; 9th CI name: Phenol, nonyl-, phosphite (3:1)) on May 25, 2000. EPA posted the submission on the ChemRTK HPV Challenge website on June 13, 2000

(<http://www.epa.gov/oppt/chemrtk/pubs/summaries/phsphite/c12615tc.htm>). EPA comments on the original submission were posted to the website on October 6, 2000. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 14, 2000 and November 15, 2006, which were posted to the ChemRTK website without a posting date and on January 11, 2007, respectively.

1. Chemical Identity

1.1 Identification and Purity

The following description is taken from the 2006 Test Plan and Robust Summary:

CASRN 26523-78-4 is produced by reaction between nonylphenol and phosphorus trichloride in the presence of organic catalyst. The purity of commercial products is 93.9 – 100% w/w CASRN 26523-78-4. Impurities include nonylphenol, phenol, di(nonylphenyl)phenylphosphite, and chlorine.

1.2 Physical-Chemical Properties

CASRN 26523-78-4 is a clear liquid with negligible to low water solubility and moderate vapor pressure. A summary of physical-chemical and environmental fate data submitted is provided in Table 1.

It should be noted that this material cannot have a linear nonyl group on the phenol as the name implies. Commercial substances based on nonylphenol are known to be highly branched due to the use of propylene to produce an oligomer from which a “cut” is made from which the “nonyl” is derived. It is this “nonyl” that is used for ring alkylation. Although the sponsor indicates by a SMILES notation that the test substance contains linear nonyl group, the structure below is shown with the more appropriate “tripropylene” group to represent the “nonyl” group.

Property	Value
CASRN	26523-78-4
Molecular Weight	689.02
Physical State	Liquid
Melting Point	6°C (measured pour point)
Boiling Point	Initial decomposition begins at 357°C
Vapor Pressure	3.4×10 ⁻⁴ mm Hg at 20°C (measured)
Water Solubility	<0.6 mg/L at 24°C (measured; hydrolysis may occur)
Dissociation Constant (pK _a)	Not applicable

Property	Value
Henry's Law Constant	6.5×10^{-4} atm-m ³ /mole (estimated) ²
Log K _{ow}	20.0 (estimated) ²

¹Phosphite Manufacturers Consortium (PMC). November 15, 2006. Revised Robust Summary for Phenol, nonyl-, phosphite (3:1). Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/phsphite/c12615tc.htm> as of March 22, 2010

²U.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 March 22, 2010.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

According to the 2006 IUR submissions, CASRN 26523-78-4 had an aggregated production and/or import volume in the United States between 10 and 50 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other plastics product manufacturing and plastics packaging materials and unlaminated film and sheet manufacturing as stabilizers; resin and synthetic rubber manufacturing as “other”; and tire manufacturing as “other”. Non-confidential commercial and consumer uses of this chemical include electrical and electronic products; lawn and garden products (non-pesticidal); and rubber and plastic products.

2.2 Environmental Exposure and Fate

CASRN 26523-78-4 is expected to have low mobility in soil. CASRN 26523-78-4 was not readily biodegradable using a closed bottle test (OECD 301D), modified Sturm test (OECD 301B), and a modified MITI test (OECD 301C). Due to a lack of solubility in water, CASRN 26523-78-4 is essentially unavailable for biodegradation. Any solubilized CASRN 26523-78-4 will eventually hydrolyze to phosphorous acid and nonylphenol. The latter is expected to biodegrade in the environment. The rate of hydrolysis is considered moderate to slow under environmental conditions and moderate when measured in a water/acetonitrile mixture. The rate of volatilization is considered moderate based on its Henry's Law constant. CASRN 26523-78-4 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	Value
Photodegradation Half-life	2.7 hours (estimated) ²
Hydrolysis Half-life	13–14 hours at 22°C and pH 4, 7, and 9 (measured in 1/1 [v/v] mixture of acetonitrile/water) ^{1b} In water, about 100% hydrolyzed in 13-14 days. The hydrolysis products are expected to be branched nonylphenol, mono- and dinonylphenol phosphite and phosphorous acid.
Biodegradation	<4% after 28 days (not readily biodegradable); 1% after 29 days (not readily biodegradable); 0% after 28 days (not readily biodegradable) ^{3,4}
Bioaccumulation Factor	BAF = 0.9 (estimated) ²
Log K _{oc}	13 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	<0.1
Water (%)	6.5
Soil (%)	93.5
Sediment (%)	<0.1
Persistence ⁵	P1 (low)
Bioaccumulation ⁵	B1 (low)

¹Phosphite Manufacturers Consortium (PMC). November 15, 2006. Revised Robust Summary for Phenol, nonyl-, phosphite (3:1). Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/phsphite/c12615tc.htm>. As of March 22, 2010. ^{1b} MIDI Database available online from: http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of April 20,2010.

²U.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 March 22, 2010.

³National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from: http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of March 22, 2010.

⁴Although no mineralization was observed, the test substance was partially hydrolyzed during the biodegradation test.

⁵Federal 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 Effects

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

Acute Oral Toxicity

Albino rats (5/sex/dose, strain not specified) were fasted for 18 hours and administered a single dose of CASRN 26523-78-4 (purity not specified) in cottonseed oil via gavage at 8190, 11,320, 16,380, 22,620 or 32,720 mg/kg. Animals were observed for up to 14 days following dosing. Mortalities occurred at $\geq 11,320$ mg/kg during the first 5 days.

LD₅₀ = 19,500 mg/kg

Acute Dermal Toxicity

(1) New Zealand white rabbits (5/sex) were administered CASRN 26523-78-4 (no vehicle, purity not specified) via the dermal route at 2000 mg/kg-bw under occlusive conditions for 24 hours and observed for 14 days following exposure. No mortality occurred.

LD₅₀ > 2000 mg/kg-bw

(2) Tif:RAI f1 rats (5/sex) were administered CASRN 26523-78-4 (>94% purity) via the dermal route at 2000 mg/kg-bw to clipped, intact skin under semi-occlusive conditions for 24 hours and observed for 14 days following exposure. No mortality occurred.

LD₅₀ > 2000 mg/kg-bw

Repeated-Dose Toxicity

(1) Weanling rats (6/sex/dose, strain not specified) were administered CASRN 26523-78-4 (purity not specified) via the diet at 0, 0.2, 1.0 or 5.0% (0, approximately 100, 500 or 2500 mg/kg-bw/day) for 90 days. Appearance and behavior were inspected daily and body weight and food intake were recorded weekly. Hematological and clinical chemistry evaluations were made at 12 weeks for 2 animals/sex/dose and gross pathology was examined. At 2500 mg/kg-bw/day, 2 out of 6 females died and growth (i.e. body weight) was significantly depressed in both sexes. Necropsy examinations of the females that died noted pulmonary pathology (i.e., fibrinous exudate in the thorax and hemorrhagic lungs). There was no difference in liver weight or liver histopathology between the treated and control animals. Acute and chronic pyelonephritis with hydronephrosis was observed in the kidneys of 8 of 9 animals at 2500 mg/kg-bw/day. No changes in hematology or clinical chemistry occurred at any dose.

LOAEL ~ 2500 mg/kg-bw/day (based on mortality, decreased growth, and kidney toxicity)

NOAEL ~ 500 mg/kg-bw/day

(2) Beagle dogs (3/sex/dose) were administered CASRN 26523-78-4 via the diet at 0, 1000, 3300 or 10,000 ppm (0, approximately 25, 83 or 250 mg/kg-bw/day) for 2 years. Appearance, behavior, and survival were inspected daily. Body weight was recorded weekly for the first 12 weeks and then every 4 weeks. Toxicological measures included neurological tests, clinical tests, blood chemistry, organ weights, and histopathology. One female at 10,000 ppm and one female at 1000 ppm died of encephalitic meningitis unrelated to the treatment and were replaced. At 10,000 ppm, slightly decreased hemoglobin and hematocrit were observed in both sexes and

elevated cholesterol levels were observed in females at 100 weeks (significance not stated). One male dog exhibited chronic inflammation of the renal pelvis at 10,000 ppm. Slight to moderate thyroid hyperplasia was observed in 2 of 3 female dogs at 10,000 ppm.

LOAEL ~ 250 mg/kg-bw/day (based on thyroid hyperplasia in females, chronic inflammation of the renal pelvis in males, and changes in blood chemistry)

NOAEL ~ 83 mg/kg-bw/day

Reproductive Toxicity

In a reproductive/developmental toxicity screening test (OECD 421), Sprague-Dawley rats (10/sex/dose in the F0 generation, 5/sex/litter for the F1 generation) were administered 0, 50, 200 or 1000 mg/kg-day of CASRN 26523-78-4 in corn oil via gavage. F0 males were dosed for 4 weeks (2 weeks pre-mating, 2 weeks mating), F0 females were dosed for 10 weeks (2 weeks pre-mating, 2 weeks mating, 3 weeks gestation and 3 weeks lactation) and F1 offspring were dosed from weaning (postnatal day (PND) 22) through 85 days of age. Complete histology was performed on 5/sex/group in the control and 1000 mg/kg-day dose in the F0 and F1 generations. All F0 parental animals, non-selected F1 weanlings and retained F1 adults were necropsied. Mortality in females occurred as a result of dosing errors at 200 and 1000 mg/kg-day. At 1000 mg/kg-day, 3 out of 10 females were found dead on day 22 of gestation, evidently as a result of dystocia, since the pups appeared normal. These effects are not considered treatment-related. At 1000 mg/kg-day, significant decreases in body weight and body weight gain were observed in males. At 1000 mg/kg-day, F0 males showed significantly reduced absolute and relative kidney weight with concurrent corticomedullary junction mineralization and F0 females showed significantly reduced absolute and relative ovarian weight. No treatment-related changes were seen in necropsy or histopathology. At 1000 mg/kg-day, reduced litter size on postnatal day 4 and decreased relative paired epididymides weight in F1 males were observed. Two adult F1 males had corticomedullary junction mineralization of the kidneys at the highest dose. No effects on gestation length, number of implantations, postimplantation loss, total pups per litter, anogenital distance, pup body weight, estrous cycle or andrology were observed.

LOAEL (parental systemic toxicity) = 1000 mg/kg-day (based on decreased body weight and kidney effects in males)

NOAEL (parental systemic toxicity) = 200 mg/kg-day

LOAEL (reproductive toxicity) = 1000 mg/kg-day (based on reduced ovarian weights and reduced litter size on PND 4)

NOAEL (reproductive toxicity) = 200 mg/kg-day

Developmental Toxicity

In the reproductive and developmental toxicity screening test described previously, F1 litters were culled on PND 4 to 5/sex/litter and culled pups received complete necropsy with external and visceral examinations. Results showed that 1000 mg/kg-day of CASRN 26523-78-4 resulted in significantly reduced live litter size on PND 4, F1 males had significantly decreased relative paired epididymides weight, and 2 out of 5 adult F1 males had treatment-related corticomedullary junction mineralization of the kidneys. Toxicological significance of the effects on epididymides is uncertain since absolute organ weight was not affected and similar effects were not seen in the F0 generation. There were no treatment-related changes noted in

gross necropsy and histopathology in F1 females and no effects on gestation length, number of implantations, postimplantation loss, total pups per litter, anogenital distance, pup body weight, estrous cycle or andrology.

LOAEL (developmental toxicity) = 1000 mg/kg/day (based on reduced live litter size, decreased epididymides weight, and kidney effects in adult F1 male offspring)

NOAEL (developmental toxicity) = 200 mg/kg/day

Genetic Toxicity – Gene Mutation

In vitro

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 uvrA were exposed to CASRN 26523-78-4 in acetone at concentrations of 0, 75, 200, 600, 1800 and 5000 µg/plate in the presence and absence of metabolic activation. Positive and negative controls responded as expected. Precipitate was observed at 600 µg/plate and higher, but cytotoxicity was not observed at any dose.

CASRN 26523-78-4 was not mutagenic in this assay.

(2) *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to CASRN 26523-78-4 in acetone at concentrations of 313, 625, 1250, 2500 and 5000 µg/0.1 mL in the presence and absence of metabolic activation. Positive and negative controls were tested concurrently, but responses were not provided. Precipitate was observed at 2500 and 5000 µg/0.1 mL, but cytotoxicity was not observed at any dose.

CASRN 26523-78-4 was not mutagenic in this assay.

(3) Mouse lymphoma L5178Y cells were exposed to CASRN 26523-78-4 at concentrations of 0, 5, 10, 25, 50, 100 or 150 µg/mL in the presence and absence of metabolic activation. Positive controls were tested concurrently and responded appropriately. Precipitate was observed at concentrations of 100 µg/mL and higher, but cytotoxicity was not reported at any concentration.

CASRN 26523-78-4 was not mutagenic in this assay.

(4) Chinese hamster V79 cells were exposed to CASRN 26523-78-4 in ethanol at concentrations ranging from 0.6 to 16 µg/mL in the presence of metabolic activation, and 0.3 to 8.0 µg/mL in the absence of metabolic activation. Concentrations were chosen based upon a preliminary toxicity assay. Positive and negative controls were tested concurrently, but responses were not provided.

CASRN 26523-78-4 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

(1) Chinese hamster ovary (CHO) cells were exposed to CASRN 26523-78-4 at concentrations of 0, 18.75, 37.5, 75, 150 or 200 µg/mL in the absence of metabolic activation for 4 hours; 0, 6.25, 12.5, 25, 50 or 150 µg/mL in the absence of metabolic activation for 20 hours; or 0, 18.75, 37.5, 75, 150 or 200 µg/mL in the presence of metabolic activation for 4 hours. Reductions in mitotic index were observed at the highest dose in the presence and absence of metabolic activation. Positive and negative controls were tested concurrently and responded as expected.

CASRN 26523-78-4 did not induce chromosomal aberrations in this assay.

(2) CHO cell line CCL61 was exposed to CASRN 26523-78-4 in acetone at concentrations of 31.25, 65.5, 125 or 250 µg/mL in the presence and absence of metabolic activation. Reductions in mitotic index were observed at 250 µg/mL. Positive and negative controls were tested concurrently, but responses were not provided.

CASRN 26523-78-4 did not induce chromosomal aberrations in this assay.

Additional Information

Skin Irritation

(1) Three New Zealand white rabbits (1 male, 2 females) were administered 0.5 mL CASRN 26523-78-4 (purity not specified) via the dermal route to intact skin under semi-occluded conditions for 4 hours and observed for erythema and edema for a minimum of 72 hours following patch removal. Very slight erythema occurred in 3/3 animals at 4 hours and the reaction reversed by 24 hours. No edema was observed at any time point.

CASRN 26523-78-4 was slightly irritating to rabbit skin.

(2) New Zealand white rabbits (3/sex) were administered 0.5 mL CASRN 26523-78-4 (purity not specified) via the dermal route to intact and abraded skin under occluded conditions for 24 hours and observed for 7 days following exposure. In 3 of 6 animals, application sites showed necrosis. In 5 of 6 animals, erythema extended beyond the treated areas. Erythema and edema reversed within 7 days, except in two abraded sites where erythema was still moderate to severe.

CASRN 26523-78-4 was moderately irritating to rabbit skin.

Eye Irritation

(1) Undiluted CASRN 26523-78-4 (0.1 mL, 99.3% purity) was instilled into the left eye of New Zealand white rabbits (2/sex) and examined for 21 days following treatment. Eyes were not rinsed. Slight conjunctival redness and chemosis was observed in all exposed eyes starting at 1 hour that resolved in all animals by 48 hours after treatment.

CASRN 26523-78-4 was slightly irritating to rabbit eyes.

(2) CASRN 26523-78-4 (0.1 mL, purity not specified) was instilled into the left eye of New Zealand white rabbits (3/sex) and examined for 7 days following exposure. Three eyes were rinsed with saline 30 seconds after exposure and three were not rinsed. Slight redness and chemosis were observed and were reversible within 7 days in the rinsed eyes. Minimal irritation was observed in rinsed and unrinsed eyes.

CASRN 26523-78-4 was slightly irritating to rabbit eyes.

Skin Sensitization

(1) In a guinea pig maximization test, albino guinea pigs (10/sex) were administered CASRN 26523-78-4 (>94% purity) as a 5% solution via intradermal injection in the neck region for the first induction in week 1, 10% CASRN 26523-78-4 via occlusive dermal exposure over the

previous injection site for the second induction in week 2, and 1% of CASRN 26523-78-4 via occlusive dermal exposure to the flanks for the challenge exposure in week 5. Control animals (5/sex) were treated with adjuvant (not identified) and vehicle (oleum arachidis for intradermal injection and Vaseline for dermal exposure) during induction and with the vehicle as well as CASRN 26523-78-4 during challenge. Positive sensitization reactions were observed in 12/20 animals at 24 hours and 15/20 animals at 48 hours following challenge. No positive sensitization occurred in the control animals.

CASRN 26523-78-4 was sensitizing to guinea pigs in this assay.

(2) In a Buehler test, guinea pigs (10/sex) were administered 0.4 ml of undiluted test substance (99.3% purity) that was applied to intact skin under occluded conditions for 6 hours once per week for 3 consecutive weeks. Positive controls were treated in the same manner and untreated negative controls were tested concurrently. The challenge phase consisted of occluded dermal exposure to CASRN 26523-78-4 for 6 hours on new skin sites. No treated animals exhibited erythema or edema at the 24 and 48 hour observation point during the challenge phase. All positive controls were sensitized and no negative controls were sensitized when challenged.

CASRN 26523-78-4 was not sensitizing to guinea pigs in this assay.

Conclusion: Acute oral toxicity of CASRN 26523-78-4 to rats and acute dermal toxicity to rats and rabbits is low. In a 90-day repeated-dose toxicity study in rats, dietary administration of CASRN 26523-78-4 resulted in increased mortality at 2500 mg/kg-bw/day; the NOAEL for systemic toxicity is 500 mg/kg-bw/day. Repeated-dose dietary administration of CASRN 26523-78-4 to rats and beagle dogs for two years resulted in decreased body weight gain and increased liver weights in rats at 500 mg/kg-bw/day and altered hematological and clinical chemistry in beagle dogs at 250 mg/kg-bw/day; the NOAELs for systemic toxicity in rats and beagle dogs are 167 and 83 mg/kg-bw/day respectively. In a reproductive/developmental toxicity screening test, administration of CASRN 26523-78-4 via gavage to rats resulted in decreased body weight and kidney effects in males at 1000 mg/kg-day; the NOAEL for systemic toxicity is 200 mg/kg-day. In this study, reproductive effects consisted of reduced ovarian weight and reduced litter size on postnatal day 4 at 1000 mg/kg-day. Developmental effects consisted of decreased relative paired epididymides weights and kidney mineralization in male offspring at 1000 mg/kg-day; the NOAEL for reproductive and developmental toxicity is 200 mg/kg-day. CASRN 26523-78-4 did not induce gene mutations in bacteria or mammalian cells or chromosomal aberrations in mammalian cells *in vitro*. CASRN 26523-78-4 is irritating to rabbit skin and irritating to the rabbit eye. Based upon the maximization test in guinea pigs, CASRN 26523-78-4 is a skin sensitizer.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data	
Endpoints	SPONSORED CHEMICAL Tris(nonylphenyl) Phosphite (CASRN 26523-78-4)
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	19,000
Acute Dermal Toxicity LD₅₀ (mg/kg-bw)	> 2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-day)	(beagle) NOAEL ~ 83 LOAEL ~ 250
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-day)	(rat) NOAEL ~ 200 LOAEL ~ 1000
Developmental Toxicity NOAEL/LOAL Oral (mg/kg-day)	
Developmental Toxicity	NOAEL ~ 200 LOAEL ~ 1000
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative
Additional Information	
Skin irritation	Moderately irritating (24-hour exposure)
Eye irritation	Slightly irritating
Skin sensitization	Sensitizing in maximization test Not sensitizing in Buehler test

4. Hazard to the Environment

Tris(nonylphenyl) phosphate (TNPP; CASRN 26523-78-4) is known to hydrolyze in water to NP (nonylphenol) and phosphorus acid ($t_{1/2} = 13 - 14$ d in H_2O). Relevant OECD guidelines regarding hydrolytically unstable compounds were employed to conduct aquatic toxicity tests with TNPP. All test solutions were prepared and then allowed to hydrolyze for 78 hours prior to exposure. Chronic toxicity to aquatic organisms would provide more detailed information regarding toxicity of CASRN 26523-78-4 in aquatic systems due to its hydrolysis properties to NP.

Acute Toxicity to Fish

Rainbow trout (*Oncorhynchus mykiss*) were exposed to a solution of hydrolyzed tris(nonylphenyl) phosphite at nominal concentrations of 0, 1.6, 3.1, 6.3, 12.5, 25, 50 or 100 mg/L under static conditions for 96 hours. Stock solutions were allowed to hydrolyze for 78 hours before supernatants were drawn off for use in the study. No mortality occurred and no effects were observed at all effects levels.

96-h LC₅₀ = no effects at saturation

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to a solution of hydrolyzed tris(nonylphenyl) phosphite at nominal concentrations of 0, 0.02, 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5 or 10 mg/L under static conditions for 48 hours. Stock solutions were allowed to hydrolyze for 78 hours before supernatants were drawn off for use in the study. At 48-hours, no immobilization occurred at 0, 0.02, 0.04, 0.08 or 0.16 mg/L. Immobilization of 75% and 90% occurred at 0.31 and 0.63 mg/L, respectively, and 100% immobilization occurred at higher concentration levels. Observed toxicity is believed to be physical due to particles or undissolved materials observed in assay reported in the data summary.

48-h LC₅₀ = no effects at saturation

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to a solution of hydrolyzed tris(nonylphenyl) phosphite at nominal concentrations of 1.6, 3.1, 6.3, 12.5, 25, 50 and 100 mg/L under static conditions for 96 hours. Stock solutions were allowed to hydrolyze for 78 hours before supernatants were drawn off for use in the study. A 42-fold increase in cell density was observed in control cultures after 72-hours. The cell density at in the highest tested concentration was 344% greater than controls. Results indicated that hydrolysis of tris(nonylphenyl) phosphite causes growth stimulation due to the liberation of phosphorus.

72-h EC₅₀ = no effects at saturation

Conclusion: The acute 96-hour LC₅₀ value for CASRN 26523-78-4 in fish, aquatic invertebrates, and aquatic plants is no effects at saturation.

Table 5. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data	
Endpoints	Tris(nonylphenyl) phosphite (CASRN 26523-78-4)
Fish 96-h LC₅₀ (mg/L)	NES
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	NES
Aquatic Plants 72-h EC₅₀ (mg/L)	NES
Aquatic Invertebrates Chronic	No data

NES = No effects at saturation.