

SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL

1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (CASRN 27676-62-6)

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>27676-62-6</p>
<p>Chemical Abstract Index Name</p>	<p>1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-</p>
<p>Structural Formula</p>	
<p style="text-align: center;">Summary</p> <p>CASRN 27676-62-6 is a white powder with negligible water solubility and negligible vapor pressure. This chemical is expected to have low mobility in soil. Volatilization is considered low based on its Henry's Law constant. The rate of biodegradation is expected to be very slow and the rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid; however, the extent of degradation is not known and it is not expected to exist in the vapor phase in the atmosphere where this reaction occurs. CASRN 27676-62-6 is expected to have high persistence (P3) and low bioaccumulation potential (B1).</p> <p>The acute oral and dermal toxicity of CASRN 27676-62-6 is low in rats. Two 13-week oral repeated-dose toxicity studies in rats exposed via dietary administration showed no mortality or treatment-related effects at the highest concentrations tested; 900 - 750 mg/kg-bw/day (males - females) in one study and 500 - 600 mg/kg-bw/day (males-females) in the second study. A 90-day oral repeated-dose toxicity study revealed no significant treatment effects in dogs exposed via dietary administration; the NOAEL for systemic toxicity is 250 mg/kg-bw/day (highest dose tested). A standard reproductive toxicity study was not available; however, no effects were seen in a small group of rats that were mated and assessed for reproductive effects during a two-year feeding study using a single dose group of 100 mg/kg-bw/day. An oral prenatal developmental</p>	

toxicity study in rats revealed no effects in dams at doses up to 1000 mg/kg-day, the highest dose tested; the NOAEL for maternal toxicity is 1000 mg/kg-day. Signs of developmental toxicity included skeletal anomalies (accelerated and/or delayed ossification) at 100 mg/kg-day, the lowest dose tested; the NOAEL for developmental toxicity is not established. CASRN 27676-62-6 did not induce gene mutations *in vitro* or chromosomal aberrations *in vivo*. No increase in tumor incidence was noted during a two-year carcinogenicity study in rats.

The aquatic studies submitted for fish, aquatic invertebrates, and aquatic plants are considered invalid. All testing was done at concentrations greater than the water solubility. However, because of the physicochemical properties of the chemical, EPA considers it unlikely that acute or chronic exposure would result in adverse effects to aquatic organisms, and no further testing is necessary for the purposes of the HPV Challenge Program.

No data gaps were identified under the HPV Challenge Program.

The sponsor, Rubber and Plastic Additives (RAPA) Panel of the American Chemistry Council, submitted a Test Plan and Robust Summaries to EPA for the Hindered Phenols category on December 18, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 15, 2002 (<http://www.epa.gov/HPV/pubs/summaries/hndrdphn/c13382tc.htm>). In response to EPA comments, the sponsor divided the Hindered Phenols category into two separate categories; styrenated phenols and bridged alkyl phenols and two stand-alone chemicals; 4-methylphenol, reaction products with dicyclopentadiene and isobutylene (CASRN 68610-51-5) and 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (CASRN 27676-62-6). The sponsor submitted a revised Test Plan and Robust Summaries for CASRN 27676-62-6 on July 11, 2003 and February 1, 2007; these were posted to the ChemRTK website on September 1, 2004 and April 2, 2007, respectively. The RAPA panel submitted developmental toxicity data for this chemical on February 8, 2007. EPA comments on the revised submission were posted to the website on March 15, 2007.

1. Chemical Identity

1.1 Identification and Purity

Commercial grade formulations were indicated for CASRN 27676-62-6. Purity of test article, where noted in the revised 2003 Robust Summaries, ranged between 95 - 98.3%.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 27676-62-6 are summarized in Table 1. This chemical is a white powder with negligible water solubility and negligible vapor pressure.

Table 1. Physical-Chemical Properties of 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]⁻¹	
Property	Value
CASRN	27676-62-6
Molecular Weight	784.10
Physical State	White to off-white powder
Melting Point	219.5–225.5°C (measured)
Boiling Point	>350°C (decomposition)
Vapor Pressure	<1.0×10 ⁻¹⁰ mm Hg at 25°C (estimated) ²
Water Solubility	<1 mg/L at 20°C (measured); (This is based on limit of detection. The chemical should be very insoluble.) <1.0×10 ⁻¹⁰ mg/L (estimated) ²
Dissociation Constant (pK _a)	11.63 (estimated) ³ ; 11.65 (estimated) ³ ; 11.67 (estimated) ³
Henry's Law Constant	<1.0×10 ⁻¹⁰ atm·m ³ /mole (estimated) ²
Log K _{ow}	15.2 (estimated) ²

¹ Rubber and Plastic Additives Panel of The American Chemistry Council. July 11, 2003. Test Plan and Robust Summary for 1,3,5-Triazine-2,4,6(1H,3H,5H)-Trione, 1,3,5-Tris[[3,5-Bis(1,1-Dimethylethyl)-4-Hydroxyphenyl]methyl]-. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/hndrdphn/c13382tc.htm> as of May 7, 2010.

² U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. EPA, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of May 7, 2010.

³ SPARC. 2010. Online pK_a and Property Calculator, v.4.2.1405-s4.2.1408. Available online from: <http://ibmlc2.chem.uga.edu/sparc/> as of May 7, 2010.

2. General Information on Exposure

2.1 Production Volume and Exposure

According to the 2006 IUR submissions, CASRN 27676-62-6 had an aggregated production and/or import volume in the United States between 1 and 10 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other plastics product manufacturing as stabilizers; plastics bottle manufacturing as stabilizers; plastics packaging materials and unlaminated film and sheet manufacturing as stabilizers; and resin and synthetic rubber manufacturing as stabilizers. Non-confidential commercial and consumer uses of this chemical include rubber and plastic products; and not readily obtainable (NRO).

2.2 Environmental Exposure and Fate

The environmental fate properties are provided in Table 2. CASRN 27676-62-6 is expected to have low mobility in soil. This chemical was not readily biodegradable in a modified Sturm test (OECD 301B), degrading 7% at a nominal concentration of 10 mg/L and 0% at 20 mg/L as measured by CO₂ evolution. The rate of volatilization of CASRN 27676-62-6 from water and moist soil is considered low based on its estimated Henry's Law constant. The rate of hydrolysis is considered negligible under environmental conditions. CASRN 27676-62-6 is expected to have high persistence (P3) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-¹	
Property	Value
Photodegradation Half-life	1.9 hours (estimated) ²
Hydrolysis Half-life	Stable
Biodegradation	0–7% in 28 days (not readily biodegradable)
Bioaccumulation Factor	BAF = 0.90 (estimated) ²
Log K _{oc}	11.0 (estimated) ²
Fugacity (Level III Model)	
Air (%)	<0.1
Water (%)	4.5
Soil (%)	95.4
Sediment (%)	0.1
Persistence ³	P3 (high)
Bioaccumulation ³	B1 (low)

¹Rubber and Plastic Additives Panel of The American Chemistry Council. July 11, 2003. Test Plan and Robust Summary for 1,3,5-Triazine-2,4,6(1H,3H,5H)-Trione, 1,3,5-Tris[[3,5 Bis(1,1-Dimethylethyl)-4-Hydroxyphenyl]methyl]-. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/hndrdphn/c13382tc.htm> as of May 7, 2010.

²U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. EPA, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episutedl.htm> as of May 7, 2010.

³Federal 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

Tif:RAIf (SPF) rats (5/sex) received a single dose of CASRN 27676-62-6 via oral gavage at 5000 mg/kg (vehicle: 0.5% carboxymethylcellulose in 0.1% w/v polysorbate 80) and were observed for 14 days following exposure. No mortalities occurred.

LD₅₀ > 5000 mg/kg

Acute Dermal Toxicity

Tif:RAIf (SPF) albino rats (5/sex) received a single dose of CASRN 27676-62-6 (vehicle: 0.5% carboxymethylcellulose in 0.1% w/v polysorbate 80) via dermal application at 2000 mg/kg for an unspecified duration and were observed for 14 days following exposure. No mortalities occurred.

LD₅₀ > 2000 mg/kg

Repeated-Dose Toxicity

(1) Tif:RAIf (SPF) albino rats (10/sex/group) were administered CASRN 27676-62-6 in the diet at 0, 150, 800, 3000 or 15,000 ppm (~ 0, 9, 48, 180 or 900 mg/kg-bw for males and ~ 0, 7.5, 40, 150 or 750 mg/kg-bw for females) for 13 weeks. There were no deaths or treatment-related effects on clinical signs, body weight, blood chemistry, urinalysis or histology. Slightly increased food consumption was observed at 900 mg/kg-bw/day in males. Female rats exhibited elevated platelet counts (magnitude not specified) at or above 150 mg/kg-bw/day. No other effects were reported in the robust summary.

NOAEL (males/females) ~ 900/750 mg/kg-bw/day (highest dose tested)

(2) Charles River albino rats (15/sex/group) were administered CASRN 27676-62-6 in the diet at 0, 1000, 3000 or 10,000 ppm (~ 0, 60, 180, or 600 mg/kg-bw/day in males and ~ 0, 50, 150 or 500 mg/kg-bw/day in females) for 90 days. Three deaths occurred; however, these were not considered treatment-related. Two deaths were due to an acute respiratory infection and one to trauma incurred during blood collection. There were no treatment-related effects on clinical signs, body weights, hematology, clinical biochemistry or histology.

NOAEL (males/females) ~ 600/500 mg/kg-bw/day (highest dose tested)

(3) Purebred Beagle dogs (4/sex/group) were administered CASRN 27676-62-6 in the diet at 0, 1000, 3000 or 10,000 ppm (~ 0, 25, 75 or 250 mg/kg-bw/day) for 90 days. There were no treatment-related effects on mortality, clinical signs, body weights, hematology, blood biochemistry, ophthalmology or histology.

NOAEL ~ 250 mg/kg-bw/day (highest dose tested)

Reproductive Toxicity

(1) In the previously described repeated-dose toxicity studies (two in rats and one in dogs), no treatment-related effects on reproductive organs were observed.

(2) No effects were noted in a two-year carcinogenicity study in which a small satellite of Wistar rats (one male and five females) were mated after seven months of dietary exposure to CASRN 27676-62-6 at 100 mg/kg-bw/day. All first generation (F1) offspring appeared normal. Five males and five females from the F1 group were treated at 100 mg/kg-bw/day and mated six months later to obtain the second generation (F2). All F2 offspring appeared normal. Ten animals from the F1 and 10 animals from the F2 generation were selected for autopsy. Macroscopic examination and histopathology (lung, liver, spleen, kidney and genitalia) showed no treatment-related effects.

LOAEL/NOAEL = Not established (one dose tested)

Developmental Toxicity

Pregnant Sprague-Dawley Crl:CD[®] (SD) IGS BR rats (96 females, number per dose not specified) were administered CASRN 27676-62-6 (in arachis oil) via oral gavage at 0, 100, 300 or 1000 mg/kg-bw/day on gestation day (GD) 5 through 19; animals were then sacrificed on GD 20 for fetal assessments. No treatment-related maternal (mortality, clinical signs, body weights, uterine parameters, histology) or developmental (fetal viability, growth, development) effects were reported. Significant treatment-related increases ($p < 0.05$) in offspring with seven or more ossified post lumbar vertebral centra were observed; however, all group means were within the range of historical controls. Dams treated at 300 and 1000 mg/kg-bw/day showed a significant increase ($p < 0.05$) in offspring having greater than six ossified metatarsals and a significant decrease ($p < 0.01$ at 100 and 1000 mg/kg-bw; $p < 0.05$ at 300 mg/kg-bw) in offspring showing two or more ossified phalanges. Study authors submit that ossification of the phalanges normally occurs later in development, hence this effect, (precocious ossification) was not considered biologically significant. Significant increases ($p < 0.01$) in offspring showing a medium fontanelle were observed at all doses; this effect was attributed to biological variation (*i.e.*, increased incidence of small fontanelles in control offspring when compared to historical values). The study authors concluded that there were no treatment-related effects on skeletal development. EPA does not concur, as the available data are insufficient to support this claim.

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

LOAEL (developmental toxicity) = 100 mg/kg-day, lowest dose tested (based on skeletal anomalies)

NOAEL (developmental toxicity) = Not established

Genetic Toxicity – Gene Mutation

In vitro

(1) *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 were exposed to CASRN 27676-62-6 at concentrations of 200, 780, 3130, 12,500 and 50,000 $\mu\text{g/mL}$ in the presence or absence of metabolic activation. The test substance was dissolved in acetone, which

was also used as a negative control. Positive controls were tested, but their responses were not provided. Precipitation of the test substance was observed at 12,500µg/mL.

CASRN 27676-62-6 was not mutagenic in this assay.

(2) Chinese hamster V79 cells were exposed to CASRN 27676-62-6 at concentrations of 27.5, 55, 110, 220, 330, 440 and 550 µg/mL in the presence or absence of metabolic activation for 7 – 8 days. Administration of the test substance was carried out using a dimethylsulfoxide (DMSO) vehicle. Appropriate responses were observed with positive and negative controls.

CASRN 27676-62-6 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

Chinese hamsters (*Cricetulus griseus*; random outbred strain) received a single administration of CASRN 27676-62-6 (in 0.5% carboxymethylcellulose) via oral gavage at 5000 mg/kg. Test animals were sacrificed 24 hours after administration and harvested bone marrow was stained with May-Grunwald solution. Positive and negative controls were included and yielded appropriate results.

CASRN 27676-62-6 did not induce micronuclei in this assay.

Additional Information

Carcinogenicity

In a two-year carcinogenicity study, Wistar rats (20/sex) received CASRN 27676-62-6 via dietary administration at 100mg/kg-bw/day. Six males and one female died during the course of this study (cause of death not specified). No malignant tumors were reported.

Conclusion: The acute oral and dermal toxicity of CASRN 27676-62-6 is low in rats. Two 13-week oral repeated-dose toxicity studies in rats exposed via dietary administration showed no mortality or treatment-related effects at the highest concentrations tested; 900 - 750 mg/kg-bw/day (males - females) in one study and 500 - 600 mg/kg-bw/day (males-females) in the second study. A 90-day oral repeated-dose toxicity study revealed no significant treatment effects in dogs exposed via dietary administration; the NOAEL for systemic toxicity is 250 mg/kg-bw/day (highest dose tested). A standard reproductive toxicity study was not available; however, no effects were seen in a small group of rats that were mated and assessed for reproductive effects during a two-year feeding study using a single dose group of 100 mg/kg-bw/day. An oral prenatal developmental toxicity study in rats revealed no effects in dams at doses up to 1000 mg/kg-day, the highest dose tested; the NOAEL for maternal toxicity is 1000 mg/kg-day. Signs of developmental toxicity included skeletal anomalies (accelerated and/or delayed ossification) at 100 mg/kg-day, the lowest dose tested; the NOAEL for developmental toxicity is not established. CASRN 27676-62-6 did not induce gene mutations *in vitro* or chromosomal aberrations *in vivo*. No increase in tumor incidence was noted during a two-year carcinogenicity study in rats.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data	
Endpoints	SPONSORED CHEMICAL 1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (CASRN 27676-62-6)
Acute Toxicity Oral LD₅₀ (mg/kg)	> 5000
Acute Dermal Toxicity LD₅₀ (mg/kg)	> 2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	600 - 900 (male rat; hdt) 500 -750 (female rat; hdt) 250 (dog; hdt)
Reproductive/ Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day)	No effects were seen following evaluation of reproductive organs in 13-week oral repeated-dose toxicity studies in rats and dogs.
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day)	
Maternal Toxicity	NOAEL = 1000 (hdt)
Developmental Toxicity	LOAEL = 100 NOAEL = Not Established
Genetic Toxicity - Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity - Chromosomal Aberrations <i>In vivo</i>	Negative
Additional Information Carcinogenicity	Negative

hdt = highest dose tested

4. Hazard to the Environment

The environmental hazard data are summarized in Table 4.

Toxicity to Fish, Aquatic Invertebrates, and Aquatic Plants

1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (CASRN 27676-62-6)

The aquatic studies submitted for fish, aquatic invertebrates, and aquatic plants are considered invalid. All testing was done at concentrations greater than the water solubility. However, because of the physicochemical properties of the chemical, EPA considers it unlikely that acute or chronic exposure would result in adverse effects to aquatic organisms, and no further testing is necessary for the purposes of the HPV Challenge Program.

Conclusion:

The aquatic studies submitted for fish, aquatic invertebrates, and aquatic plants are considered invalid. All testing was done at concentrations greater than the water solubility. However, because of the physicochemical properties of the chemical, EPA considers it unlikely that acute or chronic exposure would result in adverse effects to aquatic organisms, and no further testing is necessary for the purposes of the HPV Challenge Program.