

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### **1,6-Hexamethylene bis(3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate) (CASRN 35074-77-2)**

The High Production Volume (HPV) Challenge Program<sup>1</sup> was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set<sup>1,2</sup>) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental

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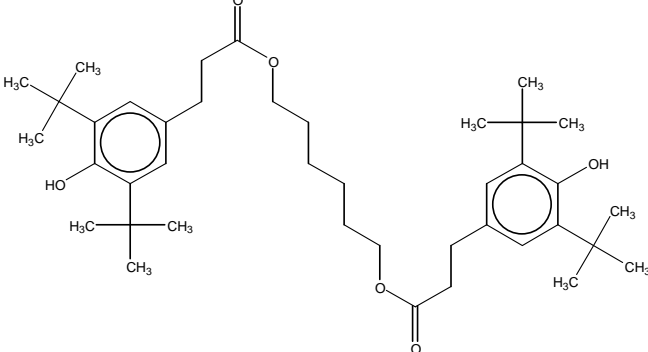
<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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

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

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 information previously not readily available to the public.

<p><b>Chemical Abstract Service Registry Number (CASRN)</b></p>	<p><b>35074-77-2</b></p>
<p><b>Chemical Abstracts Index Name</b></p>	<p><b>Benzenepropanoic acid 3,5-bis(1,1-dimethyl ethyl)-4-hydroxy-, 1,6-hexanediyl ester</b></p>
<p><b>Structural Formula</b></p>	
<p style="text-align: center;"><b>Summary</b></p> <p>CASRN 35074-77-2 is a white powder with negligible water solubility and negligible vapor pressure. It is expected to have low mobility in soil. Volatilization from water and moist soils is low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. It is expected to have high persistence (P3) and low bioaccumulation potential (B1).</p> <p>Acute toxicity is low for CASRN 35074-77-2 in mice, rabbits and rats when administered via oral, dermal or inhalation routes, respectively. Oral repeated-dose studies in rats revealed an increased incidence of thyroid hyperplasia at 50 mg/kg-bw/day and fatty infiltration of the liver at 100 mg/kg-bw/day; increased liver weight occurred at 100mg/kg-bw/day. Increased liver weight was also observed in dogs following repeated oral exposure at 250 mg/kg-bw/day. The NOAEL for systemic toxicity was 20 mg/kg-bw/day in rats and 75 mg/kg-bw/day in dogs. A reproductive toxicity study was not available; however, no effects on male or female reproductive organs were observed in the repeated-dose toxicity studies. A prenatal developmental toxicity study in rats showed reduced body weight gain in dams treated at 750 mg/kg-bw/day; fetal examination on gestation day 21 revealed incomplete ossification of phalangeal nuclei at 2000 mg/kg-bw/day. The NOAEL values for maternal and developmental toxicity were 150 and 750 mg/kg-bw/day, respectively. No reliable genetic toxicity data were available; however, a two-year chronic toxicity study showed no evidence of tumors following dietary exposure in rats.</p> <p>The available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates the 96-hour LC<sub>50</sub> for fish is &gt;100 mg/L. The 48-hour EC<sub>50</sub> for aquatic invertebrates is &gt; 100 mg/L and the 96-hour EC<sub>50</sub> for aquatic plants is &gt;100 mg/L. CASRN 35074-77-2 was tested above its water solubility limit.</p> <p>Gene mutation and chromosomal aberrations were identified as data gaps under the HPV Challenge Program; however, a two-year carcinogenicity study showed no evidence of tumors in rats. Therefore, these endpoints do not represent data needs at this time.</p>	

The sponsor, Ciba Specialty Chemicals Corporation, submitted a Test Plan and Robust Summaries to EPA for 1,6-hexamethylene bis (3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate) (IRGANOX 259; CASRN 35074-77-2) dated July 29, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on August 22, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/16hexhyd/c13896tc.htm>). EPA comments on the original submission were posted to the website on December 20, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 26, 2003, which were posted to the ChemRTK website on October 23, 2003.

## 1. Chemical Identity

### 1.1 Identification and Purity

The sponsor's Test Plans indicated > 98% purity for CASRN 35074-77-2.

### 1.2 Physical-Chemical Properties

The physical-chemical properties are summarized in Table 1. CASRN 35074-77-2 is a white powder with negligible water solubility and vapor pressure.

<b>Table 1. Physical-Chemical Properties of 1,6-Hexamethylene bis (3,5-di-(<i>tert</i>)-butyl-4-hydroxyhydrocinnamate)<sup>1</sup></b>	
<b>Property</b>	<b>Value</b>
CASRN	35074-77-2
Molecular Weight	639
Physical State	White to off-white crystalline powder
Melting Point	104–108°C (measured)
Boiling Point	654.41°C (estimated)
Vapor Pressure	$2.23 \times 10^{-15}$ mm Hg at 25°C (estimated) <sup>3</sup>
Water Solubility	$2.83 \times 10^{-7}$ mg/L at 25°C (estimated) <sup>3</sup>
Dissociation Constant (pK <sub>a</sub> )	11.76 (estimated) <sup>2</sup>
Henry's Law Constant	$7.05 \times 10^{-17}$ atm·m <sup>3</sup> /mole (estimated)
Log K <sub>ow</sub>	>11.74 (estimated)

<sup>1</sup>Ciba Specialty Chemicals Corporation. October 23, 2003. Revised Test Plan and Robust Summary for 1,6-Hexamethylene bis (3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate) (Irganox 259). <http://www.epa.gov/chemrtk/pubs/summaries/16hexhyd/c13896tc.htm>.

<sup>2</sup>SPARC. 2008. Online pKa and Property Calculator v. 4.2.1405-s4.2.1408. Accessed September 7, 2008. <http://ibmlc2.chem.uga.edu/sparc/>.

<sup>3</sup>EPI Estimation Program, Syracuse Research Corporation; MPBPWIN v. 1.41 (used measured MP of 104 °C for estimation)

## 2. General Information on Exposure

### 2.1 Production Volume and Use Pattern

CASRN 35074-77-2, previously an HPV chemical, had an aggregated production volume in the United States of less than 500,000 pounds during the 2005 calendar year.

All industrial processing and use information reported to the IUR was claimed confidential. The HPV submission for this chemical states that it is a sterically hindered phenolic antioxidant primarily used as a stabilizer for organic substrates such as plastics, synthetic fibers, and elastomers. This chemical has been cleared by the FDA for use in polymers, resins or adhesives intended for food contact applications and in lubricants with incidental food contact.

## 2.2 Environmental Exposure and Fate

No quantitative information is available on releases of this chemical to the environment.

The environmental fate properties are provided in Table 2. CASRN 35074-77-2 is expected to have low mobility in soil. Volatilization from water and moist soils is low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. It is expected to have high persistence (P3) and low bioaccumulation potential (B1).

<b>Table 2. Environmental Fate Characteristics of 1,6-Hexamethylene bis (3,5-di-(<i>tert</i>)-butyl-4-hydroxyhydrocinnamate)<sup>1</sup></b>	
<b>Property</b>	<b>Value</b>
Photodegradation Half-life	2.73 hours (estimated)
Hydrolysis Half-life	59 days at pH 8 (estimated); 1.6 years at pH 7 (estimated)
Biodegradation	1% in 28 days (not readily biodegradable)
Bioconcentration	BCF = 3.1 (estimated) <sup>2</sup>
Log K <sub>oc</sub>	11 (estimated)
Fugacity (Level III Model)	Air = 0.0118% Water = 1.1% Soil = 41.0% Sediment = 57.9%
Persistence <sup>3</sup>	P3 (high)
Bioaccumulation <sup>3</sup>	B1 (low)

<sup>1</sup>Ciba Specialty Chemicals Corporation. October 23, 2003. Revised Test Plan and Robust Summary for of IRGANOX 259 (1,6-Hexamethylene bis (3,5-di-(*tert*)-butyl-4-hydroxyhydrocinnamate).

<http://www.epa.gov/chemrtk/pubs/summaries/16hexhyd/c13896tc.htm>.

<sup>2</sup>US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA.

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

<sup>3</sup>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 toxicity data are summarized in Table 3.

#### *Acute Oral Toxicity*

Tif:MAG (SPF) mice (5/sex/dose) were administered CASRN 35074-77-2 via oral gavage at 0, 4640, 6000 or 7750 mg/kg-bw and observed for 14 days. There were no mortalities.

**LD<sub>50</sub> > 7750 mg/kg-bw**

#### *Acute Inhalation Toxicity*

Tif:RA1 rats (9/sex) were administered CASRN 35074-77-2 via inhalation (20% suspension in ethanol) at 1688 mg/m<sup>3</sup> (~1.69 mg/L) for 4 hours. Animals were observed for 7 days. There were no mortalities.

**LC<sub>50</sub> > 1.69 mg/L**

#### *Acute Dermal Toxicity*

New Zealand White rabbits (4/sex/dose) were administered CASRN 35074-77-2 via the dermal route (50% suspension in NaCl solution) at 0, 2500 or 10,000 mg/kg-bw for 24 hours using intact or abraded skin. Animals were observed for 14 days then tissues were examined microscopically. Specific results were not reported.

**LD<sub>50</sub> > 10,000 mg/kg-bw**

#### *Repeated-Dose Toxicity*

(1) Sprague-Dawley rats (15/sex/dose) were administered CASRN 35074-77-2 via their diet at 0, 1000, 3000 or 10,000 ppm (~ 0, 50, 150 or 500 mg/kg-bw/day) for 13 weeks. There were no mortalities. Hyperplasia and hypertrophy of the thyroid follicular epithelium were observed at all doses, exhibiting increased incidence and severity with increasing dose.

**LOAEL = 50 mg/kg-bw/day** (based on increased incidence of focal hypertrophy of thyroid follicular epithelium).

**NOAEL = Not established**

(2) Sprague-Dawley rats (sex, group size not specified) were administered CASRN 35074-77-2 via the diet at 0, 2000, 10,000 or 30,000 ppm (~ 0, 100, 500 or 1500 mg/kg-bw/day) via the diet for 13 weeks. There were no mortalities. Dose-related increases in thyroid and liver hypertrophy were observed in all treatment groups. Decreased body weight was observed at the two higher doses and fatty infiltration of the liver was observed at the highest dose.

**LOAEL = 100 mg/kg-bw/day** (based liver and thyroid hypertrophy)

**NOAEL = Not established**

(3) SPF Wistar rats (10/sex/dose) were administered CASRN 35074-77-2 via the diet at 0, 400, 2000, 10,000 or 30,000 ppm (~ 0, 20, 100, 500 or 1500 mg/kg-bw/day) for 13 weeks. There were no mortalities. Increased body weight was observed in males treated at the two lowest

doses. Increases in liver and thyroid weights were observed in both sexes. Increased liver weight was observed at the highest dose and increased thyroid weight was observed at the two highest doses. Thyroid epithelial hyperplasia was also noted at or above 100 mg/kg-bw/day (sex not specified). No other details were provided in the robust summary.

**LOAEL = 100 mg/kg-bw/day** (based on thyroid epithelial hyperplasia)

**NOAEL = 20 mg/kg-bw/day**

(4) Beagle dogs (4/sex/dose) were administered CASRN 35074-77-2 via the diet at 0, 500, 1500 or 5000 ppm (~ 0, 25, 75 and 250 mg/kg-bw/day) for 13 weeks. There were no mortalities.

Minimal congestion of the intestinal mucosa was observed at all doses. Bile duct hyperplasia and associated inflammation was evident in animals (sex not specified) treated at the two higher doses. Increased liver weight was also observed at the highest dose (sex not specified).

**LOAEL = 250 mg/kg-bw/day** (based on bile duct hyperplasia and increased liver weight)

**NOAEL = 75 mg/kg-bw/day**

### ***Reproductive Toxicity***

A reproductive toxicity test was not submitted; however, an evaluation of reproductive organs from the 90-day repeated-dose toxicity studies and the availability of a developmental toxicity study address the reproductive toxicity endpoint for the purposes of the HPV Challenge Program.

In the 90-day repeated-dose toxicity studies described previously, no macroscopic or microscopic effects on reproductive organs were observed at any of the doses tested.

### ***Developmental Toxicity***

Pregnant Sprague-Dawley female rats (25/dose group) were administered CASRN 35074-77-2 via gavage at 0, 150, 750 or 2000 mg/kg-bw/day on days 6 – 15 of gestation. Reduced food consumption was observed at all levels of treatment and decreased body weight gain was apparent in dams treated at the two highest doses. Fetal examinations on gestation day 21 revealed treatment-related increases in the number of incompletely ossified phalangeal nuclei at the highest dose.

**LOAEL (maternal toxicity) = 750 mg/kg-bw/day** (based on reduced body weight in dams)

**NOAEL (maternal toxicity) = 150 mg/kg-bw/day**

**LOAEL (developmental toxicity) = 2000 mg/kg-bw/day** (based on incomplete ossification of phalangeal nuclei)

**NOAEL (developmental toxicity) = 750 mg/kg-bw/day**

### ***Genetic Toxicity – Gene Mutation***

No adequate data were submitted for this endpoint.

### ***Genetic Toxicity – Chromosomal Aberrations***

No adequate data were submitted for this endpoint.

### *Additional Information*

#### *Chronic Toxicity/Carcinogenicity*

Sprague Dawley rats (60/sex/dose) were administered CASRN 35074-77-2 via the diet at 0, 50, 150 or 450 ppm (~ 0, 2.5, 7.5 or 22.5 mg/kg-bw/day) for 104 weeks. Reduced food consumption was observed in females treated at the highest dose. Tumors (mammary, pituitary and subcutaneous) and renal disease were the most common cause of death, but none were considered treatment related (sex not specified).

**CASRN 35074-77-2 did not induce treatment related toxicity or tumorigenicity in the 2-year chronic dietary toxicity study described above.**

**Conclusion:** Acute toxicity is low for CASRN 35074-77-2 in mice, rabbits and rats when administered via oral, dermal or inhalation routes, respectively. Oral repeated-dose studies in rats revealed an increased incidence of thyroid hyperplasia at 50 mg/kg-bw/day and fatty infiltration of the liver at 100 mg/kg-bw/day; increased liver weight occurred at 100mg/kg-bw/day. Increased liver weight was also observed in dogs following repeated oral exposure at 250 mg/kg-bw/day. The NOAEL for systemic toxicity was 20 mg/kg-bw/day in rats and 75 mg/kg-bw/day in dogs. A reproductive toxicity study was not available; however, no effects on male or female reproductive organs were observed in the repeated-dose toxicity studies. A prenatal developmental toxicity study in rats showed reduced body weight gain in dams treated at 750 mg/kg-bw/day; fetal examination on gestation day 21 revealed incomplete ossification of phalangeal nuclei at 2000 mg/kg-bw/day. The NOAEL values for maternal and developmental toxicity were 150 and 750 mg/kg-bw/day, respectively. No reliable genetic toxicity data were available; however, a two-year chronic toxicity study showed no evidence of tumors following dietary exposure in rats.

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

The environmental hazard data are summarized in Table 3.

##### *Acute Toxicity to Fish*

Zebrafish (*Brachydanio rerio*) were exposed to CASRN 35074-77-2 at a nominal concentration of 100 mg/L under static conditions for 96 hours. There were no mortalities. The substance was tested above its water solubility limit. EPA considers the no effect concentration as the water solubility limit (saturation) which for CASRN 35074-77-2 would be  $\sim 2.83 \times 10^{-7}$  mg/L.

**No effects at saturation**

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

Water fleas (*Daphnia magna*) were exposed to CASRN 35074-77-2 at nominal concentrations of 0, 10, 18, 32, 58 or 100 mg/L under static conditions for 24 hours. There were no mortalities and no immobilization was seen at any concentration. The substance was tested above its water solubility limit. EPA considers the no effect concentration as the water solubility limit (saturation) which for CASRN 35074-77-2 would be  $\sim 2.83 \times 10^{-7}$  mg/L.

**No effects at saturation**

*Toxicity to Aquatic Plants*

Green algae (*Scenedesmus subspicatus*) were exposed to CASRN 35074-77-2 at nominal concentrations of 0, 1.23, 3.7, 11, 33 or 100 mg/L under static conditions for 72 hours. Cell densities were not provided at each test concentration. Based on limited information provided in the study summary, cell density appears to have been the only endpoint measured. The substance was tested above its water solubility limit. EPA considers the no effect concentration as the water solubility limit (saturation) for CASRN 35074-77-2 ( $\sim 2.83 \times 10^{-7}$  mg/L).

**No effects at saturation**

**Conclusion:** The available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates the 96-hour LC<sub>50</sub> for fish is >100 mg/L. The 48-hour EC<sub>50</sub> for aquatic invertebrates is > 100 mg/L and the 96-hour EC<sub>50</sub> for aquatic plants is >100 mg/L. CASRN 35074-77-2 was tested above its water solubility limit.

<b>Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program</b>	
<b>Endpoints</b>	<b>SPONSORED CHEMICAL IRGANOX 259 (CASRN 35074-77-2)</b>
<b>Summary of Human Health Data</b>	
<b>Structural Formula</b>	
<b>Acute Oral Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>&gt; 7750</b>
<b>Acute Inhalation Toxicity LC<sub>50</sub> (mg/L)</b>	<b>&gt; 1.69</b>
<b>Acute Dermal Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>&gt; 10,000</b>
<b>Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)</b>	<b>NOAEL = 20 LOAEL = 50</b>

<b>Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program</b>	
<b>Endpoints</b>	<b>SPONSORED CHEMICAL IRGANOX 259 (CASRN 35074-77-2)</b>
<b>Reproductive Toxicity</b>	No data No effects were seen in evaluation of reproductive organs from 13-week repeated-dose toxicity studies in rats and dogs.
<b>Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)</b>	
<b>Maternal Toxicity</b>	<b>NOAEL = 150 LOAEL = 750</b>
<b>Developmental Toxicity</b>	<b>NOAEL = 750 LOAEL = 2000</b>
<b>Genetic Toxicity – Gene Mutation</b>	Data Gap
<b>Genetic Toxicity – Chromosomal Aberrations</b>	Data Gap
<b>Additional Information Carcinogenicity</b>	<b>No increase in tumorigenicity in a chronic oral toxicity study</b>
<b>Summary of Environmental Effects – Aquatic Toxicity Data</b>	
<b>Fish 96-h LC<sub>50</sub> (mg/L)</b>	<b>No effects at saturation</b>
<b>Aquatic Invertebrates 48-h EC<sub>50</sub> (mg/L)</b>	<b>No effects at saturation</b>
<b>Aquatic Plants 72-h EC<sub>50</sub> (mg/L)</b>	<b>No effects at saturation</b>