# SCREENING-LEVEL HAZARD CHARACTERIZATION

## Thiobis Propanoic Acid Derivatives Category

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| **3,3'-Thiodipropionic acid didodecyl ester (DLTDP)** | **CASRN 123-28-4** |
| **3,3'-Thiodipropionic acid ditridecyl ester (DTTDP)** | **CASRN 10595-72-9** |
| **3,3'-Thiodipropionic acid dioctadecyl ester (DSTDP)** | **CASRN 693-36-7** |

The High Production Volume (HPV) Challenge Program[1] 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

[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.

Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

| | |
|---|---|
| **Chemical Abstract Service Registry Number (CASRN)** | **123-28-4**<br>**10595-72-9**<br>**693-36-7** |
| **Chemical Abstract Index Name** | **Propanoic acid, 3,3'-thiobis-, didodecyl ester**<br>**Propanoic acid, 3,3'-thiobis-, ditridecyl ester**<br>**Propanoic acid, 3,3'-thiobis-, dioctadecyl ester** |
| **Structural Formula** | **See Table 1** |

**Summary**

The thiobis propanoic acid derivatives category is composed of high-molecular weight dithiopropionate esters that differ only in the chain length (C12-C18) of the dialkyl ester functions. The category contains two solids and one liquid substance. The category members possess low vapor pressure and negligible water solubility. The thiobis propanoic acid derivatives are expected to have low mobility in soil. Volatilization is considered moderate based on the estimated Henry's Law constants. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate to high. The substances in the thiobis propanoic acid derivatives category are expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute oral toxicity of CASRN 123-28-4 in rats and mice is low. The acute oral toxicity of CASRNs 10595-72-9 and 693-36-7 in rats is low. The acute inhalation of CASRN 10595-72-9 in rats is low. In a 90-day oral repeated-dose toxicity study in rats, CASRN 123-28-4 showed possible heart effects at 1000 mg/kg-day; the NOAEL for systemic toxicity is 350 mg/kg-day. In a two-year dietary toxicity study in rats with CASRN 693-36-7, there were no effects observed on any parameters measured at doses up to ~1125 mg/kg-bw/day, the highest dose tested. No reproductive toxicity studies are available; however, the 90-day oral repeated-dose toxicity study with CASRN 123-28-4 showed no adverse treatment-related effects on reproductive organs. In four oral prenatal developmental toxicity studies with CASRN 123-28-4, there were no maternal or developmental effects observed at the highest doses tested (1600 mg/kg-day in rats, mice and hamsters; and 1000 mg/kg-day in rabbits). CASRNs 123-28-4 and 693-36-7 did not induce chromosomal aberrations in *in vitro* tests (human lung cell and Chinese hamster cells). CASRN 123-28-4 did not induce chromosomal effects in male rats *in vivo*. In a dominant lethal assay, CASRN 123-28-4 did not induce genetic mutations in rats *in vivo*. In a host mediated assay, CASRN 123-28-4 induced genetic mutations in mice *in vivo*. CASRN 123-28-4 is irritating to the rabbit eye. CASRN 10595-72-9 is irritating to the rabbit skin but not the rabbit eye. CASRN 693-36-7 was not irritating to the rabbit skin and eye.

The potential acute and chronic hazards of these chemicals to fish, aquatic invertebrates and

aquatic plants are considered to be “no effects at saturation” based on low water solubility and high estimated log $K_{ow}$ values for category members.

No data gaps were identified under the HPV Challenge Program.

The sponsor, The Thioesters Association, submitted a Test Plan and Robust Summaries to EPA for thiobis propanoic acid derivatives dated December, 14, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January, 15, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/thiobpad/c13379tc.htm). EPA comments on the original submission were posted to the website on October 9, 2002. There were no public comments posted on the HPV Challenge website for this submission. The sponsor submitted updated/revised documents on February, 11, 2003, which were posted to the ChemRTK website on February, 24, 2003.

## Category Justification

The sponsor's primary justification for the category is based on the expectation that close structural similarities between category members should result in properties that are either similar or follow a pattern that correlates with changes in the molecular weights of the category members. Based on structures and molecular weights of category members, as well as data provided by the sponsor, which demonstrate that the category members generally exhibit mammalian toxicities that are similar (e.g., acute oral $LD_{50}$ values, acute irritation thresholds, genotoxicity) or follow a pattern that parallels changes in molecular weight (e.g., repeated-dose results), predictive methods and extrapolation and interpolation of data among category members is considered appropriate. Generally, the strategy to be used to predict aquatic toxicity and mammalian toxicity endpoints among category members for which test results were not provided by the sponsor is read-across from the category member exhibiting the highest degree of toxicity (i.e., lowest appropriate toxicity value for a given endpoint).

## 1. Chemical Identity

### 1.1 Identification and Purity

The following description is taken from the information presented in the original Test Plan (2001) and in the revised robust summaries (2003):

The category consists of three thiobis, propanoic acid di-esters as designated above. The molecular structure of all three category members is essentially the same. The general structure for the category is defined as "3,3'-thiodipropionates." This describes a molecule with a propanoic ester backbone, in which the functional side chains are extended with aliphatic groups in place of a hydrogen atom. The only structural difference in the three substances is the length of the aliphatic chains. The different aliphatic groups are dodecyl-, iso-tridecyl and octadecyl. CASRN 123-28 is an organic solid with a purity greater than 97% w/w; CASRN 10595-72-9 4 is an organic liquid with a purity of 99% w/w and CASRN 693-36-7 is an organic solid with a purity that is greater than or equal to 98% w/w. The generic molecular structures of all category members are shown in Table 1.

Throughout this document the following acronyms will be used for the sponsored chemicals in this category:

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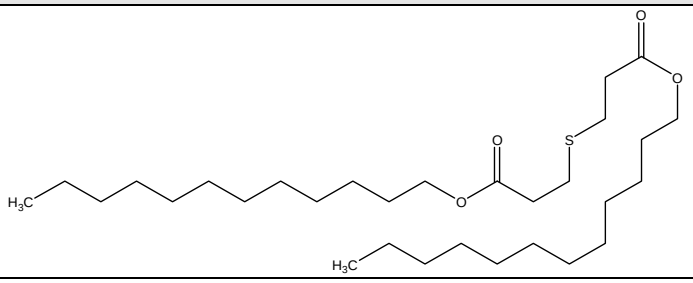
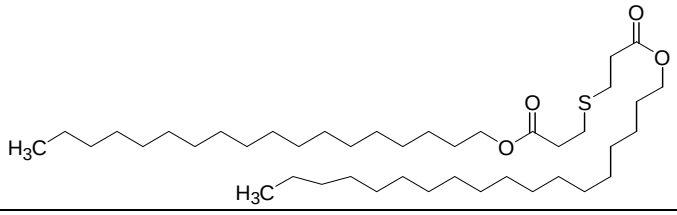
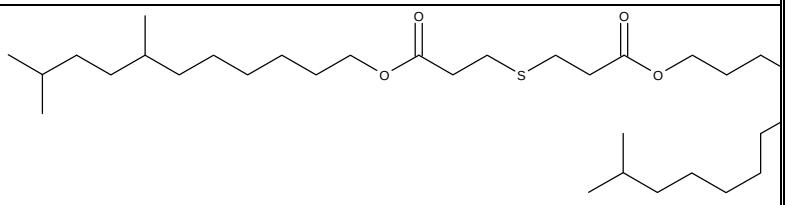
|---|---|
| **3,3'-Thiodipropionic acid didodecyl ester** | **CASRN 123-28-4 (DLTDP)** |
| **3,3'-Thiodipropionic acid ditridecyl ester** | **CASRN 10595-72-9 (DTTDP)** |
| **3,3'-Thiodipropionic acid dioctadecyl ester** | **CASRN 693-36-7 (DSTDP)** |

## 1.2 Physical-Chemical Properties

The thiobis propanoic acid derivatives category is composed of high-molecular weight dithiopropionate esters that differ only in the chain length (C12-C18) of the dialkyl ester functions. The category contains two solids and one liquid substance. The category members possess low vapor pressure and negligible water solubility. The chemical name for CASRN 10595-72-9 (propanoic acid, 3,3'-thiobis-, 1,1'-ditridecyl ester) implies a linear structure; however, the Test Plan states that the C13 chain is made from an alcohol feedstock that contains various *n*-primary branched alcohol isomers. The structure shown for 10595-72-9 is representative. It reflects the fact that iso-tridecyl alcohol, used to manufacture 10595-72-9 may contain more than one methyl branch.

The chemical structures of these category members are provided in Table 1. The physical-chemical properties of thiobis propanoic acid derivatives are summarized in Table 2.

**Table 1. Thiobis Propanoic Acid Derivatives Category: Chemical Structures**

| Chemical Name | CASRN | Structure[1] |
|---|---|---|
| Propanoic acid, 3,3'-thiobis-, 1,1'-didodecyl ester **(DLTDP)** | 123-28-4 |  |
| Propanoic acid, 3,3'-thiobis-, 1,1'-dioctadecyl ester **(DSTDP)** | 693-36-7 |  |
| Propanoic acid, 3,3'-thiobis-, 1,1'-ditridecyl ester **(DTTDP)** | 10595-72-9 |  |

[1] The chemical name for CASRN 10595-72-9 (propanoic acid, 3,3'-thiobis-, 1,1'-ditridecyl ester) implies a linear structure; however, the Test Plan states that the C13 chain is made from an alcohol feedstock that contains various *n*-primary branched alcohol isomers. The structure shown for 10595-72-9 is representative. It reflects the fact that iso-tridecyl alcohol, used to manufacture 10595-72-9, may contain more than one methyl branch.

| Table 2. Physical-Chemical Properties of the Thiobis Propanoic Acid Derivatives[1] | | | |
|---|---|---|---|
| **Property** | **DLTDP** | **DSTDP** | **DTTDP** |
| CASRN | 123-28-4 | 693-36-7 | 10595-72-9 |
| Molecular Weight | 514.85 | 683.16 | 542.90 |
| Physical State | Solid | Solid | Liquid |
| Melting Point | 40°C (measured) | 64–67°C (measured) | <25°C (measured) |
| Boiling Point | 300°C (decomposition) | 300°C (decomposition) | 226°C (decomposition) |
| Vapor Pressure | 0.2 mm Hg at 163°C (measured); 3.3 mm Hg at 230°C (measured); $2.1\times10^{-6}$ mm Hg at 25°C (estimated)[2] | $4.95\times10^{-8}$ mm Hg at 20°C (measured) | $2.7\times10^{-8}$ mm Hg at 25°C (estimated)[3] |
| Water Solubility | $2.2\times10^{-7}$ mg/L at 25°C (estimated)[3] | <1 mg/L at 20°C (measured); $1.1\times10^{-13}$ (estimated)[3] | $7.7\times10^{-8}$ mg/L at 25°C (estimated)[3] |
| Dissociation Constant ($pK_a$) | Not applicable | Not applicable | Not applicable |
| Henry's Law Constant | $5.7\times10^{-7}$ atm-$m^3$/mole (estimated)[3] | $3.6\times10^{-5}$ atm-$m^3$/mole (estimated)[3] | $3.5\times10^{-6}$ atm-$m^3$/mole (estimated)[3] |
| Log $K_{ow}$ | 11.8 (estimated)[3] | 17.7 (estimated)[3] | 12.3 (estimated)[3] |

[1] Thioesters Association. February 03, 2003. Test Plan and Robust Summary for Thiobis Propanoic Acid Derivatives. Available online from: http://www.epa.gov/chemrtk/pubs/summaries/thiobpad/c13379tc.htm as of May 6, 2010.
[2] NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.
[3] 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/episuitedl.htm as of May 8, 2010.

## 2. General Information on Exposure

### 2.1 Production Volume and Use Pattern

According to the 2006 IUR submissions, the thiodiproprionates category chemicals had an aggregated production and/or import volume in the United States between 3 million pounds and 30 million pounds.

- CASRN 123-28-4: 1 to <10 million pounds;
- CASRN 693-36-7: 1 to <10 million pounds; and
- CASRN 10595-72-9: 1 to <10 million pounds.

CASRN 123-28-4:
Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other plastics product manufacturing as stabilizers; all other chemical product and preparation manufacturing as "other"; plastics packaging materials and unlaminated film and sheet manufacturing as stabilizers; and not readily obtainable (NRO). Non-confidential commercial and consumer uses of this chemical include rubber and plastic products; and not readily obtainable (NRO).

CASRN 693-36-7:
Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other plastics product manufacturing as stabilizers; and all other chemical product and preparation manufacturing as "other". Non-confidential commercial and consumer uses of this chemical include rubber and plastic products.

CASRN 10595-72-9:
Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include plastics packaging materials and unlaminated film and sheet 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 of thiobis propanoic acid derivatives are summarized in Table 3.

The thiobis propanoic acid derivatives are expected to have a low mobility in soil. Propanoic acid, 3,3'-thiobis-, 1,1'-didodecyl ester and propanoic acid, 3,3'-thiobis-, 1,1'-dioctadecyl ester were not readily biodegradable in modified Sturm tests (OECD 301B); however, both substances were readily biodegradable using a modified MITI test (OECD 301C). Propanoic acid, 3,3'-thiobis-, 1,1'-didodecyl ester achieved 82% of its theoretical biochemical oxygen demand (BOD) over the course of a 28-day incubation period and propanoic acid, 3,3'-thiobis-, 1,1'-dioctadecyl ester achieved 51% of its theoretical BOD in 14 days. Volatilization is considered moderate based on the estimated Henry's Law constants. The rate of hydrolysis is considered negligible for each category member. The three substances in the thiobis propanoic acid derivatives category are expected to have low persistence (P1) and low bioaccumulation potential (B1).

| Table 3. Environmental Fate Characteristics of the Thiobis Propanoic Acid Derivatives[1] | | | |
|---|---|---|---|
| **Property** | **DLTDP** | **DSTDP** | **DTTDP** |
| CASRN | 123-28-4 | 693-36-7 | 10595-72-9 |
| Photodegradation Half-life | 2.5 hours (estimated) | 1.9 hours (estimated) | 2.3 hours (estimated) |
| Hydrolysis Half-life | 104 days at pH 8 (estimated)[2]; 2.8 years at pH 7 (estimated)[2] | 104 days at pH 8 (estimated)[2]; 2.8 years at pH 7 (estimated)[2] | 72 days at pH 8 (estimated)[2]; 2.0 years at pH 7 (estimated)[2] |
| Biodegradation | 57% after 28 days (not readily biodegradable); 82% after 28 days (readily biodegradable)[3] | 15% after 28 days (not readily biodegradable); 0% after 28 days (not readily biodegradable); 60% after 28 days (inherently biodegradable); 51% after 14 days (readily biodegradable)[3] | No data 57% after 28 days (not readily biodegradable); 82% after 28 days (readily biodegradable)[3] (RA) |
| Bioaccumulation Factor | BAF = 1.0 (estimated)[2] | BAF = 0.9 (estimated)[2] | BAF = 1.0 (estimated)[2] |
| Log $K_{oc}$ | 7.0 (estimated)[2] | 10.1 (estimated)[2] | 7.2 (estimated)[2] |
| Fugacity (Level III Model)[2] | | | |
| Air (%) | 0.4 | 0.1 | 0.1 |
| Water (%) | 22.4 | 16.4 | 16.2 |
| Soil (%) | 77.0 | 83.4 | 83.5 |
| Sediment (%) | 0.2 | <0.1 | 0.1 |
| Persistence[4] | P1 (low) | P1 (low) | P1 (low) |
| Bioaccumulation[4] | B1 (low) | B1 (low) | B1 (low) |

[1] Thioesters Association. February 03, 2003. Test Plan and Robust Summary for Thiobis Propanoic Acid Derivatives. Available online from: http://www.epa.gov/chemrtk/pubs/summaries/thiobpad/c13379tc.htm as of May 6, 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/episuitedl.htm as of May 8, 2010.
[3] National 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 May 5, 2010.
[4] 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

A summary of health effects data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

### *Acute Oral Toxicity*

***DLTDP (CASRN 123-28-4)***

(1) Rats (5 at 2000 mg/kg/day and 10 at 2500 mg/kg/day; strain and sex unspecified) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage in olive oil and observed for 7 days following dosing. No mortalities were observed.
**$LD_{50}$ > 2500 mg/kg**

(2) Male rats (10 at 50 and 500 mg/kg/day, 12 at 5000 mg/kg/day; strain unspecified) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage in physiological saline and observed for 5 days. Animals were necropsied on day 6 following dosing. No mortalities were observed.
**$LD_{50}$ > 5000 mg/kg**

(3) Mice (19, 10, 20 and 20/dose at 300, 500, 1000 and 2000 mg/kg/day respectively; strain and sex unspecified) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage in olive oil and observed for 1 week following dosing. Mortalities were observed in 4/19 mice at 300 mg/kg/day and 1/20 mice at 2000 mg/kg/day.
**$LD_{50}$ > 2000 mg/kg**

***DTTDP (CASRN 10595-72-9)***

Female rats (4/dose, strain unspecified) were administered 3,3'-thiodipropionic acid ditridecyl ester via oral gavage in corn oil at doses of 500, 1000 and 2000 mg/kg/day and observed for 14 days following dosing. No mortalities were observed.
**$LD_{50}$ > 2000 mg/kg**

***DSTDP (CASRN 693-36-7)***

(1) Male rats (3/dose; strain unspecified) were administered 3,3'-thiodipropionic acid dioctadecyl ester via oral gavage in a 10% corn oil solution, at doses of 126, 252, 500, 1000 or 2000 mg/kg/day and observed for 14 days following dosing. One animal from each dose was sacrificed for necropsy 24 hours after dosing. The two remaining animals at each dose was sacrificed after the 14 day observation period.
**$LD_{50}$ > 2000 mg/kg**

(2) Rats (5 at 2000 and 12 at 2500 mg/kg/day; strain and sex unspecified) were administered 3,3'-thiodipropionic acid dioctadecyl ester via oral gavage in olive oil and observed for 1 week following dosing. One rat was reported dead on day 2 after receiving 2500 mg/kg/day of the test material. All other animals survived to the end of the study.
**$LD_{50}$ > 2500 mg/kg**

(3) Mice (10/dose; strain and sex unspecified) were administered 3,3'-thiodipropionic acid dioctadecyl ester dissolved in olive oil via oral gavage at 300 and 500 mg/kg/day. Two additional groups of 18 and 20 mice received 2000 mg/kg/dose. Mortalities were observed at 300 (1/10); 2000 (1/18) and 2000 mg/kg/day (4/20).
**$LD_{50}$ > 2000 mg/kg**

***Acute Inhalation Toxicity***

***DTTDP (CASRN 10595-72-9)***
Female rats (4/dose; strain unspecified) were exposed to 3,3'-thiodipropionic acid ditridecyl ester via inhalation at a nominal concentration of 0.19 mg/L for 7 hours and observed on days 1, 8 and 15 following dosing. No mortalities were observed.
**$LC_{50}$ > 0.19 mg/L**

***Repeated-Dose Toxicity***

***DLTDP (CASRN 123-28-4)***
Sprague-Dawley rats (10/sex/dose) were administered 3,3'-thiodipropionic acid didodecyl ester (in 1% aqueous carboxymethyl cellulose) via oral gavage at 0, 125, 350 or 1000 mg/kg-day for 13-weeks. An additional group of 5 rats/sex were given 0 or 1000 mg/kg-day for 13-weeks and observed for 4 weeks following cessation of treatment. Parameters evaluated included morbidity and mortality, body weights and food consumption, ophthalmoscopy, hematology, urinalysis, clinical chemistry, organ weights, and histopathology of liver, kidneys, lungs, and heart. Increases in serum cholesterol and alanine aminotransferase and aspartate aminotransferase activities were reported in females at 1000 mg/kg-day (statistical significance not provided). These increases were reversible after 4 weeks without treatment. A slight decrease in urinary pH was reported in both sexes at 1000 mg/kg-day. Minor differences in weight changes of the major organs, including the liver and kidney, were considered by the study authors as of no toxicological significance because they occurred in the absence of any microscopic lesions. Microscopic examinations of the heart in both sexes at 1000 mg/kg-day were suggestive of early myocarditis (small foci of degenerative or necrotic fibers associated with minimal to moderate mononuclear cell infiltration). This effect was reversible after 4 weeks without treatment. No deaths and no other effects were reported.
**LOAEL (systemic toxicity) = 1000 mg/kg-day** (based on possible heart effects)
**NOAEL (systemic toxicity) = 350 mg/kg-day**

***DSTDP (CASRN 693-36-7)***
Rats (20 males/dose) were administered 3,3'-thiodipropionic acid didodecyl ester via the diet at 0, 0.5, 1 or 3% (~ 0, 188, 375 or 1125 mg/kg-bw/day) for 2 years. Parameters evaluated included morbidity and mortality, body weights and food consumption, as well as gross pathologic examinations of rats that died during the study. There were no significant dose-related effects on mortality, food consumption body weight gain or gross pathology.
**NOAEL (systemic toxicity) ~ 1125 mg/kg-bw/day** (based on no adverse effects observed at the highest dose tested)

***Reproductive Toxicity***

There are no standard reproductive toxicity studies available for any category member.

***DLTDP (CASRN 123-28-4)***
In the 13-week oral repeated-dose toxicity study described previously, histopathology was performed on reproductive organs of both sexes in the highest dose group (1000 mg/kg-day) and controls. Reproductive organs examined included the epididymides, mammary glands, ovaries, prostate, seminal vesicles, testes and uterus (horn and cervix). No macroscopic or microscopic effects were observed.

***Developmental Toxicity***

***DLTDP (CASRN 123-28-4)***
(1) Pregnant Wistar rats (19 – 21/dose) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage in corn oil at doses of 0, 16, 74, 350 and 1600 mg/kg-day on gestation days 6 to 15. Dams were assessed for clinical signs, food consumption and body weight. On gestation day 20, caesarian sections were performed and the numbers of implantations, resorption sites, and live and dead fetuses were recorded. Fetuses were examined for gross external abnormalities and all live fetuses were weighed. One-third of the fetuses from each litter were subjected to visceral examinations; the remaining two-thirds of the fetuses were examined for skeletal abnormalities. No treatment-related effects were reported in the dams or on the numbers of implantations, incidences of visceral or skeletal abnormalities, or fetal survival rates at doses up to 1600 mg/kg/day.
**NOAEL (maternal/developmental toxicity) = 1600 mg/kg-day** (based on no adverse effects observed at the highest dose tested)

(2) Pregnant CD-1 mice (20 – 22/dose) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage in corn oil at doses of 0, 16, 74, 350 and 1600 mg/kg-day on gestation days 6 to 15. Pregnant mice were assessed for clinical signs, food consumption and body weight. On gestation day 17, caesarian sections were performed and the numbers of implantations, resorption sites, and live and dead fetuses were recorded. Fetuses were examined for gross external abnormalities and all live fetuses were weighed. One-third of the fetuses from each litter were subjected to visceral examinations; the remaining two-thirds of the fetuses were examined for skeletal abnormalities. No maternal toxic effects or differences in the numbers of implantations, incidences of visceral or skeletal abnormalities, or fetal survival rates were reported at any dose.
**NOAEL (maternal/developmental toxicity) = 1600 mg/kg-day** (based on no adverse effects observed at the highest dose tested)

(3) Pregnant Dutch rabbits (8-13/dose) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage in corn oil at doses of 0, 2.5, 10, 45, 216 and 1000 mg/kg-day on gestation days 6 to 18. On gestation day 29, caesarian sections were performed and the numbers of corpora lutea, implantations, resorption sites, live and dead fetuses, and fetal body weight were recorded. Each live fetus was grossly examined and incubated for 24 hours to assess neonatal survival. All surviving pups were sacrificed, and examined for visceral abnormalities by

dissection. No maternal toxic effects or differences in the numbers of implantations, incidences of visceral or skeletal abnormalities were reported at any dose.
**NOAEL (maternal/developmental toxicity) = 1000 mg/kg-day** (based on no adverse effects observed at the highest dose tested)

(4) Pregnant Golden hamsters (20 – 23/dose) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage in corn oil at doses of 0, 16, 74, 350 or 1600 mg/kg-day on gestation days 6 – 10. Animals were assessed for clinical signs, food consumption and body weight. On day 14, caesarian sections were performed and the numbers of implantations and resorption sites, and live and dead fetuses were recorded. Fetuses were examined for gross external abnormalities and all live fetuses were weighed. One-third of the fetuses from each litter were subjected to visceral examinations; the remaining two-thirds of the fetuses were examined for skeletal abnormalities. No maternal toxic effects or differences in the numbers of implantations, incidences of visceral or skeletal abnormalities were reported at any dose.
**NOAEL (maternal/developmental toxicity) = 1600 mg/kg-day** (based on no adverse effects observed at the highest dose tested)

***Genetic Toxicity – Gene Mutation***

***In vitro***

***DLTDP (CASRN 123-28-4)***
*Salmonella typhimurium* strains TA 98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* strain WP2 were exposed to 3,3'-thiodipropionic acid didodecyl ester at concentrations of 3.3 or 10 (*Salmonella typhimurium* strain TA100 only), 33.3, 100, 333, 1000, 2500, 3333, 5000, 6667 or 10,000 µg/plate in the presence and absence of metabolic activation. Positive controls were included, but their responses were not reported in the robust summary. Precipitation was noted at the two highest test concentrations.
**3,3'-Thiodipropionic acid didodecyl ester was not mutagenic in these assays.**

***DSTDP (CASRN 693-36-7)***
*Salmonella typhimurium* strains TA98, TA100 and TA1537 were treated with 3,3'-thiodipropionic acid didodecyl ester (dissolved in acetone) at concentrations of 313, 625, 1250, 2500 and 5000 µg/0.1 mL in the presence and absence of metabolic activation. Acetone and positive controls were included, but their responses were not reported in the robust summary.
**3,3'-Thiodipropionic acid didodecyl ester was not mutagenic in this assay.**

***Genetic Toxicity – Chromosomal Aberrations***

***In vitro***
***DSTDP (CASRN 693-36-7)***

Chinese hamster V79 cells were treated with 3,3'-thiodipropionic acid didodecyl ester in a homogenous suspension at 300 µg/mL in the absence of S9 activation and 285 µg/mL in the presence of S9 activation. Test concentrations were 0, 1, 0.6, 0.75, 1.5, 3, 5, 6, 10, 20, 30, 40 and 300 µg/mL, in the absence of S9 activation and 0, 1, 0.6, 0.75, 1.5, 3, 5, 6, 10, 20, 30, 40 and 285 µg/mL, in the presence of metabolic activation. Positive controls were included, and were stated to have responded appropriately. In one experiment, the highest test concentration caused cycotoxicity with metabolic activation, but not without metabolic activation. Cytotoxicity was not induced in the other experiment.
**3,3'-Thiodipropionic acid didodecyl ester did not induce chromosomal aberrations in this assay.**

***In vivo***
***DLTDP (CASRN 123-28-4)***
Male rats (5/dose) were administered 3,3'-thiodipropionic acid didodecyl ester once via oral gavage at dose levels of 50, 500 and 5000 mg/kg/day in a marrow micronucleus test. Rats were sacrificed 6, 24 or 48 hours after dosing. Positive and negative controls were included, but their responses were not reported in the robust summary.
**3,3'-Thiodipropionic acid didodecyl ester did not induce micronuclei in this assay.**

***Genetic Toxicity-Other Information***

***In vivo***

***DLTDP (CASRN 123-28-4)***
(1) Male rats (10/dose; strain not specified) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage at dose levels of 50, 500, and 5000 mg/kg/day for 5 days. The males were then mated with two virgin female rats per week, 5 days/week for 8 weeks. The female rats were remove and housed separately until sacrifice. Two new virgin female rats per week were again mated 5 days/week for 7 weeks with the male rats. The females were sacrificed using carbon dioxide after 14 days of separation from the male rats. The uterus was necropsied and examined for early and late fetal deaths and total implantations. There was no clear pattern of treatment related effects when compared to the controls. The positive control was administered intraperitoneal at 0.3 mg/kg/day.
**3,3',-Thiodipropionic acid didodecyl ester was not mutagenic in this assay.**

(2) Male ICR mice (10/dose) were administered 3,3'-thiodipropionic acid didodecyl ester via oral gavage at dose levels of 50, 500, and 5000 mg/kg/day for 3 hours. The positive controls received 100 mg/kg of dimethylnitrosamine treated Salmonella (his G-46 and TA-1535) and 350 mg/kg of ethylmethane sulfonate treated Saccharomyces (D-3). All groups received 2 mL of the indicated organism intraperitoneally. Animals were sacrificed and fluid was removed from the peritoneal

cavity. A tenfold serial dilution was made from 100 through $10^{-7}$. Total bacterial counts were made at $10^{-6}$ and $10^{-7}$ dilutions and incubated for 18 hours. Total mutant counts were made to 100th dilution and incubated for 40 hours. For yeast mitotic recombination, ten-fold serial dilutions were made from 100 to $10^{-5}$ then plated at $10^{-5}$, $10^{-4}$ and $10^{-3}$ (10 plates each), then incubated for 40 hours. Total population was determined using the $10^{-5}$ dilution and mutations were determined using the $10^{-4}$ and $10^{-3}$ dilutions after an additional 40 hours of incubation at $4^{o}$C.

**3,3'-Thiodipropionic acid didodecyl ester induced genetic mutations in Salmonella G-46 strain in this assay.**

***Additional Information***

***Skin Irritation***

***DTTDP (CASRN 10595-72-9)***

Rabbits (number, strain and sex not specified) were given applications of 3,3'-thiodipropionic acid ditridecyl ester (concentration unspecified) to test for skin irritation. Applications were given 5 times/day (uncovered) at 0.1 mL to the ear and 3 times/day at 0.5 mL to intact and abraded abdominal skin (occluded) for 24 hours after each application. All three sites were examined during the test period and up to 10 days following the last exposure. Effects could be seen following the second application. Reported effects during the treatment period included moderate redness, necrosis, slight edema and exfoliations on the ear and slight redness with slight edema at the intact and abraded abdominal sites. Recovery at all sites was noted during post-treatment observation.

**3,3'-Thiodipropionic acid ditridecyl ester was irritating to the rabbit skin in this study.**

***DSTDP (CASRN 693-36-7)***

(1) White rabbits (number and sex not specified) were given 10 dermal applications of 3,3'-thiodipropionic acid dioctadecyl ester (concentration/amount unspecified) to intact skin during a 14-day period and 3 consecutive daily dermal applications to abraded skin sites. Solution concentrations were not provided. Application sites were covered. Each site was graded 24 hours following dosing and 3 and 10 days following the last application.

**3,3'-Thiodipropionic acid dioctadecyl ester was not irritating to the rabbit skin in this study.**

(2) Rabbits (number and sex not specified) were given a single dermal application (to intact skin) of 3,3'-thiodipropionic acid dioctadecyl ester (concentration/volume unspecified). Application sites were covered for 24 hours. Application sites were examined at 24, 48 and 72 hours following application of test substance.

**3,3'-Thiodipropionic acid dioctadecyl ester was not irritating to the rabbit skin in this study**.

***Eye Irritation***

***DLDTP (CASRN 123-28-4)***
Rabbits (number, strain and sex unspecified) were administered 500 mg of 3,3'-thiodipropionic acid didodecyl ester (neat) in the eyes and observed for 24 hours. Mild irritation was observed.
**3,3'-Thiodipropionic acid didodecyl ester was irritating to rabbit eyes in this study.**

***DTTDP (CASRN 10595-72-9)***
One female rabbit (strain unspecified) was administered 1 mL of undiluted 3,3'-thiodipropionic acid ditridecyl ester in both eyes. One eye was washed shortly after the application while the other eye remained unwashed. The animal was observed 1 and 24 hours after dosing. There was no evidence of pain or effects to the conjunctiva, cornea or iris of either eye.
**3,3'-thiodipropionic acid ditridecyl ester was not irritating to the rabbit eye in this study.**

***DSTDP (CASRN 693-36-7)***
One male rabbit was administered 3,3'-thiodipropionic acid dioctadecyl ester in both eyes (dose unspecified). After 30 seconds of exposure, the right eye was washed for 2 minutes while the left eye was not washed. Prior to dosing, both eyes were stained with fluorescein and rested for 24 hours. Both eyes were observed at 1, 24 and 48 hours and 7 days after treatment. Slight pain and conjunctival irritation was noted in both eyes immediately after application. There was no evidence of corneal injury, conjunctival irritation or corneal effects in either eye at any of the other observation periods.
**3,3'-Thiodipropionic acid dioctadecyl ester was not irritating to the rabbit eye in this study.**

**Conclusions:** The acute oral toxicity of CASRN 123-28-4 in rats and mice is low. The acute oral toxicity of CASRNs 10595-72-9 and 693-36-7 in rats is low. The acute inhalation of CASRN 10595-72-9 in rats is low. In a 90-day oral repeated-dose toxicity study in rats, CASRN 123-28-4 showed possible heart effects at 1000 mg/kg-day; the NOAEL for systemic toxicity is 350 mg/kg-day. In a two-year dietary toxicity study in rats with CASRN 693-36-7, there were no effects observed on any parameters measured at doses up to ~1125 mg/kg-bw/day, the highest dose tested. No reproductive toxicity studies are available; however, the 90-day oral repeated-dose toxicity study with CASRN 123-28-4 showed no adverse treatment-related effects on reproductive organs. In four oral prenatal developmental toxicity studies with CASRN 123-28-4, there were no maternal or developmental effects observed at the highest doses tested (1600 mg/kg-day in rats, mice and hamsters; and 1000 mg/kg-day in rabbits). CASRNs 123-28-4 and 693-36-7 did not induce chromosomal aberrations in *in vitro* tests (human lung cell and Chinese hamster cells). CASRN 123-28-4 did not induce chromosomal effects in male rats *in vivo*. In a dominant lethal assay, CASRN 123-28-4 did not induce genetic mutations in rats *in vivo*. In a host mediated assay, CASRN 123-28-4 induced genetic mutations in mice *in vivo*. CASRN 123-28-4 is irritating to the rabbit eye. CASRN 10595-72-9 is irritating to the rabbit skin but not the rabbit eye. CASRN 693-36-7 was not irritating to the rabbit skin and eye.

**Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data**

| Endpoints | DLTDP<br><br>(CASRN 123-28-4) | DTTDP<br><br>(CASRN 10595-72-9) | DSTDP<br><br>(CASRN 693-36-7) |
|---|---|---|---|
| **Acute Oral Toxicity**<br>**$LD_{50}$ (mg/kg-bw)** | **> 2000** (mouse) | **> 2000** (rat) | **> 2000** (rat and mouse) |
| **Acute Inhalation Toxicity**<br>**$LC_{50}$ (mg/L)** | No Data<br>> 0.19<br>(RA) | **> 0.19** | No Data<br>> 0.19<br>(RA) |
| **Repeated-Dose Toxicity**<br>**NOAEL/LOAEL**<br>**Oral Gavage (mg/kg-day)**<br>**Rat**<br><br>**Oral Diet (mg/kg-bw/day)** | **NOAEL = 350**<br>**LOAEL = 1000** | No Data<br>NOAEL = 350<br>LOAEL = 1000<br>(RA) | **NOAEL = 1125**<br>**LOAEL = Not established** |
| **Reproductive Toxicity**<br>**NOAEL/LOAEL**<br>**Oral (mg/kg-day)**<br>**Rat**<br>**Reproductive Organs** | **Reproductive organs were evaluated in a 13-week repeated-dose study. No effects were observed at 1000.** | No Data<br>(RA) | No Data<br>(RA) |
| **Developmental Toxicity**<br>**NOAEL/LOAEL**<br>**Oral Gavage (mg/kg-day)**<br><br>**Maternal/Developmental Toxicity**<br>**(Rats, hamsters, mice, and rabbits)** | **NOAEL = 1600 (rats, hamsters, mice)**<br>**LOAEL = Not established**<br>**NOAEL = 1000 (rabbits)** | No Data<br>NOAEL = 1600<br>LOAEL = Not established<br>NOAEL = 1000<br>(RA) | No Data<br>NOAEL = 1600<br>LOAEL = Not established<br>NOAEL = 1000<br>(RA) |

**Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data**

| Endpoints | DLTDP (CASRN 123-28-4) | DTTDP (CASRN 10595-72-9) | DSTDP (CASRN 693-36-7) |
|---|---|---|---|
| **Genetic Toxicity – Gene Mutation** ***In vitro*** | **Negative** | No Data<br>Negative<br>(RA) | **Negative** |
| **Genetic Toxicity – Chromosomal Aberrations** ***In vitro*** | **Negative** | No Data<br>Negative<br>(RA) | **Negative** |
| **Genetic Toxicity – Chromosomal Effects** ***In vivo*** | **Negative** | No Data<br>Negative<br>(RA) | No Data<br>Negative<br>(R) |
| **Additional Information Genetic Toxicity-Genetic Mutation** ***In vivo***<br>Dominant Lethal<br>Host Mediated | <br><br>**Negative**<br>**Positive** | <br><br>Negative<br>Positive<br>(RA) | <br><br>Negative<br>Positive<br>(RA) |
| **Additional Information**<br><br>**Skin Irritation (rabbit)**<br>**Eye Irritation (rabbit)** | <br><br>**Irritating** | <br><br>**Irritating**<br>**Not irritating** | <br><br>**Not irritating**<br>**Not Irritating** |

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

## 4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

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

The sponsor provided robust summaries of studies for the category members, CASRNs 123-28-4 and 693-36-7; these studies were intended to assess the acute toxicity to fish and aquatic invertebrates and toxicity to aquatic plants endpoints. However, the studies employed test substance concentrations that greatly exceeded the water solubility limits for all category members, thus rendering the studies inadequate. However, no further testing of category members is necessary due to their extremely low water solubility (< 0.001 mg/L for CASRN

693-36-7 and estimated at $4.94 \times 10^{-8}$ mg/L for CASRN 123-28-4) and high estimated log $K_{ow}$ values.

**Conclusion:** The potential acute and chronic hazards of these chemicals to fish, aquatic invertebrates and aquatic plants are considered to be "no effects at saturation" based on low water solubility and high estimated log $K_{ow}$ values for category members.

**Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data**

| Endpoints | 3,3'-Thiodipropionic acid didodecyl ester (CASRN 123-28-4) | 3,3'-Thiodipropionic acid ditridecyl ester (CASRN 10595-72-9) | 3,3'-Thiodipropionic acid dioctadecyl ester (CASRN 693-36-7) |
|---|---|---|---|
| **Fish 96-h $LC_{50}$ (mg/L)** | NES | NES | NES |
| **Aquatic Invertebrates 48-h $EC_{50}$ (mg/L)** | NES | NES | NES |
| **Aquatic Plants 72-h $EC_{50}$ (mg/L)** | NES | NES | NES |
| **Chronic Aquatic Invertebrates 21-d $EC_{50}$ (mg/L)** | NES | NES | NES |

NES = No effects at saturation (water solubility limit)