SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL
Thiodipropionitrile (CASRN 111-97-7)

SUPPORTING CHEMICALS
Propionitrile (CASRN 107-12-0)
Butyronitrile (CASRN 109-74-0)
Isobutyronitrile (CASRN 78-82-0)

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.

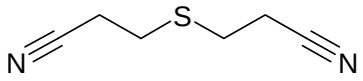
The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness 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.

[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.

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.

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.

Chemical Abstract Service Registry Number (CASRN)	**111-97-7**
Chemical Abstracts Index Name	**Propanenitrile, 3, 3'-thiobis -**
Structure	

Summary

Thiodipropionitrile is a low melting solid or a liquid/partial solid when purity is around 96.5% or less with high water solubility and low vapor pressure. It is expected to have moderate mobility in soil. Volatilization of this chemical is considered low based on it's Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow. Thiodipropionitrile is expected to have high persistence (P2) and low bioaccumulation potential (B1).

The acute oral toxicity of this chemical to mice, the acute inhalation toxicity to mice, rats and guinea pigs, and the acute dermal toxicity to rabbits is low. It is not irritating to rabbit skin, but slightly irritating to rabbit eyes. Adequate data were not submitted for the repeated-dose reproductive/developmental toxicity endpoints. This chemical did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells *in vitro*.

The 96-hour LC_{50} of this chemical to fish is 41 mg/L, the 48-hour EC_{50} to aquatic invertebrates is 250 mg/L, and the 96-hour EC_{50} to aquatic plants is 87.8 mg/L (biomass).

The repeated-dose/reproductive/developmental toxicity endpoints remain as data gaps under the HPV Challenge Program.

The sponsor, Thioesters Association, submitted a Test Plan and Robust Summaries to EPA for thiodipropionitrile (CASRN 111-97-7; CA Index name: propanenitrile, 3,3'-thiobis-) on December 16, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on January 23, 2004 (http://www.epa.gov/oppt/chemrtk/pubs/summaries/thioprpn/c14907tc.htm). EPA comments on the original submission were posted to the website on June 25, 2004. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on September 21, 2004 and April 4, 2005, which were posted to the ChemRTK website on September 30, 2004 and September 14 2005, respectively.

The sponsor proposed reduced health effects testing under the HPV Challenge Program claiming that thiodipropionitrile is a closed system intermediate (CSI). The Agency reviewed information in the HPV submission and updates/revised documents and determined that this chemical did not meet the Challenge Program guidance for a CSI.

Justification for Supporting Chemicals

In the revised submission, the sponsor provided data on three supporting chemicals, isobutyronitrile (CASRN 78-82-0), propionitrile (CASRN 107-12-0) and butyronitrile (CASRN 109-74-0) to address data gaps for the aquatic toxicity endpoints. The supporting chemicals are structurally similar except for the presence of a single sulfur molecule on the thiodipropionitrile moiety which will does not affect the overall toxicity to aquatic organisms. The measured toxicity values for the supporting chemicals for all three environmental effects endpoints are low and would serve as a reasonable estimate for the aquatic toxicity of thiodipropionitrile. EPA agrees that use of the supporting chemicals is appropriate for addressing ecotoxicity endpoints.

1. Chemical Identity

1.1 Identification and Purity

Robust Summaries submitted by the sponsor indicate purity of the test substance as ≥90% (w/w).

1.2 Physical-Chemical Properties

The physical-chemical properties for thiodipropionitrile are summarized in Table 1. This chemical is a low melting solid or a liquid/partial solid when purity is around 96.5% or less with high water solubility and low vapor pressure.

Table 1. Physical-Chemical Properties of Thiodipropionitrile[1]	
Property	**Value**
CASRN	111-97-7
Molecular Weight	140.20
Physical State	Solid when pure or a liquid or partial solid when purity is around 96.5% or less
Melting Point	25–29°C (measured) (28.6°C according to NIST http://webbook.nist.gov/cgi/cbook.cgi?ID=111-97-7&Units=SI&cTC=on&cTP=on)
Boiling Point	163–164°C at 0.75 mm Hg (measured)
Vapor Pressure	5.74×10^{-5} mm Hg at 25°C (measured)
Water Solubility	25,000 mg/L at 30°C (measured)
Dissociation Constant (pK_a)	Not applicable
Henry's Law Constant	2.38×10^{-10} atm-m^3/mole (estimated)
Log K_{ow}	-0.05 (estimated)

[1]The Thioesters Association. April 8, 2005. Revised Robust Summary and Test Plan for 3,3'-Thiodipropionitrile. http://www.epa.gov/oppt/chemrtk/pubs/summaries/thioprpn/c14907tc.htm.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

Thiodipropionitrile had an aggregated production and /or import volume in the United States between 1 million and 10 million pounds during the 2005 calendar year.

Non-confidential information in the IUR indicated that the industrial processing and use of this chemical include intermediates in the manufacture of other basic organic chemicals. The HPV submission for this chemical stated that it is solely used as a CSI. The Agency reviewed information in the HPV submission and updates/revised documents and determined that the chemical did not meet the guidance requirements for a CSI.

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. Thiodipropionitrile is expected to have moderate mobility in soil. Volatilization of this chemical is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow. It is expected to have high persistence (P2) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of Thiodipropionitrile [1]	
Property	**Value**
Photodegradation Half-life	33 hours (estimated)
Hydrolysis Half-life	>1 year at pH 4, 7, and 9
Biodegradation	0% in 28 days (measured, not readily biodegradable)
Bioconcentration	BCF = 3.162 (estimated)[2]
Log K_{oc}	2.25 (estimated)
Fugacity (Level III Model)	Air = 0.007% Water = 49.3% Soil = 50.6% Sediment = 0.0917%
Persistence[3]	P2 (high)
Bioaccumulation[3]	B1 (low)

[1]The Thioesters Association. April 8, 2005. Revised Robust Summary and Test Plan for 3,3'-Thiodipropionitrile. http://www.epa.gov/oppt/chemrtk/pubs/summaries/thioprpn/c14907tc.htm.
[2]U.S. 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.
[3]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 human health toxicity data submitted for SIDS endpoints is provided in Table 2. The table also indicates where data for supporting chemicals are read-across (RA) to the sponsored substance.

Acute Oral Toxicity

Male albino mice (13/dose, strain not reported) were administered thiodipropionitrile via oral gavage at 3, 4 and 5 mL/kg-bw (~ 3330, 4440 and 5550 mg/kg-bw) and observed for 10 days. Mortality occurred at all dose levels.
LD_{50} = 3750 mg/kg-bw

Acute Dermal Toxicity

Albino rabbits (3/dose, sex and strain not reported) received a single dermal application of thiodipropionitrile at 1, 4 or 8 mL/kg-bw (~ 1110, 4440 or 8876 mg/kg-bw). The test material was applied to shaved skin under occluded conditions for 22 hours and animals were observed for 6-10 days. Mortality occurred at the highest dose.
LD_{50} > 8876 mg/kg-bw

Acute Inhalation Toxicity

Mice, rats and guinea pigs (7/species/concentration, sex and strain not reported) were exposed to thiodipropionitrile vapor at 15.5 ppm (~ 0.0889 mg/L) for 6 hours. No mortality occurred.
LC_{50} > 0.0889 mg/L

Repeated-Dose Toxicity

Data Gap

Reproductive Toxicity

Data Gap

Developmental Toxicity

Data gap

Genetic Toxicity – Gene Mutation

In vitro

Thiodipropionitrile (CASRN 111-97-7)
Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA- were exposed to thiodipropionitrile at concentrations of 50, 150, 500, 1500 or 5000 μg/plate in the presence and absence of metabolic activation. No cytotoxicity or precipitation was observed at any concentration tested. Positive and negative controls were tested concurrently and responded appropriately.
Thiodipropionitrile was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Thiodipropionitrile (CASRN 111-97-7)
Rat lymphocyte cells were exposed to thiodipropionitrile at concentrations of 22.19, 44.38, 88.75, 177.5, 355, 710 or 1420 μg/mL for 4 hours with and without metabolic activation. A second test group was exposed at concentrations of 11.0, 22.19, 44.38, 88.75, 177.5, 355, 710 or 1420 μg/mL for 24 hours in the absence of metabolic activation. Cytotoxicity occurred at 1420 μg/mL. Positive and negative controls were tested concurrently and responded appropriately.
Thiodipropionitrile did not induce chromosomal aberrations in this assay.

Additional Information

Skin Irritation

Thiodipropionitrile (CASRN 111-97-7)
Six rabbits (sex and strain not specified) received dermal applications of thiodipropionitrile at 1.0 mL/kg-bw/day. Test material was applied to clipped abdominal skin under occluded conditions for 2 weeks (22 hours/day, 5 days/week). Animals were examined daily after each exposure and for an additional 10 days thereafter. No skin irritation was noted in treated animals.
Thiodipropionitrile was not irritating to rabbit skin in this assay.

Eye Irritation

Thiodipropionitrile (CASRN 111-97-7)
Three albino rabbits (sex and strain not specified) received a single application of 0.5 mL thiodipropionitrile in the conjunctival sac of the left eye (right eye served as control). Animals were evaluated 1, 4 and 24 hours after treatment and daily thereafter for 1 week. Clinical signs of toxicity occurred immediately after application and included blinking, scrambling, vascularization of the sclera and nictitating membrane and some edema of the upper eyelid. Mild erythema was also observed in two of three rabbits. All eyes appeared normal after 1 hour. **Thiodipropionitrile was slightly irritating to rabbit eyes in this assay.**

Conclusion: The acute oral toxicity of this chemical to mice, the acute inhalation toxicity to mice, rats and guinea pigs, and the acute dermal toxicity to rabbits is low. It is not irritating to rabbit skin, but slightly irritating to rabbit eyes. Adequate data were not submitted for the repeated-dose reproductive/developmental toxicity endpoints. This chemical did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells *in vitro*.

4. Hazards to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 2. The table also indicates where data for supporting chemicals are read-across (RA) to the sponsored substance.

Acute Toxicity to Fish

Propionitrile (CASRN 107-12-0, supporting chemical)
(1) Fathead minnows (*Pimephales promelas*) were exposed to measured concentrations of 0, 375, 611, 887, 1100 and 2188 mg/L under flow–through conditions for 96 hours. One fish exposed to 1100 mg/L and all fish exposed to 2188 mg/L died by 24 hours.
96-h LC_{50} = 1520 mg/L

(2) Bluegill sunfish (*Lepomis macrochirus*) were exposed to nominal concentrations of 0, 10, 18, 32, 56 and 100 mg/L under static conditions for 96 hours. Mortality was 10% in the 10 and 18 mg/L groups. The mortality rate for fish exposed to 32 mg/L was 20% at 24 hours, 20% at 48 hours, 40% at 72 hours, and 50% at 96 hours. The mortality rate for fish exposed to 56 mg/L was 0% at 24 hours, 40% at 48 and 72 hours, and 50% at 96 hours. The mortality rate for fish exposed to 100 mg/L was 50% at 24 hours, and 90% at 48, 72 and 96 hours.
96-h LC_{50} = 41 mg/L

(3) Rainbow trout (*Salmo gairdneri*) were exposed to nominal concentrations of 0, 100, 180, 320, 560 and 1000 mg/L under static conditions for 96 hours. None of the fish exposed to 100 or 180 mg/L died. The mortality rate for fish exposed to 320 mg/L was 10% at 24 hours, 20% at 48 hours, 30% at 72 hours, and 40% at 96 hours. The mortality for fish exposed to 560 or 1000 mg/L was 100% by 24 hours.
96-h LC_{50} = 340 mg/L
Butyronitrile (CASRN 109-74-0, supporting chemical)

Fathead minnow (*Pimephales promelas*) were exposed to mean measured concentrations of 107 mg/L under static conditions for 96 hours. No mortality occurred and all fish exhibited normal behavior and appearance.
96-h LC_{50} > 107 mg/L

Isobutyronitrile (CASRN78-82-0, supporting chemical)
Fathead minnow (*Pimephales promelas*) were exposed to mean measured concentrations of 102.1 mg/L under static conditions for 96 hours. No mortality occurred and all fish exhibited normal behavior and appearance.
96-h LC_{50} > 102.1 mg/L

Acute Toxicity to Aquatic Invertebrates

Propionitrile (CASRN 107-12-0, supporting chemical)
Water fleas (*Daphnia magna*) were exposed to a measured concentration of propionitrile at 0, 100, 180, 320, 560 and 1000 mg/L under static conditions for 48 hours. None of the controls or daphnids exposed to 100 mg/L died during the study. Immobilization was observed at 180 mg/L between 24 and 48 hours in one daphnid. Immobilization of daphnids exposed to 180 mg/L was 5% at 24 hours and 20% at 48 hours and exposed to 320 mg/L was 50% at 24 hours and 75% at 48 hours. All daphnids exposed to 560 or 1000 mg/L exhibited immobilization within 24 hours.
48-h EC_{50} > 250 mg/L

Butyronitrile (CASRN 109-74-0, supporting chemical)
Water fleas (*Daphnia magna*) were exposed to a mean measured concentration of 110 mg/L under static conditions for 48 hours. All daphnids, but one (immobilization), exposed to the test-article exhibited behavior comparable to controls.
48 h EC_{50} > 110 mg/L

Isobutyronitrile (CASRN 78-82-0, supporting chemical)
Water fleas (*Daphnia magna*) were exposed to mean measured concentration of 94.3 mg/L under static conditions for 48 hours. All daphnids exposed to test-article exhibited behavior comparable to controls.
48 h EC_{50} > 94.3 mg/L
Toxicity to Aquatic Plants

Propionitrile (CASRN 107-12-0, supporting chemical)
No test data were submitted for propionitrile. A 96-hour ECOSAR estimated EC_{50} value for green algae was provided.
96-h EC_{50} = 789 mg/L

Butyronitrile (CASRN 109-74-0, supporting chemical)
Green algae (*Pseudokirchneriella subcapitata*) were exposed to mean measured concentration 133.4 mg/L under static conditions for 72 hours. Algae exposed to test material exhibited normal growth with respect to control.
EC_{50} > 133.4 mg/L

Isobutyronitrile (CASRN 78-82-0, supporting chemical)
Green algae (*Pseudokirchneriella subcapitata*) were exposed to mean measured concentration 87.8 mg/L under static conditions for 72 hours. Algae exposed to test material exhibited normal growth with respect to control.
EC_{50} > 87.8 mg/L

Conclusion: The 96-hour LC_{50} of this chemical to fish is 41 mg/L, the 48-hour EC_{50} to aquatic invertebrates is 250 mg/L, and the 96-hour EC_{50} to aquatic plants is 87.8 mg/L (biomass).

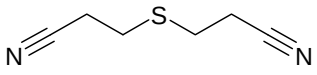
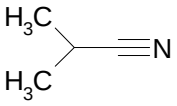
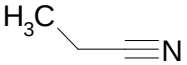
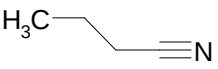
Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program				
Endpoints	**SPONSORED CHEMICAL Thiodipropionitrile (111-97-7)**	**SUPPORTING CHEMICAL Isobutyronitrile (78-82-0)**	**SUPPORTING CHEMICAL Propionitrile (107-12-0)**	**SUPPORTING CHEMICAL Butyronitrile (109-74-0)**
Structure				
Summary of Human Health Data				
Acute Oral Toxicity LD_{50} (mg/kg-bw)	~ **3750**	**–****	**–****	**–****
Acute Inhalation Toxicity LC_{50} (mg/L)	> **0.0889**	**–****	**–****	**–****
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	> **8876**	**–****	**–****	**–****
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Data Gap	**–****	**–****	**–****
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Data Gap	**–****	**–****	**–****
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Data Gap	**–****	**–****	**–****

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program				
Endpoints	**SPONSORED CHEMICAL Thiodipropionitrile (111-97-7)**	**SUPPORTING CHEMICAL Isobutyronitrile (78-82-0)**	**SUPPORTING CHEMICAL Propionitrile (107-12-0)**	**SUPPORTING CHEMICAL Butyronitrile (109-74-0)**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**	**–****	**–****	**–****
Genetic Toxicity – Chromosomal Aberrations *In vitro*	**Negative**	**–****	**–****	**–****
Additional Information				
Skin Irritation	Non irritating	**–****	**–****	**–****
Eye Irritation	Slightly irritating	**–****	**–****	**–****
Summary of Environmental Effects – Aquatic Toxicity Data				
Fish[*] 96-h LC_{50} (mg/L)	No Data 41 (RA)	**–****	**41** **340** **1520**	**–****
Aquatic Invertebrates 48-h EC_{50} (mg/L)	No Data 250 (RA)	**–****	**250**	**–****
Aquatic Plants 72-h EC_{50} (mg/L)	No Data			
(growth)	>87.8	**> 87.8**	**–****	**> 133.4**
(biomass)	>87.8 (RA)	**> 87.8**		**> 133.4**

Measured data in bold text; RA = Read Across (most conservative value); –** indicates endpoint not necessary for this chemical