

SCREENING-LEVEL HAZARD CHARACTERIZATION Sulfosuccinates Category

**Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt
(CASRN 577-11-7)**

**Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt
(CASRN 2373-38-8)**

**Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt
(CASRN 23386-52-9)**

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, EXTTOXNET, 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

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>.

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.

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)	577-11-7 2373-38-8 23386-52-9
Chemical Abstract Index Name	Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt Butanedioic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl) ester, sodium salt Butanedioic acid, sulfo-, 1,4-dicyclohexyl ester, sodium salt
Structural Formula	See Section 1
Summary	
<p>The sulfosuccinates are solids with high water solubility and negligible vapor pressure. They are expected to have moderate to high mobility in soil. The rate of volatilization of the sulfosuccinates is expected to be low based upon their Henry's Law constants. The rate of hydrolysis is expected to be negligible and the rate of atmospheric photooxidation is moderate. The sulfosuccinates are expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute oral toxicity in rats and acute dermal toxicity in rabbits is low for the members of this category. CASRN 577-11-7 is irritating to rabbit skin and eye. Oral repeated exposures to CASRN 577-11-7 in rats showed effects on the gastrointestinal tract and low weight gain at 500 mg/kg-bw/day; the NOAEL for systemic toxicity was 250 mg/kg-bw/day. Oral repeated exposures to CASRN 2373-38-8 in male rats showed no effects at the highest dose tested; the NOAEL for systemic toxicity was 510 mg/kg-bw/day. Oral repeated exposures to CASRN 23386-52-9 in rats showed no effects at the highest dose tested; the NOAEL for systemic toxicity was 960 mg/kg-bw/day. An oral three-generation reproductive toxicity study with CASRN 577-11-7 in rats showed decreased food consumption and body weights in adult animals at 500 mg/kg-bw/day; the NOAEL for systemic toxicity was 100 mg/kg-bw/day. In the same study, pup weights were decreased and there was an effect on lactation at 500 mg/kg-bw/day; the NOAEL for reproductive/developmental toxicity was 100 mg/kg-bw/day. An oral prenatal developmental toxicity study with CASRN 577-11-7 in rats showed reduced body weight gains in the dams and a significant increase in fetal resorptions and percentage of externally malformed fetuses at 1000 mg/kg-bw/day; the NOAEL for maternal and developmental toxicity was 500 mg/kg-bw/day. CASRN 577-11-7 did not show mutagenic potential in bacterial cells nor did it induce chromosomal aberrations in mammalian cells <i>in vitro</i>. CASRN 577-11-7 did not show carcinogenic potential in rats.</p> <p>The measured 96-hour LC₅₀ for the sulfosuccinates category members for fish ranged from 28 to 1200 mg/L, the measured 48-hour EC₅₀ for aquatic invertebrates ranged from 36.2 to 457 mg/L, and for aquatic plants the 96-hour EC₅₀ > 1000 mg/L (concentrations of up to and > 300 mg/L stimulated growth).</p> <p>No data gaps were identified for these chemicals under the HPV Challenge Program.</p>	

The sponsor, The SOCMA Sulfosuccinates Group (SSG) of the Synthetic Organic Chemical Manufacturers Association (SOCMA), submitted a Test Plan and Robust Summaries to EPA for the Sulfosuccinates Category on July 25, 2001. EPA posted the submission on the ChemRTK website on September 14, 2001

(<http://www.epa.gov/chemrtk/pubs/summaries/cyclodim/c13133tc.htm>). EPA comments on the original submissions were posted to the website on February 19, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on May 31, 2002, which were posted to the ChemRTK website on July 19, 2002. The sulfosuccinates category consists of three chemicals described in Table 1.

Category Justification

The three members of the sulfosuccinates category are sulfosuccinate esters with closely related molecular structures. They have a succinic ester backbone, in which a carbon alpha to one of the carboxyl functions has a sodiumsulfo group in place of a hydrogen atom. The only structural difference in the three substances is the alcohol moiety of the ester function: 2-ethylhexyl-, cyclohexyl- and 1,3-dimethylbutyl. The generic molecular structure for all category members is shown below:



where R = 2-ethylhexyl- [$\text{CH}_3(\text{CH}_2)_3\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2-$]
= 1,3-dimethylbutyl- [$(\text{CH}_3)_2\text{CHCH}^2\text{CH}(\text{CH}_3)-$]
= cyclohexyl- [cyclic $-(\text{CH}_2)_5\text{CH}-$]

The sponsor grouped the chemicals based on the similarities in structure and physicochemical and toxicological properties. In its revised submission, the sponsor expanded the discussion on metabolism by identifying the alcohol moiety formed for each ester [2-ethylhexanol (CASRN 104-76-7), methyl isobutyl carbinol (MIBC or 4-methylpentan-2-ol; CASRN 108-11-2) and cyclohexanol (CASRN 108-93-0)]. The sponsor referred to the evaluation of these metabolites in other programs. Data and information on the metabolites are now publicly available (<http://cs3-hq.oecd.org/scripts/hpv/> as summary data for CASRN 104-76-7, <http://www.chem.unep.ch/irptc/sids/OECD/SIDS/sidspub.html> for full dataset for CASRN 108-11-2 and <http://www.epa.gov/chemrtk/pubs/summaries/cyclohex/c13221tc.htm> for full dataset for CASRN 108-93-0). EPA believes these data support the grouping of these three chemicals into one category and that the use of read-across between category members is appropriate.

1 Chemical Identity

1.1 Identification and Purity

The following description is taken from the revised Test Plan and Robust Summaries (2002):

The category members are described under the category justification section. They are chemically stable at room temperature and neutral conditions.

The purity used for testing is as follows:

CASRN 577-11-7 97 to 100% purity or sodium salt commercial product or dried commercial product of 100% solids as “active ingredients”
 CASRN 2373-38-8 approximately 80% CASRN 2373-38-8, 15% water, 5% ethanol
 CASRN 23386-52-9 Environment: 80 to 97% pure
 Human Health: 80% CASRN 23386-52-9, 12% water, 8% ethanol or dried commercial product of 100% solids as “active ingredients”

Table 1. Chemical Structures of Sulfosuccinates		
CASRN	Chemical Name	Structure
577-11-7	Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt	
2373-38-8	Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt	
23386-52-9	Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt	

1.2 Physical-Chemical Properties

The physical-chemical properties of the sulfosuccinates category are summarized in Table 2. Members of the sulfosuccinates category are solids with high water solubility and negligible vapor pressure.

Table 2. Physical-Chemical Properties of Sulfosuccinates Category1

Property	Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt	Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt	Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt
CASRN	577-11-7	2373-38-8	23386-52-9
Molecular Weight	445.57	389.47	385.43
Physical State	Solid	Solid	Solid
Melting Point	153–157°C (measured)	87.4–133.2°C (estimated)	203°C (measured)
Boiling Point	>300°C (decomposes)	>300°C (decomposes)	>300°C (decomposes)
Vapor Pressure (mm Hg)	Substance is a salt with negligible vapor pressure; <7.5×10 ⁻⁶ (estimated)	Substance is a salt with negligible vapor pressure; <7.5×10 ⁻⁷ (estimated)	Substance is a salt with negligible vapor pressure; <7.5×10 ⁻⁶ (estimated)
Dissociation Constant (pK _a)	Dissociates in water	Dissociates in water	Dissociates in water
Henry's Law Constant (atm·m ³ /mol)	5.00×10 ⁻¹² (estimated)	1.62×10 ⁻¹² (estimated)	3.14×10 ⁻¹³ (estimated)
Water Solubility (mg/L)	1.5×10⁴ at 25°C (measured); 2.3×10⁴ at 40°C (measured); 3.0×10⁴ at 50°C (measured); 5.5×10⁴ at 70°C (measured)	3.0–3.2×10⁵ at 25°C (measured)	1.2×10⁵ at 25°C (measured)
Log K _{ow}	3.95 (estimated)	3.98 (estimated)	1.76 (estimated)

¹Synthetic Organic Chemical Manufacturers Association, Sulfosuccinates Group. June 6, 2002. Revised Robust Summary and Test Plan for Sulfosuccinates Category.

<http://www.epa.gov/chemrtk/pubs/summaries/cyclodim/c13133tc.htm>.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

The sulfosuccinates category chemicals had an aggregated production and/or import volume in the United States of 12 million to 70 million pounds during calendar year 2005.

- CASRN 577-11-7 10 to 50 million pounds
- CASRN 2373-38-8 1 to 10 million pounds
- CASRN 23386-52-9 1 to 10 million pounds

Non-confidential information in the Inventory Update Reporting (IUR)⁴ indicated that the industrial processing and uses of these chemicals include: processing aid in other basic chemical

⁴ USEPA, 2006 Inventory Update Reporting Database.

manufacturing, adhesive manufacturing, electrical equipment and component manufacturing, food manufacturing, textile product mills, pharmaceutical and medicine manufacturing, paint and coating manufacturing, printing ink manufacturing; surface active agent in petroleum and coal products manufacturing, paint and coating manufacturing, soap and cleaning compound manufacturing, graphic design services, iron ore mining, carpet and rug mills, and paperboard mills. Non-confidential information in the IUR indicated that the commercial and consumer products containing these chemicals include electrical and electronic products, artists supplies, fabrics, textiles and apparel, lubricants, greases and fuel additives, paints and coatings, paper products and “other”. The High Production Volume submission for this chemical category states that CASRN 577-11-7 is used as a stool softener, cosmetics, gelatin desserts, vitamins and other food and beverages. CASRN 23386-52-9 and CASRN 2373-38-8 are used as surfactants or wetting agents, and as ingredients in some adhesives, polymeric coatings, and detergents.⁵ The Hazardous Substances Data Bank (HSDB) information for CASRN 577-11-7 states that the chemical is used as a wetting agent in pharmaceutical, cosmetic, and food applications.⁶

2.2 Environmental Exposure and Fate

No quantitative information is available on environmental releases of these chemicals to the environment.

The environmental fate properties are provided in Table 3. The sulfosuccinates are expected to have moderate to high mobility in soil. The sulfosuccinates underwent degradation, but were not considered readily biodegradable using the Closed Bottle Test (OECD 301D) or Modified OECD Screening Test (OECD 301E). The rate of volatilization of the sulfosuccinates from water and moist soil is expected to be low since these compounds are salts. The rate of hydrolysis is expected to be negligible under environmental conditions. The sulfosuccinates are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt	Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt	Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt
CASRN	577-11-7	2373-38-8	23386-52-9
Photodegradation Half-life	5.6 hours (estimated)	7.3 hours (estimated)	5.2 hours (estimated)
Hydrolysis Half-life	6.7 years at pH 7 (estimated); 248 days at pH 8	156 years at pH 7 (estimated); 15.6 years at pH 8	14.5 years at pH 7 (estimated); 1.5 years at pH 8
Biodegradation	66.4% after 28 days (not readily biodegradable)	40.3% after 28 days (not readily biodegradable); 16.2% after 28 days (not	35.9% after 28 days (not readily biodegradable)

⁵ Synthetic Organic Chemical Manufacturers Association, Test Plan For Sulfosuccinates Category (Revised) May 13, 2002. Accessed: October 20, 2008. <http://www.epa.gov/chemrtk/pubs/summaries/cyclodim/c13133rt.pdf>

⁶ HSDB, 2008. Hazardous Substances Data Bank. Accessed, 10/24/08, CAS# 23386-529, 2373-38-8, 577-11-7. <http://toxnet.nlm.nih.gov/>

Property	Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt	Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt	Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt
		readily biodegradable)	
Bioconcentration	BCF = 56.2 (estimated); BCF = <0.9 (measured in carp at 0.5 mg/L) ² ; BCF = <9.3 (measured in carp at 0.05 mg/L) ²	BCF = 3.16 (estimated)	BCF = 3.16 (estimated)
Log K _{oc}	3.018 (estimated) ³	1.761 (estimated) ³	2.045 (estimated) ³
Fugacity (Level III Model)			
Air (%)	1.55	0.911	0.875
Water (%)	37.3	38.7	40.8
Soil (%)	59.9	60.3	58.3
Sediment (%)	1.33	0.101	0.1
Persistence ⁴	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation ⁴	B1 (low)	B1 (low)	B1 (low)

¹Synthetic Organic Chemical Manufacturers Association, Sulfosuccinates Group. June 6, 2002. Revised Robust Summary and Test Plan for Sulfosuccinates Category.

<http://www.epa.gov/chemrtk/pubs/summaries/cyclodim/c13133tc.htm>.

²National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law.

http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

³U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. U.S. Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

⁴Federal 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

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

(1) Male CF Nelson rats (5/dose) were orally administered a 5% aqueous dispersion of 625, 1250, 2500 or 5000 mg/kg-bw CASRN 577-11-7. Animals were observed for a period of 14 days, sacrificed and necropsied. No animals died at the two lower doses. Mortalities at 2500 and 5000 mg/kg-bw were 1/5 and 5/5 respectively. No visible lesions were noted in the surviving animals at necropsy.

LD₅₀ = 3080 mg/kg-bw

(2) Male Sprague-Dawley rats (5/dose) were administered a 20% aqueous dispersion of 14.1, 17.8, 22.4 or 25.2 ml/kg (approximately 2820, 3560, 4480 or 5040 mg/kg-bw) CASRN 577-11-7 by oral gavage. Animals were observed for a period of 14 days, sacrificed and necropsied. Mortalities to increasing doses were 0/5, 1/5, 3/5 and 5/5, respectively. No visible lesions were noted in the surviving animals at necropsy.

LD₅₀ = 4200 mg/kg-bw

(3) Female Wistar rats (5/dose) were orally administered a 10% aqueous solution or emulsion ranging from 252 to 7950 mg/kg-bw CASRN 577-11-7 by oral gavage. Animals were observed for a period of 14 days, sacrificed and necropsied. No clinical signs or toxicity at necropsy were described. The robust summary states “(T)he actual doses given and the number of deaths at each dose was not listed.”

LD₅₀ ~ 2000 mg/kg-bw

(4) Male ARS/ICR mice (10/dose) were orally administered 2.5 to 5.0 ml/100g CASRN 577-11-7 in 4% acacia by gastric intubation. Animals were observed for a period of 14 days, sacrificed and necropsied. Mortality rates for exposure to 2340, 2520, 2690, 2880, 3090, 3310, 3550 or 3825 mg/kg-bw were 3/10, 6/10, 4/10, 7/10, 5/10, 7/10, 7/10 and 9/10, respectively. No clinical signs or toxicity at necropsy were described.

LD₅₀ = 2643 mg/kg-bw

Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)

Male albino rats (20) were treated with single oral exposures ranging from 310 to 2500 mg/kg-bw CASRN 2373-38-8. All animals treated at 2500 mg/kg-bw died within 24 hours, but all survived treatment at the lower doses. Moderate to severe irritation with hemorrhage of the gastrointestinal tract was seen during necropsy. Necropsy of survivors revealed distension of the intestines.

LD₅₀ = 1750 mg/kg-bw

Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)

Male Wistar rats (5/dose) were orally administered 1250, 2500, 5000 or 10,000 mg/kg-bw 20% w/v aqueous CASRN 23386-52-9. Animals were observed for behavior and death for 14 days after which they were sacrificed and necropsied. All animals at the two higher doses died. No animals at the two lower doses died.

LD₅₀ = 3540 mg/kg-bw

Acute Dermal Toxicity

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

Male New Zealand White rabbits (5) were administered 10 ml/kg CASRN 577-11-7 by dermal application to clipped unbraided skin for 24 hours. Animals were observed for 14 days, sacrificed and necropsied. None of the animals died.

LD₅₀ > 10,000 mg/kg-bw

Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)

Male albino rabbits (12) were dosed with 2.5, 5 or 10 ml/kg CASRN 2373-38-8 to closely-clipped skin for 24 hours. Animals were observed for 7 days, sacrificed and necropsied. All animals exposed to 10 ml/kg died within one to three days following the removal of the test substance. The mortality rate at the two lower doses was 25%; with necropsy revealing no gross pathology that was considered treatment-related.

LD₅₀ ~ 4000 mg/kg-bw

Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)

Male albino rabbits (10) were dermally treated with 5000 mg/kg-bw CASRN 23386-52-9 as an aqueous paste held under an impervious cuff in continuous 24-hour contact with the shaved skin. Animals were observed for up to 14 days. One out of 10 rabbits died. Gross necropsies of all survivors were normal.

LD₅₀ > 5000 mg/kg-bw

Repeated-Dose Toxicity

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

(1) In a 16-week study, 21-day old male Osborne-Mendel rats (5/dose) were administered CASRN 577-11-7 in the diet at concentrations of 0, 2, 4 and 8% (corresponding to 0 and approximately 2000, 4000 and 8000 mg/kg-bw/day, respectively⁷). Animals receiving 8% had severe gastrointestinal symptoms and died within the first week of treatment. Only one animal at 4% survived for the duration of the study. Rats receiving 2% gained less weight than controls and had evidence of gastrointestinal irritation upon necropsy.

LOAEL ~ 2000 mg/kg-bw/day (based on low weight gain and gastrointestinal irritation)

NOAEL = Not established

(2) In a 26-week study, rats (strain not given; 12/sex/dose) were administered CASRN 577-11-7 in the diet at concentrations of 0, 0.5, 1.0 and 1.5% (corresponding to 0 and approximately 250, 500 and 750 mg/kg-bw/day, respectively). Two control animals and four test animals (sex not specified) given 1.5% died. Two out of the four treated dead animals had hemorrhagic gastroenteritis. No other effects on body weights, food consumption, clinical chemistry or histopathology were observed.

LOAEL ~ 500 mg/kg-bw/day (based on low weight gain and hemorrhagic gastroenteritis)

NOAEL ~ 250 mg/kg-bw/day

(3) In a one-year study, Beagle dogs (4/sex/dose) were administered CASRN 577-11-7 via oral tablet at 0 or 30 mg/kg-bw once a day, 7 days/week. No adverse treatment-related effects on body weights, food consumption, clinical chemistry, hematology and urinalysis parameters or histopathology were observed. No evidence of gastric irritation was noted.

NOAEL = 30 mg/kg-bw/day (based on no treatment related effects at the only dose tested)

⁷ Because the animals were 21-days old/weanlings at the start of the study, a factor of 10X was used instead of 20X for the dose conversion from ppm in diet to mg/kg-bw/day.

Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)

Male albino rats (10/dose) were administered CASRN 2373-38-8 in the diet at concentrations of 0, 0.125, 0.25 and 0.5% (corresponding to 0, 130, 250 and 510 mg/kg-bw/day, respectively) for 32 days. No clinical signs of toxicity were evident in treated animals over the study period. No mortality was noted. Mean daily food intake of animals receiving 0.125 % (18.8 g) was markedly lower than control (19.6 g). Mean weight gain of this group (165 g) also was significantly different (statistics not provided) from control (177 g). There was no difference in food consumption or body weight gain of the other two groups with respect to control. Histopathology did not reveal any treatment-related findings.

NOAEL = 510 mg/kg-bw/day (based on no effects at the highest dose tested)

Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)

In a 32-day study, Wistar rats (10/sex in the control group and 5/sex in the treated groups) were administered CASRN 23386-52-9 in the diet at concentrations of 0, 0.25, 0.5 and 1% (corresponding to 0, 240, 470 and 960 mg/kg-bw/day, respectively). No mortality or clinical sign of toxicity were noted. No adverse treatment related effects on body weights, food consumption or gross pathology were observed.

NOAEL = 960 mg/kg-bw/day (based on no effects at the highest dose tested)

Reproductive Toxicity

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

In a three-generation reproductive toxicity study, male and female Crl:CD(SD)BR rats were administered CASRN 577-11-7 in the diet at concentrations of 0, 0.1, 0.5 and 1% concentrations (corresponding to approximately 0, 100, 500 and 1000 mg/kg-bw/day, respectively) during pre-mating, mating (males and females) and during gestation for three generations (F0, F1, F2) until weaning of the third generation (F3). Food consumption of F0, F1 and F2 males treated with 1.0% ethylhexyl ester was markedly less than controls during week 4; weeks 2, 4, 8 and 10; and weeks 2 and 10, respectively. Body weights of F1 males and females treated with 1.0% were markedly lower than controls, and final weights of F1 and F2 males and females treated with 1.0% and F2 males treated with 0.5% were lower than their respective controls. Mean birth weight of male and female pups born to animals treated with 1.0% was markedly lower than control. All three generations of male and female pups born to animals treated with 0.5 or 1.0% weighed less than controls on day 21. No milk was found in the abdomens on lactation day 4 in 3 control F2 pups, 7 F2 pups in the 0.1% dose group, 18 F2 pups and 1 F3 pup in the 0.5% dose group, and 10 F2 pups and 17 F3 pups in the 1.0% dose groups. There were no treatment-related effects on the total number of pups or litters, litter size or sex ratio. Perinatal pup survival across the three generations was 99% for controls. There were no treatment-related mortality or microscopic observations in any animals examined (F0, F1 and F2 adults and F3 weanlings).

LOAEL (systemic toxicity) ~ 500 mg/kg-bw/day (based on effect on food consumption and body weights)

NOAEL (systemic toxicity) ~ 100 mg/kg-bw/day

LOAEL (reproductive/developmental toxicity) ~ 500 mg/kg-bw/day (based on decreased fetal body weight, effect on lactation)

NOAEL (reproductive/developmental toxicity) ~ 100 mg/kg-bw/day

*Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)
and Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)*

No appropriate reproductive toxicity data were submitted for these category members⁸.

However, information for the alcohol metabolites of these category members (MIBC and cyclohexanol) have similar profiles in that MIBK and HMP (metabolites of MIBC) and cyclohexanol showed reproductive toxicity at high doses. Available data for the ethylhexyl ester category member address this endpoint for these two category members using read across.

Developmental Toxicity

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

(1) Female Sprague-Dawley rats were administered CASRN 577-11-7 in the diet at concentrations of 0, 1 and 2% (corresponding to approximately 0, 500 and 1000 mg/kg-bw/day, respectively) on days 6 – 15 of gestation. At a 2% dietary intake, reduced weight gain in dams, marked increase in fetal resorptions and a large percentage of externally malformed fetuses were observed. The abnormalities consisted primarily of exencephaly, which was frequently associated with spina bifida and microphthalmia. There was also incomplete ossification of various cranial bones and curved or open vertebral columns.

LOAEL (maternal toxicity) ~ 1000 mg/kg-bw/day (based on reduced weight gain in dams)

NOAEL (maternal toxicity) ~ 500 mg/kg-bw/day

LOAEL (developmental toxicity) ~ 1000 mg/kg-bw/day (based on significant increase in fetal resorptions and a significant percentage of externally malformed fetuses)

NOAEL (developmental toxicity) ~ 500 mg/kg-bw/day

(2) Female Sprague-Dawley rats were administered CASRN 577-11-7 in the diet at concentrations of 0 or 2% (approximately 0 or 1000 mg/kg-bw/day) on days 6 – 16 of gestation. At the only dose tested, there was a significant decrease in maternal body weight, food consumption and body weight gain. Fetuses had decreased weight, decreased crown-rump length and increased skeletal anomalies (primarily unossified sternebra).

LOAEL (maternal toxicity) ~ 1000 mg/kg-bw/day (based on decreases in body weight, food intake and body weight gain; only dose tested)

NOAEL = Not established

LOAEL (developmental toxicity) ~ 1000 mg/kg-bw/day [based on decreases in fetal body weights and crown-rump length and increases in skeletal anomalies (unossified sternebra)]

NOAEL = Not established

***Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)
and Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)***

⁸ Ninety-day studies for both category members were submitted that contained statements about the evaluation of reproductive organs as meeting the HPV Challenge program requirements for reproductive toxicity. However, both of these studies were performed at Industrial Bio-Test Laboratories (IBT). Based on guidance on the acceptance and use of IBT studies (OECD HPV Manual Section 3.1.8 <http://www.oecd.org/dataoecd/13/15/36045203.pdf>), when the study has not been audited by either EPA or FDA or by Industry, and if the findings of the IBT study were consistent with a study conducted at later date in another laboratory, then the data may be used but should be considered as weak supporting evidence. The IBT studies were not used by EPA to address this endpoint.

No developmental toxicity data were submitted for these category members. However, information for the alcohol metabolites of these category members (MIBC and cyclohexanol) have similar profiles in that MIBK (a metabolite of MIBC) and cyclohexanol showed developmental toxicity at high doses. Available data for the ethylhexyl ester category member address this endpoint for these two category members using read across.

Genetic Toxicity – Gene Mutation

In vitro

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

Mutagenicity potential of CASRN 577-11-7 was evaluated in Ames assays using strains of *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of metabolic activation up to 2,500 µg/plate of test substance. Cytotoxicity was observed at 500, 1000 and 2500 µg/plate. The negative and positive controls behaved appropriately. No increases in mutation frequency were reported at any concentration tested with or without metabolic activation.

CASRN 577-11-7 salt was not mutagenic in these assays.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

Chinese hamster ovary cells were exposed to the test substance at concentrations ranging from 9.3 – 470 µg/mL with and without metabolic activation. Appropriate responses were seen for negative and positive controls. The test substance did not induce chromosome aberrations in cells exposed without metabolic activation. The test substance was clastogenic at cytotoxic concentrations, but not at non-cytotoxic concentrations.

CASRN 577-11-7 did not induce chromosomal aberrations in this assay.

Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)

and Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)

No adequate genetic toxicity data were submitted for these category members. However, information for the alcohol metabolites of two category members (MIBC and cyclohexanol) support the read across in that all available data show negative results for gene mutations and chromosomal aberrations (except for one positive *in vitro* result with cyclohexanol; which showed negative *in vivo* results in a micronucleus assay in mice). Available data for the ethylhexyl ester category member address the endpoint using read across.

Additional Information

Skin Irritation

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

Rabbit skin was exposed to 10 mg CASRN 577-11-7 for 24 hours. Moderate irritation was observed (Journal of Pharmacology and Experimental Therapeutics, 1944).

CASRN 577-11-7 was moderately irritating to rabbit skin.

Eye Irritation

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

(1) Rabbit eye was exposed to 250 µg CASRN 577-11-7. Mild irritation was observed (Archives of Ophthalmology, 1945).

CASRN 577-11-7 was mildly irritating to rabbit eye.

(2) Rabbit eye was exposed to 1% CASRN 577-11-7. Severe irritation was observed (Journal of the American Pharmaceutical Association, 1949).

CASRN 577-11-7 salt was severely irritating to rabbit eye.

Carcinogenicity

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

In a two-year feeding assay, male Osborne-Mendel rats (12/dose) were administered 0.25, 0.5 or 1.0% CASRN 577-1-7 in the diet. No effect of the test substance on food intake was observed. Consumption of 1.0% test substance was associated with decreased weight gain. No other treatment-related effects were observed.

CASRN 577-11-7 salt showed no carcinogenicity potential in this assay.

Conclusion: The acute oral toxicity in rats and acute dermal toxicity in rabbits is low for the members of this category. CASRN 577-11-7 is irritating to rabbit skin and eye. Oral repeated exposures to CASRN 577-11-7 in rats showed effects on the gastrointestinal tract and low weight gain at 500 mg/kg-bw/day; the NOAEL for systemic toxicity was 250 mg/kg-bw/day. Oral repeated exposures to CASRN 2373-38-8 in male rats showed no effects at the highest dose tested; the NOAEL for systemic toxicity was 510 mg/kg-bw/day. Oral repeated exposures to CASRN 23386-52-9 in rats showed no effects at the highest dose tested; the NOAEL for systemic toxicity was 960 mg/kg-bw/day. An oral three-generation reproductive toxicity study with CASRN 577-11-7 in rats showed decreased food consumption and body weights in adult animals at 500 mg/kg-bw/day; the NOAEL for systemic toxicity was 100 mg/kg-bw/day. In the same study, pup weights were decreased and there was an effect on lactation at 500 mg/kg-bw/day; the NOAEL for reproductive/developmental toxicity was 100 mg/kg-bw/day. An oral prenatal developmental toxicity study with CASRN 577-11-7 in rats showed reduced body weight gains in the dams and a significant increase in fetal resorptions and percentage of externally malformed fetuses at 1000 mg/kg-bw/day; the NOAEL for maternal and developmental toxicity was 500 mg/kg-bw/day. CASRN 577-11-7 did not show mutagenic potential in bacterial cells nor did it induce chromosomal aberrations in mammalian cells in vitro. CASRN 577-11-7 did not show carcinogenic potential in rats.

Table 4. Summary of Human Health Data			
Endpoints	Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)	Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)	Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	2000 – 4200 (rat) 2643 (mouse)	1750 (rat)	3540 (rat)
Acute Dermal Toxicity Rabbit LD ₅₀ (mg/kg-bw)	> 10,000	4000	> 5000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	(rat) NOAEL = Not established (16-wk) LOAEL ~ 2000 (rat, 16-wk) NOAEL ~ 250 (26-wk) LOAEL ~ 500 (26-wk) (dog) NOAEL = 30 (1-year)	(rat) NOAEL = 510 (hdt, 32-d)	(rat) NOAEL = 960 (hdt, 32-d)
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day) Systemic Toxicity	NOAEL ~ 100 LOAEL ~ 500	No Data NOAEL ~ 100 LOAEL ~ 500	No Data NOAEL ~ 100 LOAEL ~ 500
Reproductive Toxicity	NOAEL ~ 100 LOAEL ~ 500	NOAEL ~ 100 LOAEL ~ 500 (RA)	NOAEL ~ 100 LOAEL ~ 500 (RA)
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day) Maternal Toxicity	NOAEL ~ 500 LOAEL ~ 1000	No Data NOAEL ~ 500 LOAEL ~ 1000	No Data NOAEL ~ 500 LOAEL ~ 1000
Developmental Toxicity	NOAEL ~ 500 LOAEL ~ 1000	NOAEL ~ 500 LOAEL ~ 1000 (RA)	NOAEL ~ 500 LOAEL ~ 1000 (RA)
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative	No Data Negative (RA)	No Data Negative (RA)
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative	No Data Negative (RA)	No Data Negative (RA)

Table 4. Summary of Human Health Data			
Endpoints	Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)	Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)	Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)
Additional Information			
Skin Irritation	Moderate	—**	—**
Eye Irritation	Mild to Severe	—**	—**
Carcinogenicity	Negative in rats	—**	—**

Measured data in bold text; (RA) = Read Across; hdt = highest dose tested; —** Indicates endpoint is not necessary for this chemical

4 Hazards 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

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

(1) Bluegills (*Lepomis macrochirus*; 10/concentration) were exposed to CASRN 577-11-7 at nominal concentrations of 32, 42, 56, 75 and 100 mg/L under static conditions for 96 hours. All solutions had undissolved test substance present from time zero, which was still present at 56, 75, and 100 mg/L after 24 hours. By 24 hours, 100% mortality was observed in the 56, 75 and 100 mg/L tanks. Mortality (100%) was observed at 42 mg/L after 96 hours.

96-h LC₅₀ = 37 mg/L

(2) Rainbow trout (*Salmo gairdneri*; 10/concentration) were exposed to CASRN 577-11-7 at nominal concentrations of 10, 20, 40 and 80 mg/L under static conditions for 96 hours. All fish exposed to 40 or 80 mg/L died within 24 hours of exposure.

96-h LC₅₀ = 28 mg/L

(3) Rainbow trout (*Oncorhynchus mykiss*; 10/concentration) were exposed to CASRN 577-11-7 at nominal concentrations of 0, 6.25, 12.5, 25, 50 and 100 mg/L under static conditions for 96 hours. At 96 hours, no mortality was observed up to 25 mg/L, where 20% of fish died. All fish exposed to 50 mg/L and higher concentrations died within an hour of exposure.

96-h LC₅₀ = 28 mg/L

Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)

(1) Rainbow trout (*Oncorhynchus mykiss*) were exposed to CASRN 2373-38-8 at nominal concentrations of 0, 250, 500, 1000, 2000 and 4000 mg/L under static conditions for 96 hours.

At 96 hours, no mortality was observed up to 1000 mg/L, where 10% of fish died. The mortalities at 96 hours for fish exposed to 2000 and 4000 ppm were 100 percent; most of these deaths occurred within 24 hours.

96-h LC₅₀ = 1200 mg/L

(2) Bluegills (*Lepomis macrochirus*; 10/concentration) were exposed to CASRN 2373-38-8 at nominal concentrations of 0, 100, 180, 320, 560 and 1000 mg/L under static conditions for 96 hours. All solutions in the range of 100 – 1000 mg/L were cloudy at 48 – 96 hours. Mortality (10%) was only observed at 1000 mg/L after 96 hours.

96-h LC₅₀ > 1000 mg/L

Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)

Bluegills (*Lepomis macrochirus*; 10/concentration) were exposed to CASRN 23386-52-9 at nominal concentrations of 0, 240, 320, 420, 560, 750 and 1000 mg/L under static conditions for 96 hours. All solutions in the range of 100 – 1000 mg/L were cloudy at 48 – 96 hours; 1000 mg/L was cloudy at 24 hours. No mortalities were observed up to 320 mg/L. Mortalities at 48 and 96 hours for fish exposed to 420, 560, 750 and 1000 mg/L were 20, 90, and 100% and 100%, respectively.

96-h EC₅₀ = 470 mg/L

Acute Toxicity to Aquatic Invertebrates

Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)

Daphnia magna (20/concentration) were exposed to CASRN 577-11-7 nominal concentrations of 0, 5, 10, 20, 40 and 80 mg/L under static conditions for 48 hours. At 48 hours, mortality was observed at 20 mg/L (5%), 40 mg/L (60%) and 80 mg/L (100%).

48-h EC₅₀ = 36.2 mg/L

Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)

Daphnia magna (20/concentration) were exposed to CASRN 23386-52-9 at measured concentrations of 0, 8.1, 27, 90, 300 and 1000 mg/L under static conditions for 48 hours. At 48 hours, immobility was observed at 300 mg/L (15%). At 24 hours, there was 100% immobilization of the 1000 mg/L group. Individual treatment solutions were prepared as water accommodated fractions (WAFs).

48-h EC₅₀ = 457 mg/L

Toxicity to Aquatic Plants

The only submitted data for acute toxicity to green algae are for CASRN 23386-52-9 and indicate no effects on growth or growth rate. In its comments on the original test plan (dated February 14, 2001), EPA suggested that the sponsor conduct an algal toxicity study on CASRN 577-11-7 because this chemical is the most lipophilic in the category. In response, the sponsor provided that testing was not needed because: (1) CASRN 577-11-7 has a consistent 10-fold greater toxicity to fish, daphnia and terrestrial plants than CASRN 23386-52-9 and (2) the algal toxicity for CASRN 577-11-7 can thus be estimated (up to greater than 100 mg/L). EPA agrees

that the available toxicity data for fish and daphnia for CASRN 577-11-7 and algal toxicity data on CASRN 23386-52-9 show low toxicity. Furthermore, EPA notes that because green algae is the least sensitive species for the anionic surfactant chemical class, algal toxicity for CASRN 577-11-7 can reasonably be estimated to be in a similar range as that for fish and daphnia for that chemical. Therefore, although its reasoning is different, EPA agrees with the conclusion that algal toxicity testing is not a data gap under the HPV Challenge Program.

Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)

Pseudokirchneriella subcapitata were exposed to CASRN 23386-52-9 as Water Accommodated Fractions (WAFs) under static conditions for 96 hours. The loading rates were 0, 8.1, 27, 90, 300 or 1000 mg/L. The effect observed was stimulatory instead of inhibitory and no EC₅₀ or NOEL could be determined. Incubation for 72 hours stimulated growth by 35.1, 44.1 and 20.2% (64.5, 57.8 and 38.2% at 96 hours), corresponding to 8.1, 90 and 300 mg/L respectively.

96-h EC₅₀ > 1000 mg/L (growth was stimulated rather than inhibited at concentrations up to 100 mg/L)

Conclusion: The measured 96-hour LC₅₀ for the sulfosuccinates category members for fish ranged from 28 to 1200 mg/L, the measured 48-hour EC₅₀ for aquatic invertebrates ranged from 36.2 to 457 mg/L, and for aquatic plants the 96-hour EC₅₀ > 1000 mg/L (concentrations of up to and > 300 mg/L stimulated growth).

Table 5. Summary of Environmental Effects – Aquatic Toxicity Data

Endpoints	Succinic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (CASRN 577-11-7)	Succinic acid, sulfo-, 1,4-bis(1,3-dimethylbutyl)ester, sodium salt (CASRN 2373-38-8)	Succinic acid, sulfo-, 1,4-bis(dicyclohexyl)ester, sodium salt (CASRN 23386-52-9)
Fish 96-h LC₅₀ (mg/L)	28 (m) 37 (m)	> 1000 (m) 1200 (m)	470 (m)
Invertebrate 48-h EC₅₀ (mg/L)	36.2 (m)	No Data 36.2 (RA)	457 (m)
Alga 96-h EC₅₀ (mg/L)	No Data >1000 mg/L (RA)	No Data >1000 mg/L (RA)	Growth stimulated (96-h) (m) > 1000 mg/L

(m) = measured data (i.e., derived from testing); (e) = estimated data (i.e., derived from modeling); (RA) = Read Across