

## SCREENING-LEVEL HAZARD CHARACTERIZATION Sorbitan Esters Category

### SPONSORED CHEMICALS (See Section 1)

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

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

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

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial

---

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

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

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

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.

<b>Chemical Abstract Service Registry Number (CASRN)</b>	1338-39-2 1338-41-6 1338-43-8 26266-58-0 8007-43-0 68514-36-9
<b>Chemical Abstract Index Name</b>	See Section 1
<b>Structural Formula</b>	See Section 1
<b>Summary</b>	
<p>The Sorbitan Esters category is comprised of six substances; four are monoesters, one is a diester and one is a triester. All category members are liquids except for CASRN 1338-41-6, which is a solid. Members of the Sorbitan Esters category have negligible vapor pressures and are dispersible in water based on their respective structures and commercial uses. These substances are expected to have low mobility in soil with the exception of two category members, CASRN 1338-41-6 and CASRN 1338-43-8, which are expected to have high and moderate mobility, respectively. Volatilization is considered low for this category based on the estimated Henry's Law constants. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate to rapid; however, this is not expected to be an important environmental fate process since these substances are not expected to exist in the vapor phase in the atmosphere. Members of the Sorbitan Esters category are expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute oral toxicity of the Sorbitan Esters category is low in rats. A 13-week oral repeated-dose toxicity study with CASRN 1338-39-2 in rats showed decreased body weight and significantly increased relative brain and kidney weights (both sexes) at or above 2200 mg/kg-bw/day; a NOAEL for systemic toxicity is not established. A 16-week dietary study with CASRN 1338-43-8 revealed changes in clinical chemistry (significantly decreased protein/albumin and urea levels) in males treated at 3100 mg/kg-bw/day and renal effects (increased relative kidney weight, dilatation and vacuolation of proximal convoluted tubule) in females treated at 3700 mg/kg-bw/day; the NOAEL for systemic toxicity is 1850 mg/kg-bw/day. An 80-week repeated-dose toxicity study with CASRN 1338-41-6 in mice showed enlarged kidneys and nephrosis following dietary exposure at 5200 mg/kg-bw/day; the NOAEL for systemic toxicity is 2600 mg/kg-bw/day. No effects on reproductive organs (testes, ovaries, uterus) were noted in these studies. A combined, repeated-dose/reproductive/developmental toxicity screening test with CASRN 1338-41-6 in rats showed negative effects on reproductive performance, fetal growth and lactation in three successive generations of dams treated at 10,000 mg/kg-bw/day. A dose-related trend toward increased pup mortality was also reported at this dose; the NOAEL for maternal, developmental and reproductive toxicity is 5000 mg/kg-bw/day. No adequate gene mutation studies were available; however, CASRN 1338-41-6 induced chromosomal aberrations in Chinese hamster lung cells when tested <i>in vitro</i>.</p> <p>No adequate aquatic toxicity data are available for the Sorbitan Esters category. Acute toxicity to fish and aquatic invertebrates, toxicity to aquatic plants, and gene mutation endpoints were identified as data gaps under the HPV Challenge Program.</p>	

The sponsor, the American Chemistry Council Aliphatic Esters Panel, submitted a Test Plan and Robust Summaries to EPA for the Sorbitan Esters category on November 26, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on January 22, 2004 (<http://www.epa.gov/oppt/chemrtk/pubs/summaries/alipestr/c13466tc.htm>). Robust summaries for the proposed analog, sorbitan tetraester with C6-C10 fatty acids (CASRN 228573-47-5), were also submitted. EPA comments on the original submission were posted to the website on February 20, 2007. Public comments were also received and posted to the website. The Sorbitan Esters category consists of the following six substances:

Sorbitan, monolaurate	CASRN 1338-39-2
Sorbitan, monostearate	CASRN 1338-41-6
Sorbitan, monooleate	CASRN 1338-43-8
Sorbitan, trioleate	CASRN 26266-58-0
Sorbitan, sesquioleate	CASRN 8007-43-0
Fatty acids, coco, monoesters with sorbitan	CASRN 68154-36-9

### **Category Justification**

The sponsor's rationale for grouping substances in the Sorbitan Esters category is based on proposed similarities in chemical structure. Category members share a common structural motif which consists of a series of analogous esters comprised of sorbitan and natural fatty acids; however, they exhibit differences in chain length (C12 – C18), degree of esterification and extent of unsaturation associated with carboxylic acid functional groups. These structural differences may reasonably be expected to influence physicochemical properties (partition coefficient, water solubility), environmental fate and toxicity endpoints. Although insufficient human health and ecological effects data are available to fully support the sponsor's claim of chemical similarity, overall, this category grouping appears justified. EPA accepts the sponsor's proposed read-across approach for human health effects, based on structural homology among category members and comparable effects on target organs.

### **Justification for Supporting Chemicals**

The sponsor proposed use of sorbitan, fatty acids, C6 – 10, tetraester (CASRN 228573-47-5) as a supporting chemical for the Sorbitan Esters category based on similarities in chemical structure. EPA does not accept this justification, as the proposed supporting chemical cannot adequately represent the full range of water solubility and log  $K_{ow}$  values estimated for members of this category. In addition, CASRN 228573-47-5, unlike other members of the Sorbitan Esters category, has no free hydroxyl groups. EPA has stated that additional data are needed to demonstrate chemical similarity. The sponsor has not provided this information; therefore, data for the supporting chemical, CASRN 228573-47-5 are not included in this hazard characterization.

## 1. Chemical Identity

### 1.1 Identification and Purity

The following description is taken from the 2003 Test Plan:

The Sorbitan Esters category consists of six members that are mono-, di- or triesters ranging in carbon number from C18 to C60. Chemically, the sorbitan esters may be regarded as carbohydrate-derived esters with ester linkage(s) to the hydroxy group(s) of sorbitan. Four of the substances in this category (CASRNs 1338-39-2, 1338-41-6, 1338-43-8 and 68154-36-9) are monoester derivatives of sorbitan and two (CASRNs 8007-43-0 and 26266-58-0), contain multiple ester linkages, which are expected to increase lipophilicity. Chemical purity was not indicated in the Robust Summaries. Chemical structures for sponsored substances in the Sorbitan Esters category are provided in Table 1.

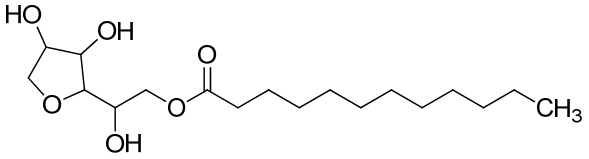
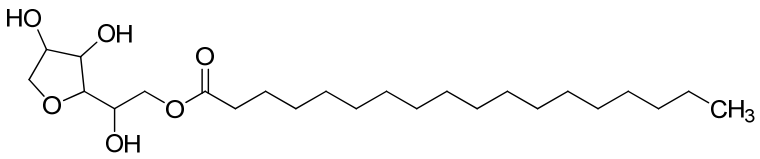
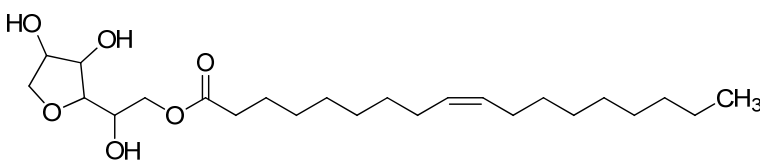
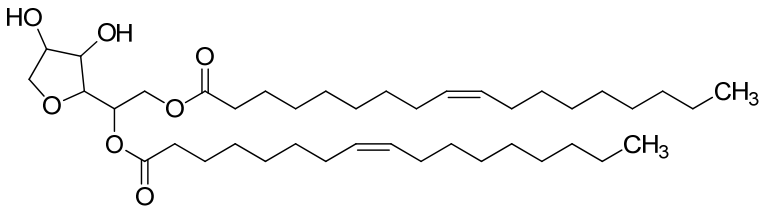
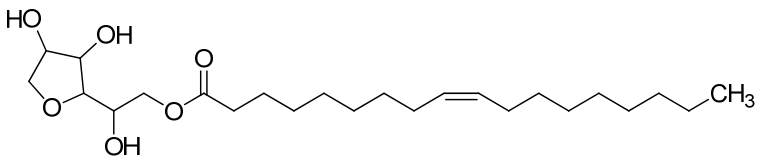
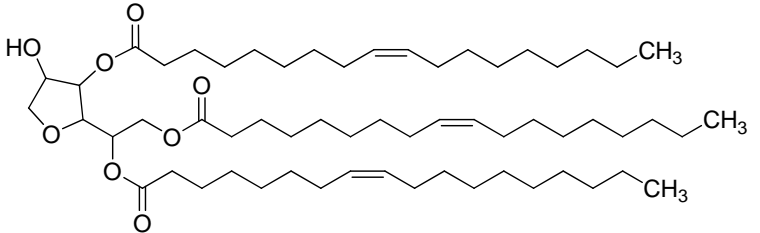
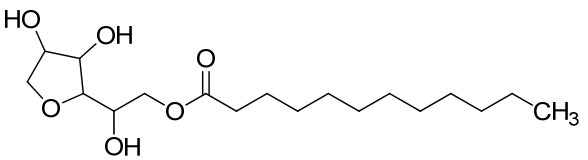
Table 1. Sponsored Chemicals in Sorbitan Esters Category		
Chemical Name	CASRN	Structure
Sorbitan, monododecanoate	1338-39-2	
Sorbitan, mono-octadecanoate	1338-41-6	
Sorbitan, mono-(9Z)-9-octadecenoate	1338-43-8	

Table 1. Sponsored Chemicals in Sorbitan Esters Category		
Chemical Name	CASRN	Structure
<b>Sorbitan, (9Z)-9-octadecenoate (2:3)</b>	<b>8007-43-0</b>	 <p>The sponsor indicates dioleic ester is ~50% of the mixture<sup>1</sup></p>
		 <p>The sponsor indicates monooleic ester is ~50% of the mixture<sup>1</sup></p>
<b>Sorbitan, tri-(9Z)-9-octadecenoate</b>	<b>26266-58-0</b>	
<b>Fatty acids, coco, monoesters with sorbitan</b>	<b>68154-36-9</b>	 <p>Representative structure<sup>2</sup></p>

<sup>1</sup> Sorbitan, (9Z)-9-octadecenoate (2:3) is a mixture of the monoester and diester of oleic acid and sorbitan. The ratio is specified by the sponsor as 1:1 or from the systematic name (2:3) indicating 1.5 times oleic acid to sorbitan. Data for the monoester, sorbitan, mono-(9Z)-9-octadecenoate (CASRN 1338-43-8) is listed in a separate column as it is also a sponsored chemical in the sorbitan esters.

<sup>2</sup> The sponsor specifies that C12 and C14 fatty acid esters of sorbitan are the dominant components of the test substance. Fatty acids, coco, monoesters with sorbitan (CASRN 68154-36-9) but does not specify an exact ratio. The typical fatty acid composition of coconut oil (CASRN 8001-31-8) is (12:0, lauric; 48.5%), (14:0, myristic; 17.6%), (16:0, palmitic; 8.4%), (8:0, caprylic; 8%), (18:1, oleic, 6.5%), (10:0, capric, 6.4%), (18:0, stearic, 2.5%), (18:2, linoleic, 1.5%), (6:0, caproic, 0.5%), and (20:0, arachidic, 0.1%). The representative structure shown in the appendix (sorbitan, monododecanoate CASRN 1338-39-2) is the major component of the mixture since it is the monoester of lauric acid. As cited in Hasenhuettl, G. L. 2005. Fats and Fatty Oil. In: Kirk-Othmer Encyclopedia of Chemical Technology. Volume 10. John Wiley & Sons, Inc.

## 1.2 Physical-Chemical Properties

The physical-chemical properties of the Sorbitan Esters category are summarized in Table 2. This category contains solids and liquids with negligible vapor pressures; these substances are expected to be dispersible in water based on structure and use as surfactants and emulsifiers.

## 2. General Information on Exposure

### 2.1 Production Volume and Use Pattern

The Sorbitan Esters Category chemicals had aggregated production and/or import volume in the United States between 23 and 130 million pounds during calendar year 2005.

- CASRN 1338-39-2: 1 to <10 million pounds;
- CASRN 1338-41-6: 10 to <50 million pounds;
- CASRN 1338-43-8: 10 to <50 million pounds;
- CASRN 8007-43-0: 1 to <10 million pounds; and
- CASRN 26266-58-0: 1 to <10 million pounds.

CASRN 68154-36-9 was not reported in the 2006 IUR.

CASRN 1338-39-2:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include intermediates. Commercial and consumer uses were claimed confidential.

CASRN 1338-41-6:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include surface active agents. Commercial and consumer uses were claimed confidential.

CASRN 1338-43-8:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as intermediates; and other basic organic chemical manufacturing as processing aid, not otherwise listed. Non-confidential commercial and consumer uses of this chemical include fabrics, textiles and apparel.

CASRN 8007-43-0:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include leather and hide tanning and finishing as processing aid, not otherwise listed. Non-confidential commercial and consumer uses of this chemical include leather products.

CASRN 26266-58-0:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as intermediates and surface active agents; and synthetic dye and pigment manufacturing as surface active agents. Commercial and consumer uses were claimed confidential.

**Table 2. Physical-Chemical Properties of the Sorbitan Esters of the Aliphatic Esters Category<sup>1,2</sup>**

Property	Sorbitan, monododecanoate	Sorbitan, mono-octadecanoate	Sorbitan, mono-(9Z)-9-octadecenoate	Sorbitan, (9Z)-9-octadecenoate (2:3) <sup>3</sup>	Sorbitan, tri-(9Z)-9-octadecenoate	Fatty acids, coco, monoesters with sorbitan <sup>4</sup>
CASRN	<b>1338-39-2</b>	<b>1338-41-6</b>	<b>1338-43-8</b>	<b>8007-43-0</b>	<b>26266-58-0</b>	<b>68154-36-9</b>
Molecular Wt	346.46	430.62	428.60	679.02 (diester)	957.49	346.46 (typical for C12) <sup>4</sup>
Physical State	Liquid, yellow <sup>5</sup>	Solid; white to tan waxy; flakes <sup>6</sup>	Liquid, yellow oil <sup>5</sup>	Viscous liquid, light yellow <sup>7</sup>	Viscous liquid, clear dark brown <sup>7</sup>	Liquid (based on CASRN 1338-39-2)
Melting Point	<25°C (liquid)	49–65°C (measured) <sup>5</sup>	0–10°C (measured) <sup>8</sup>	<25°C (liquid)	<25°C (liquid)	<25°C (liquid)
Boiling Point	>300°C (est.) <sup>9</sup>	>300°C (est.) <sup>9</sup>	>300°C (est.) <sup>9</sup>	>300°C (diester, est.) <sup>9</sup>	>300°C (est.) <sup>9</sup>	>300°C (est.) <sup>9</sup>
Vapor Pressure	<1.0×10 <sup>-10</sup> (est.) <sup>9</sup>	<1.0×10 <sup>-10</sup> (estimated) <sup>9</sup>	<1.0×10 <sup>-10</sup> (est.) <sup>9</sup>	<1.0×10 <sup>-10</sup> (diester est) <sup>9</sup>	<1.0×10 <sup>-10</sup> (est.) <sup>9</sup>	<1.0×10 <sup>-10</sup> (estimated) <sup>9</sup>
Water Solubility	Dispersible	Dispersible	Dispersible	Dispersible	Dispersible	Dispersible
Dissociation Constant (pK <sub>a</sub> )	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Henry's Law Constant	<1.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (est.) <sup>9</sup>	<1.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (est.) <sup>9</sup>	<1.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (est.) <sup>9</sup>	<1.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (diester, est.) <sup>9</sup>	<1.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (est.) <sup>9</sup>	<1.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (est.) <sup>9</sup>
Log K <sub>ow</sub>	Not applicable due to dispersibility <sup>2</sup>	Not applicable due to dispersibility <sup>2</sup>	Not applicable due to dispersibility <sup>2</sup>	Not applicable due to dispersibility <sup>2</sup>	Not applicable due to dispersibility <sup>2</sup>	Not applicable due to dispersibility <sup>2</sup>

<sup>1</sup> American Chemistry Council, Aliphatic Esters Panel. November 26, 2003. Revised Robust Summary for the Sorbitan Esters of the Aliphatic Esters Category Chemicals. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm> as of April 30, 2010.

<sup>2</sup> The Sorbitan Esters category are large molecules considered non-ionic surfactants and have structures that contain a hydrophilic, polar head (sorbital) and a hydrophobic, non-polar tail (fatty acids). Chemical properties of these substances do not estimate well due to their potential to form micelles in aqueous environments, which cannot be accounted for in the estimation method. Measuring or estimating water solubility, log K<sub>ow</sub>, and BCF/BAF is difficult, as these substances tend to accumulate at the interface between hydrophobic and hydrophilic phases. As cited in Boethling, R.S., Mackay, D. 2000. Surface-active chemicals. In: Handbook of Property Estimation Methods for Chemicals. pp.419-445.

<sup>3</sup> Sorbitan, (9Z)-9-octadecenoate (2:3) is a mixture of the monoester and diester of oleic acid and sorbitan. The ratio is specified by the sponsor as 1:1 molar ratio or from the systematic name (2:3) indicating 1.5 times oleic acid to 1 mole sorbitan. Data for the monoester, sorbitan, mono-(9Z)-9-octadecenoate (CASRN 1338-43-8) is listed in a separate column as it is also a sponsored chemical in the sorbitan esters.

<sup>4</sup> The sponsor specifies that C12 and C14 fatty acid esters of sorbitan are the dominant components of the mixture fatty acids, coco, monoesters with sorbitan (CASRN 68154-36-9) but does not specify an exact ratio. The typical fatty acid composition of coconut oil (CASRN 8001-31-8) is (12:0, lauric; 48.5%), (14:0, myristic; 17.6%), (16:0, palmitic; 8.4%), (8:0, caprylic; 8%), (18:1, oleic, 6.5%), (10:0, capric, 6.4%), (18:0, stearic, 2.5%), (18:2, linoleic, 1.5%), (6:0, caproic, 0.5%), and (20:0, arachidic, 0.1%). The representative structure shown in the appendix (sorbitan, monododecanoate, CASRN 1338-39-2) is the major component of the mixture since it is the monoester of lauric acid. As cited in Hasenhuettl, G. L. 1997. Fats and fatty oil. In: Kirk-Othmer Encyclopedia of Chemical Technology. Volume 10. John Wiley & Sons, Inc.

<sup>5</sup> Lide, D.R. 2008. CRC Handbook of Chemistry and Physics. 89<sup>th</sup> edition. CRC Press.

<sup>6</sup> Ash, M.; Ash, I. 2000. Handbook of Individual Surfactants. 3<sup>rd</sup> edition, Volume 2. Synapse Information Resources, Endicott, NY.

<sup>7</sup> Aldrich Chemical Company MSDS: Sorbitan sesquioleate, CASRN 8007-43-0 (<http://www.sigmaaldrich.com/catalog/AdvancedSearchPage.do>) Available as of April 30, 2010.

<sup>8</sup> IUCILID (International Uniform Chemical Information Database) Available online from: <http://www.inchem.org/> as of May 4, 2010.

<sup>9</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. EPA, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of April 30, 2010.

## 2.2 Environmental Exposure and Fate

The sorbitan esters are expected to have low mobility in soil with the exception of two members, CASRN 1338-41-6 and CASRN 1338-43-8 which are expected to have high and moderate mobility, respectively. Experimental biodegradation data were available for three members of the sorbitan esters all of which indicated these substances will readily biodegrade. CASRN 1338-39-2 was readily biodegradable achieving 57% of its theoretical biochemical oxygen demand (BOD) over a 14-day period using the modified MITI test (OECD 301C). CASRN 1338-41-6 was also readily biodegradable achieving 75–80% of its theoretical BOD over a 28-day period using the modified MITI test (OECD 301C). CASRN 1338-43-8 was readily biodegradable, achieving 58% of its theoretical BOD over a 28-day period using the modified MITI test (OECD 301C). The weight of evidence from these experimental data suggests that all of the members of the sorbitan esters category are readily biodegradable. Volatilization of all substances in this category is considered low based on the estimated Henry's Law constants. The rate of hydrolysis is considered negligible for all compounds based on estimated rates of ester hydrolysis at pH 7. The rate of atmospheric photooxidation is considered moderate to rapid for all members of the Sorbitan Esters category; however, this is not expected to be an important environmental fate process since these substances are not expected to exist in the vapor phase in the atmosphere. Members of this category are expected to have low persistence (P1) and low bioaccumulation potential (B1). The environmental fate properties are provided in Table 3.

Property	Sorbitan, monododecanoate	Sorbitan, mono-octadecanoate	Sorbitan, mono-(9Z)-9-octadecenoate	Sorbitan, (9Z)-9-octadecenoate (2:3) <sup>3</sup>	Sorbitan, tri-(9Z)-9-octadecenoate	Fatty acids, coco, monoesters w/sorbitan <sup>4</sup>
CASRN	1338-39-2	1338-41-6	1338-43-8	8007-43-0	26266-58-0	68154-36-9
Photodegradation Half-life	2.4 hours (est.) <sup>5</sup>	2.0 hours (estimated) <sup>5</sup>	1.1 hours (estimated) <sup>5</sup>	0.7 hours (diester, estimated) <sup>5</sup>	0.5 hours (estimated) <sup>5</sup>	2.4 hours (estimated) <sup>5</sup>
Hydrolysis Half-life	14.1 years at pH 7 and 1.4 years at pH 8 (estimated) <sup>5</sup>	7.7 years at pH 7 and 282 days at pH 8 (estimated) <sup>5</sup>	7.7 years at pH 7 and 282 days at pH 8 (estimated) <sup>5</sup>	2.6 years at pH 7 and 96 days at pH 8 (estimated) <sup>5</sup>	2.6 years at pH 7 and 96 days at pH 8 (estimated) <sup>5</sup>	14.1 years (estimated) <sup>5</sup>
Biodegradation	57% biodeg. in 14 days (readily biodegradable) <sup>6</sup> ; 60% biodeg. in 28 days (not readily biodegradable)	75–80% biodegradation in 28 days (readily biodegradable) <sup>5</sup>	58% biodegradation in 14 days (readily biodegradable) <sup>6</sup> ; 62% biodegradation in 28 days (readily biodegradable)	No data	No data	No data
Bioaccumulation Factor	BAF = 6.2 (estimated) <sup>5</sup>	BAF = 27.5 (estimated) <sup>5</sup>	BAF = 36.4 (estimated) <sup>5</sup>	BAF = 0.9 (estimated) <sup>5</sup>	BAF = 0.9 (estimated) <sup>5</sup>	BAF = 6.2 (estimated) <sup>5</sup>
Log K <sub>oc</sub>	1.8 (estimated) <sup>5</sup>	3.4 (estimated) <sup>5</sup>	3.4 (estimated) <sup>5</sup>	6.7 (estimated) <sup>5</sup>	13.2 (estimated) <sup>5</sup>	1.8 (estimated) <sup>5</sup>
Fugacity (Level III Model) <sup>5</sup>						
Air (%)	<0.1	0.3	<0.1	<0.1	<0.1	<0.1
Water (%)	21.6	22.3	23.7	24.4	17.7	21.6
Soil (%)	78.3	75.8	74.4	75.6	82.3	78.3
Sediment (%)	<0.1	1.6	1.8	<0.1	<0.1	<0.1
Persistence <sup>7</sup>	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation <sup>7</sup>	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)

<sup>1</sup> American Chemistry Council, Aliphatic Esters Panel. November 26, 2003. Revised Robust Summary for the Sorbitan Esters of the Aliphatic Esters Category Chemicals. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm> as of April 30, 2010.

<sup>2</sup> The Sorbitan Esters category are large molecules considered non-ionic surfactants and have structures that contain a hydrophilic, polar head (sorbitan) and a hydrophobic, non-polar tail (fatty acids). Chemical properties of these substances do not estimate well due to their potential to form micelles in aqueous environments which cannot be accounted for in the estimation method. In particular, measuring or estimating water solubility, log K<sub>ow</sub>, and BCF/BAF is difficult because these substances tend to accumulate at the interface between the hydrophobic and hydrophilic phases.

<sup>3</sup> Sorbitan, (9Z)-9-octadecenoate (2:3) is a mixture of the monoester and diester of oleic acid and sorbitan. Sponsor specified a 1:1 molar ratio; the systematic name (2:3) indicates 1.5 times oleic acid to 1 mole sorbitan. Data for the monoester, sorbitan, mono-(9Z)-9-octadecenoate (CASRN 1338-43-8) is listed in a separate column as it is also a sponsored chemical in the sorbitan esters.

<sup>4</sup> The sponsor specifies that C12 and C14 fatty acid esters of sorbitan are the dominant components of the mixture fatty acids, coco, monoesters with sorbitan (CASRN 68154-36-9) but does not specify an exact ratio. The typical fatty acid composition of coconut oil (CASRN 8001-31-8) is (12:0, lauric; 48.5%), (14:0, myristic; 17.6%), (16:0, palmitic; 8.4%), (8:0, caprylic; 8%), (18:1, oleic, 6.5%), (10:0, capric, 6.4%), (18:0, stearic, 2.5%), (18:2, linoleic, 1.5%), (6:0, caproic, 0.5%), and (20:0, arachidic, 0.1%); The representative structure shown in the appendix (sorbitan, monododecanoate CASRN 1338-39-2) is the major component of the mixture since it is the monoester of lauric acid. As cited in Hasenhuettl, G. L. 1997. Fats and fatty oil. In: Kirk-Othmer Encyclopedia of Chemical Technology. Volume 10. John Wiley & Sons, Inc.

<sup>5</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. EPA, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuite.dll> as of April 30, 2010.

<sup>6</sup> 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](http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html) as of April 30, 2010.

<sup>7</sup> Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

### 3. Human Health Hazard

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*

##### *Sorbitan monostearate (CASRN 1338-41-6)*

Wistar rats (10/sex) were administered a single dose of CASRN 1338-41-6 (purity not specified) via gavage at 15,900 mg/kg and observed for 14 days. No mortalities were observed.

**LD<sub>50</sub> > 15,900 mg/kg**

##### *Sorbitan monooleate (CASRN 1338-43-8)*

Wistar rats (10/sex) were administered CASRN 1338-43-8 (in corn oil) via oral gavage at 39,800 mg/kg and observed for 14 days. No mortalities were observed.

**LD<sub>50</sub> > 39,800 mg/kg**

##### *Sorbitan sesquioleate (CASRN 8007-43-0)*

Wistar rats (10/sex) were administered CASRN 8007-43-0 (in corn oil) via oral gavage at 39,800 mg/kg and observed for 14 days. No mortalities were observed.

**LD<sub>50</sub> > 39,800 mg/kg**

##### *Sorbitan trioleate (CASRN 26266-58-0)*

Wistar rats (10/sex) were administered CASRN 26266-58-0 (in corn oil) via oral gavage at 39,800 mg/kg and observed for 14 days following dosing. No mortalities were observed.

**LD<sub>50</sub> > 39,800 mg/kg**

#### *Repeated-Dose Toxicity*

##### *Sorbitan monolaurate (CASRN 1338-39-2)*

Wistar rats (15/sex/dose) were administered CASRN 1338-39-2 (purity not specified) via the diet at 0, 2.5, 5 and 10% (~ 0, 2100, 4200 or 8000 mg/kg-bw/day for males and 0, 2300, 4500 or 8400 mg/kg-bw/day for females) for 13 weeks. There were no mortalities. Dose-related decreases in body weight and significant increases in relative brain and kidney weights were observed in males and females at all doses tested. Hematological changes (decreased hematocrit and hemoglobin concentrations) and increases in relative liver weight were seen at or above 5%; increases in relative heart weight and small intestine weight were seen at 10%. Liver histopathology (steatosis) was observed at the highest dose (both sexes).

**LOAEL ~ 2200 mg/kg-bw/day** (based on increased relative kidney and brain weights)

**NOAEL = Not established**

##### *Sorbitan monooleate (CASRN 1338-43-8)*

Wistar rats (initially 15/sex/dose, then a second group of 10/sex/dose) were administered CASRN 1338-43-8 (purity not specified) via the diet at 0, 2.5, 5 or 10% (~ 0, 1700, 3100 or 6300

mg/kg-bw/day for males and ~ 0, 2000, 3700 or 6100 mg/kg-bw/day for females) for 16 weeks. There were no mortalities. Significantly decreased body weight and increased relative organ weights (brain, heart, liver/small intestine, and stomach/adrenals) were seen at 10% (both sexes). Significant increases in relative kidney weight were seen at all doses tested (both sexes). Changes in clinical chemistry (significantly decreased protein/albumin and urea levels) and renal effects (dilatation/vacuolation of proximal tubules) were observed in males and females, respectively at concentrations  $\geq 5\%$ . Hematological changes (significantly decreased hematocrit, hemoglobin and leukocyte counts) were seen in females treated at 10%.

**LOAEL ~ 3400 mg/kg-bw/day** (based on increased relative kidney weight, nephropathy, and clinical chemistry changes consistent with signs of kidney toxicity)

**NOAEL ~ 1850 mg/kg-bw/day**

#### ***Sorbitan monostearate (CASRN 1338-41-6)***

TO strain mice (48/sex/dose) were administered CASRN 1338-41-6 (purity not specified) via the diet at 0, 0.5, 2 or 4% (~ 0, 650, 2600 or 5200 mg/kg-bw/day, respectively) for 80 weeks. There were no treatment-related effects on mortality or body weight gain. Enlarged kidneys and an increased incidence of nephrosis were seen at 4% (both sexes). A significant decrease in total leukocyte count was also observed in females treated at 4%; however, study authors stated that this was as unlikely to be directly treatment-related.

**LOAEL ~ 5200 mg/kg-bw/day** (based on enlarged kidneys and nephrosis)

**NOAEL ~ 2600 mg/kg-bw/day**

#### ***Reproductive Toxicity***

##### ***Sorbitan monolaurate (CASRN 1338-92-2)***

In the 13-week oral repeated-dose toxicity study in Wistar rats described above, no histopathological effects were seen on male or female reproductive organs.

##### ***Sorbitan monooleate (CASRN 1338-43-8)***

In the 16-week oral repeated-dose toxicity study in Wistar rats described above, no histopathological effects were seen on male or female reproductive organs.

##### ***Sorbitan monostearate (CASRN 1338-41-6)***

Wistar rats (25 groups consisting of 12 males and 20 females/dose; F<sub>0</sub> generation) were administered CASRN 1338-41-6 (purity not specified) in the diet at 0, 5, 10 or 20% (~ 0, 2500, 5000 or 10,000 mg/kg-bw/day) for two years (spanning four generations). Matings in the F<sub>0</sub> generation were continued throughout the study. All first litter offspring were discarded at weaning. Ten rats per sex were selected from the second litters of the F<sub>1</sub> generation, then raised to maturity and mated. The second litters from the F<sub>2</sub> generation were also subjected to this feeding/breeding regimen. F<sub>3</sub> generation rats were treated similarly and raised to maturity for growth evaluation; however, these animals were not mated due to study termination (when F<sub>0</sub> rats reached two years on test). No effects on fertility, gestation, growth, lactation or mortality were noted in three successive generations following dietary exposure at doses  $\leq 10\%$ ; however, impaired lactation was seen in dams treated at the highest dose (as evidenced by decreased viability of newborn pups). The study authors attributed this outcome to laxative effects (perianal irritation) and possible neglect of offspring born to dams treated at this dose.

Reproductive performance and pregnancy rate generally tended to be lower in F<sub>2</sub> and F<sub>3</sub> generations treated at the highest dose. There was also a dose-related trend toward increased mortality in offspring born to treated dams. The study authors suggested that the observed decreases in fertility and viability of offspring born to dams treated at the highest dose may be related to decreased fat content in the treated diet (responses were improved by addition of neutral vegetable fat to the diet); however, no data were provided to support this claim.

**LOAEL (maternal toxicity) ~10,000 mg/kg-bw/day** (based on lactation and laxative effects)

**NOAEL (maternal toxicity) ~ 5,000 mg/kg-bw/day**

**LOAEL (reproductive toxicity) ~ 10,000 mg/kg-bw/day** (based on decreased reproductive performance and pregnancy rate)

**NOAEL (reproductive toxicity) ~ 5,000 mg/kg-bw/day**

### *Developmental Toxicity*

#### *Sorbitan monostearate (CASRN 1338-41-6)*

The three-generation reproductive toxicity study in Wistar rats described above showed no developmental effects in offspring born to dams treated at doses  $\geq$  5%. Decreased growth and viability (increased mortality) were noted in offspring born to dams treated at the highest dose; however, the study authors attributed this effect to decreased fat content in the diet (responses were improved by addition of neutral vegetable fat to the diet); however, no data were provided to support this claim.

**LOAEL (maternal) ~ 10,000 mg/kg-bw/day** (based on laxative effects and decreased viability of offspring)

**NOAEL (maternal) ~ 5,000 mg/kg-bw/day**

**LOAEL (developmental toxicity) ~ 10,000 mg/kg-bw/day** (based on decreased growth of offspring)

**NOAEL (developmental toxicity) ~ 5,000 mg/kg-bw/day**

### *Genetic Toxicity – Gene Mutation*

No adequate data were provided.

### *Genetic Toxicity -- Chromosomal Aberrations*

#### *In vitro*

Chinese hamster lung cells were exposed to CASRN 1338-41-6 (purity not specified; 0.5% carboxymethylcellulose sodium solution) at concentrations of ~ 0, 130, 250 or 500  $\mu$ g/mL in the absence and ~ 0, 1100, 2200 or 4300  $\mu$ g/mL in the presence of metabolic activation. Responses to positive and negative controls were not indicated. No evidence of cytotoxicity or precipitation was reported in this assay. Chromosomal aberrations occurred at all concentrations tested in the presence (but not the absence) of metabolic activation. Polyploidy was observed at all concentrations tested in the absence (but not the presence) of metabolic activation.

**CASRN 338-41-6 induced chromosomal aberrations in this assay.**

**Conclusion:** The acute oral toxicity of the Sorbitan Esters category is low in rats. A 13-week oral repeated-dose toxicity study with CASRN 1338-39-2 in rats showed decreased body weight and significantly increased relative brain and kidney weights (both sexes) at or above 2200 mg/kg-bw/day; a NOAEL for systemic toxicity is not established. A 16-week dietary study with CASRN 1338-43-8 revealed changes in clinical chemistry (significantly decreased protein/albumin and urea levels) in males treated at 3100 mg/kg-bw/day and renal effects (increased relative kidney weight, dilatation and vacuolation of proximal convoluted tubule) in females treated at 3700 mg/kg-bw/day; the NOAEL for systemic toxicity is 1850 mg/kg-bw/day. An 80-week repeated-dose toxicity study with CASRN 1338-41-6 in mice showed enlarged kidneys and nephrosis following dietary exposure at 5200 mg/kg-bw/day; the NOAEL for systemic toxicity is 2600 mg/kg-bw/day. No effects on reproductive organs (testes, ovaries, uterus) were noted in these studies. A combined, repeated-dose/reproductive/developmental toxicity screening test with CASRN 1338-41-6 in rats showed negative effects on reproductive performance, fetal growth and lactation in three successive generations of dams treated at 10,000 mg/kg-bw/day. A dose-related trend toward increased pup mortality was also reported at this dose; the NOAEL for maternal, developmental and reproductive toxicity is 5000 mg/kg-bw/day. No adequate gene mutation studies were available; however, CASRN 1338-41-6 induced chromosomal aberrations in Chinese hamster lung cells when tested *in vitro*.

<b>Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data</b>						
<b>Endpoints</b>	<b>Sorbitan, monododecanoate</b>	<b>Sorbitan, monooctadecanoate</b>	<b>Sorbitan, mono-(9Z)-9-octadecenoate</b>	<b>Sorbitan, (9Z)-9-octadecenoate (2:3)<sup>3</sup></b>	<b>Sorbitan, tri-(9Z)-9-octadecenoate</b>	<b>Fatty acids, coco, monoesters with sorbitan<sup>4</sup></b>
<b>CASRN</b>	<b>1338-39-2</b>	<b>1338-41-6</b>	<b>1338-43-8</b>	<b>8007-43-0</b>	<b>26266-58-0</b>	<b>68154-36-9</b>
<b>Acute Oral Toxicity LD<sub>50</sub> (mg/kg)</b>	No Data > 39,800 (RA)	<b>&gt; 15,900</b>	<b>&gt; 39,800</b>	<b>&gt; 39,800</b>	<b>&gt;39,800</b>	No Data > 39,800 (RA)
<b>Repeated-Dose Toxicity NOAEL/LOAEL Oral diet (mg/kg-bw/day)</b>	<b>LOAEL ~ 2200</b> NOAEL=Not established	<b>LOAEL (m) ~ 5200 (hdt)</b> <b>NOAEL (m) ~ 2600</b>	<b>LOAEL ~ 3400</b> <b>NOAEL ~ 1850</b>	No Data LOAEL ~ 3400 NOAEL ~ 1850 (RA)	No Data LOAEL ~ 3400 NOAEL ~ 1850 (RA)	No Data LOAEL ~ 3400 NOAEL ~ 1850 (RA)
<b>Reproductive Toxicity NOAEL/LOAEL Oral diet (mg/kg-bw/day)</b>	<b>No effects were seen following evaluation of reproductive organs in a 13-wk oral repeated-dose toxicity study in rats.</b>	<b>LOAEL ~ 10,000 (hdt)</b> <b>NOAEL ~ 5000</b>	<b>No effects were seen following evaluation of reproductive organs in a 16-wk oral repeated-dose toxicity study in rats.</b>	No Data LOAEL ~ 10,000 (hdt) NOAEL ~ 5000 (RA)	No Data LOAEL ~ 10,000 (hdt) NOAEL ~ 5000 (RA)	No Data LOAEL ~ 10,000 (hdt) NOAEL ~ 5000 (RA)
<b>Developmental Toxicity NOAEL/LOAEL Oral diet (mg/kg-bw/day)</b>	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)	<b>LOAEL ~ 10,000</b> <b>NOAEL ~ 5000</b>	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)
<b>Maternal/Developmental</b>	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)	<b>LOAEL ~ 10,000</b> <b>NOAEL ~ 5000</b>	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)	No Data LOAEL ~ 10,000 NOAEL ~ 5000 (RA)
<b>Genetic Toxicity – Gene Mutation <i>In vitro</i></b>	-	No Data	-	-	-	-
<b>Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i></b>	-	Positive	-	-	-	-

Measured data indicated in bold test; (RA) = Read Across; (hdt) = Highest Dose Tested; r = Rats; (m) = Mice; (-) = Endpoint not address

#### 4. Hazard to the Environment

No adequate aquatic toxicity data are available for the Sorbitan Esters category.

<b>Table 1. Summary of Physical-Chemical Properties and Environmental Fate Data</b>							
<b>Endpoints</b>	<b>Sorbitan, monolaurate (1338-39-2)</b>	<b>Fatty acids, coco, monoesters with sorbitan (68154-36-9)</b>	<b>Sorbitan monooleate (1338-43-8)</b>	<b>Sorbitan, monostearate (1338-41-6)</b>	<b>Sorbitan, sesquioleate (8007-43-0)</b>	<b>Sorbitan, trioleate (26266-58-0)</b>	<b>Sorbitan, fatty acids, C<sub>6-10</sub>, tetraester <i>Supporting Chemical</i> (228573-47-5)</b>
<b>Fish 96-h LC<sub>50</sub> (mg/L)</b>	<b>No Adequate Data</b>	No Data	<b>No Adequate Data</b>	No Data	No Data	No Data	<b>No Adequate Data*</b>
<b>Aquatic Invertebrates 48-h EC<sub>50</sub> (mg/L)</b>	No Data	No Data	No Data	No Data	No Data	No Data	<b>No Adequate Data*</b>
<b>Aquatic Plants 72-h EC<sub>50</sub> (mg/L) (growth) (biomass)</b>	No Data	No Data	No Data	No Data	No Data	No Data	<b>No Adequate Data*</b>
<b>Chronic Toxicity to Fish 21-day EC<sub>50</sub> (mg/L)</b>	No Data	No Data	No Data	No Data	No Data	No Data	No Data
<b>Chronic Toxicity to Invertebrates 21-day EC<sub>50</sub> (mg/L)</b>	No Data	No Data	No Data	No Data	No Data	No Data	No Data

(m) = measured data (i.e., derived from testing); (e) = estimated data (i.e., derived from modeling); (RA) = Read Across; \*= Toxicity value exceed the water solubility limit;

5. **References**

JETOC 1999. Information Sheet, Special Issue No. 4. Japan Chemical Industry Ecology-Toxicology & Information Center (JETOC), Japan. V+130 pp. (<http://www.jetoc.or.jp/>)