

SCREENING-LEVEL HAZARD CHARACTERIZATION

Glycol Esters Category

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, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

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>.

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.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p>SUBCATEGORY I <u>Sponsored Chemical</u> 111-60-4 67989-24-6</p> <p><u>Supporting Chemical</u> 71839-38-8 1323-39-3</p> <p>SUBCATEGORY II <u>Sponsored Chemical</u> 94-28-0 18268-70-7 68583-52-8 70729-68-9</p> <p><u>Supporting Chemical</u> 7434-40-4</p> <p>SUBCATEGORY III <u>Sponsored Chemical</u> 105-62-4 627-83-8 4222-50-4</p> <p><u>Supporting Chemical</u> 22788-19-8 68958-54-3</p>
<p>Chemical Abstract Index Name</p>	<p>SUBCATEGORY I <u>Sponsored Chemical</u> Octadecanoic acid, 2-hydroxyethyl ester 9-Octadecenoic acid (9Z)-, ester with 2,2-dimethyl-1,3-propanediol</p> <p><u>Supporting Chemical</u> Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol Octadecanoic acid, monoester with 1,2-propanediol</p> <p>SUBCATEGORY II <u>Sponsored Chemical</u> Hexanoic acid, 2-ethyl-, 1,1'-[1,2-ethanediylbis(oxy-2,1-ethanediyl)] ester Hexanoic acid, 2-ethyl-, oxybis(2,1-ethanediyl oxy-2,1-ethanediyl) ester Decanoic acid, mixed diesters with octanoic acid and triethylene glycol Heptanoic acid, 1,1'-[oxybis(2,1-ethanediyl oxy-2,1-ethanediyl)] ester</p> <p><u>Supporting Chemical</u> Heptanoic acid, 1,2-ethanediylbis(oxy-2,1-ethanediyl) ester</p>

	<p style="text-align: center;">SUBCATEGORY III</p> <p style="text-align: center;"><u>Sponsored Chemical</u></p> <p style="text-align: center;">9-Octadecenoic acid (9Z)-, 1,1'-(1-methyl-1,2-ethanediyl) ester Octadecanoic acid, 1,1'-(1,2-ethanediyl) ester 9-Octadecenoic acid (9Z)-, 1,1'-(2,2-dimethyl-1,3-propanediyl) ester</p> <p style="text-align: center;"><u>Supporting Chemical</u></p> <p style="text-align: center;">Dodecanoic acid, 1-methyl-1,2-ethanediyl ester Isooctadecanoic acid, 1-methyl-1,2-ethanediyl ester</p>
Structural Formula	See Section 1. 0
<p style="text-align: center;">Summary</p> <p>The glycol esters members of the aliphatic ester category are distinguished by all being esters of ethylene glycol or propylene glycol. The category is further divided into three subcategories. Subcategory I, Glycol Monoesters, is composed of three chemicals that are grouped together since both are hydroxyl alkyl monoesters of stearic or oleic acids. Subcategory II, Tri- and Tetraethylene Glycol Diesters, is composed of four chemicals that are grouped together with alkyl diesters bridged by either three or four repeating ethylene glycol units. Subcategory III, Ethylene and Propylene Glycol Esters, is composed of three chemicals grouped together as chemicals that are all diesters linked by either a single ethylene or propylene glycol unit. The substances of Subcategory I and II are either solids or liquids with negligible to low water solubility and negligible to low vapor pressure. The substances of Subcategory III are either solids or liquids with negligible water solubility and negligible vapor pressure. The glycol monoesters of Subcategory I are expected to have low mobility in soil. The tri- and tetraethylene glycol diesters of Subcategory II are expected to have low-to-moderate mobility in soil. The ethylene and propylene glycol esters of Subcategory III are expected to have low mobility in soil. Volatilization is low for Subcategories I and II and moderate for Subcategory III based on their Henry's Law constants; however, adsorption to suspended solids and sediment is expected to attenuate the rate of volatilization. The rate of hydrolysis is considered negligible for all members of the category. The rate of atmospheric photooxidation for Subcategories I, II and III 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. The overall weight of evidence suggests that the glycol esters members of the aliphatic ester category are all expected to have low persistence (P1) and low bioaccumulation potential (B1).</p>	

Human Health Hazard

Subcategory I: Glycol Monoesters

The acute oral toxicity for glycol monoesters is low based on testing of the subcategory member, CASRN 111-60-4, and the supporting chemical, CASRN 71839-38-8. Following repeated administration of CASRN 71839-38-8 via gavage for 28 days, male rats exhibited increased hyaline droplets and tubular basophilia in the kidneys at 1000 mg/kg-day; the NOAEL for systemic toxicity is 180 mg/kg-day. No reproductive/developmental toxicity data were provided for glycol monoesters. The supporting chemical, CASRN 71839-38-8, did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells *in vitro*.

Reproductive/developmental toxicity endpoint was identified as a data gap for Subcategory I: Glycol Monoesters under the HPV Challenge Program.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

The acute oral toxicity for tri- and tetraethylene glycol diesters is low based on testing of subcategory member, CASRN 70729-68-9. Following repeated administration of CASRN 70729-68-9 to rats via gavage for 28 days, increased leukocyte counts and aspartate transaminase activity in males and decreased alkaline phosphatase activity (both sexes) were seen at 1000 mg/kg-day, the only dose tested. No reproductive/developmental toxicity data were provided for tri- and tetraethylene glycol diesters. CASRN 70729-68-9 ester did not induce gene mutations in bacteria. No chromosomal aberration data were provided for tri- and tetraethylene glycol diesters. Members of the subcategory are predicted to be metabolized to triethylene glycol (CASRN 112-27-6) and tetraethylene glycol (CASRN 112-60-7), which can undergo further metabolism or conjugation into polar products that are either excreted or used as nutrients. Therefore, EPA considers the potential for reproductive and developmental toxicity of the metabolites, CASRN 112-27-6 and CASRN 112-60-7, to be low. These metabolites would also not likely induce *in vivo* genotoxicity. Therefore, EPA anticipates that no new information would be gained from further animal experimentation on subcategory II chemicals for the purposes of the HPV Challenge Program.

No data gaps were identified for Subcategory II: Tri- and Tetraethylene Glycol Diesters.

Subcategory III: Ethylene and Propylene Glycol Esters

The acute oral toxicity for ethylene and propylene glycol esters is low based on testing of subcategory member, CASRN 627-83-8. No repeated-dose, reproductive/developmental, gene mutation or chromosomal aberration data were provided for ethylene and propylene glycol esters. Based on physicochemical properties, absorption of the members of the subcategory is expected to be poor, resulting in limited toxicity. The low acute toxicity further supports their lack of mammalian toxicity. Therefore, EPA recommends no further testing of subcategory III for the purposes of the HPV Challenge Program.

No data gaps were identified for Subcategory III: Ethylene and Propylene Glycol Esters under the HPV Challenge Program.

Hazard to the Environment

Subcategory I: Glycol Monoesters

The Log K_{ow} values of the two subcategory members indicate that their potential to bioaccumulate is expected to be high. The subcategory member, CASRN 67989-24-6 and the supporting chemical, CASRN 71839-38-8, are not readily biodegradable, indicating that members of the glycol monoesters subcategory are expected to persist in the environment.

No adequate data were available to evaluate the potential acute hazard to fish, aquatic invertebrates and aquatic plants. Chronic toxicity testing is requested for the subcategory member CASRN 111-60-4 because of the Log K_{ow} value of 7.26.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

The Log K_{ow} value of one of the subcategory members, CASRN 68583-52-8 indicates that its potential to bioaccumulate is expected to be low. The Log K_{ow} values of the three other subcategory members (CASRNs 94-28-0, 18268-70-7, 68583-52-8) indicate that their potential to bioaccumulate is expected to be high. The supporting chemical, CASRN 7434-40-4 is not readily biodegradable, indicating that members of the tri- and tetraethylene glycol diesters subcategory are expected to persist in the environment.

No adequate data were submitted for the aquatic toxicity endpoints. Because the sponsored substances in this group have low Log K_{ow} values ranging from 2.86 to 6.73 (measured and estimated), the potential acute hazard to aquatic organisms cannot be estimated without experimental data.

Data gaps for acute toxicity to fish, acute toxicity to aquatic invertebrates, toxicity to aquatic plants and chronic aquatic toxicity endpoints were identified for Subcategory II: tri- and tetraethylene glycol diesters under the HPV Challenge Program.

Subcategory III: Ethylene and Propylene Glycol Esters

The Log K_{ow} values of the three subcategory members (CASRNs 105-62-4, 627-83-8, 42222-50-4) indicate that their potential to bioaccumulate is expected to be high. Biodegradation data for this subcategory are not available; however, based on data for a member of the glycol monoesters subcategory, which also contains a propylene glycol ester as a major component, the members of the ethylene and propylene glycol esters subcategory are expected to persist in the environment.

No data were available to evaluate the potential acute hazard to fish, aquatic invertebrates and aquatic plants. However, because the Log K_{ow} values for the members of this subcategory are estimated to be > 8 , the toxicity is expected to be no effects at saturation.

No data gaps were identified for Subcategory III: Ethylene and propylene glycol esters under the HPV Challenge Program.

The sponsor, The American Chemistry Council's (ACC) Aliphatic Esters Panel, submitted an original Test Plan and Robust Summaries to EPA for aliphatic esters dated December 20, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on February 20, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm>). EPA comments on the original submission were posted to the website on August 28, 2002. Public comments were also received and posted to the website. Upon review of the original submission, EPA identified problems in the organization and presentation of the data that were compounded by the poor documentation provided for both category components and supporting chemicals. EPA also remarked that the division of the category members into five subcategories did not support the grouping of the members under one category because there was no proposed use of data from one subcategory for use in another subcategory. In response to EPA's comments, the sponsor has divided the original aliphatic esters category into five separate category submissions: monoesters, diesters, glycol esters, sorbitan esters and polyol esters. The sponsor submitted a revised test plan and robust summaries for the glycol esters category, originally submitted as part of the larger aliphatic esters category, on December 24, 2003. EPA posted the submission on the ChemRTK website on March 25, 2004. EPA comments on the submission (specific to glycol esters) were posted to the website on August 22, 2006. This website also contains additional submissions and EPA comments for other aliphatic ester categories; however, these will not be considered for this hazard characterization. The glycol esters category is divided into three subcategories.

Category Justification

The grouping of proposed category members is based on the structural similarity of the ethylene, polyethylene and propylene glycol substructures and their adjoining fatty acid constituents. The sponsor claims that such structural similarities will result in "close commonalities in their physiochemical properties, chemical characteristics, and biological/toxicological activities." Although category members contain at least one glycol moiety and have at least one ester function, the structures differ in the length (C7 – C18) of the carboxylate chains and the number of glycol units in the alcohol portion (1, 3 or 4 units). These differences are anticipated to result in a range of properties, especially water solubility and octanol/water partition coefficient ($\log K_{ow}$), along with associated environmental fate and toxicological properties. However, the submitted data suggest that there is a pattern of values consistent with the structure of the esters. Therefore, grouping the members into a single category is supported.

Although the overall grouping of the sponsored chemicals is supported, the category members are divided into three subgroups based on differences in partition coefficients, water solubilities, molecular weights, substructural features and potential for differences in metabolism and toxicity. The three subgroups of the glycol ester category include glycol monoesters, tri- and tetraethylene glycol diesters, and ethylene and propylene glycol esters. Both the glycol monoesters and tri- and tetraethylene glycol diesters have $\log K_{ow}$ values that range between 2.8 and 8.4 and molecular weights < 500; however, the ethylene and propylene glycol esters have $\log K_{ow}$ values > 10 and molecular weights > 500. Therefore, EPA assessed the adequacy of aquatic toxicity endpoint data independently for the ethylene and propylene glycol esters. Glycol monoesters contain a hydroxyl group and are therefore structurally distinct from the tri- and

tetraethylene glycol diesters. Because of the hydroxyl function, the glycol monoesters may be metabolized differently than the tri- and tetraethylene glycol diesters. Therefore, EPA assessed the adequacy of health effects endpoint data and for aquatic toxicity independently for each of the three subgroups.

9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CASRN. 67989-24-6) has been included in the glycol monoesters subcategory since it contains a hydroxyl group in one of its components; however, the biodegradation data provided for this substance can be read across to the ethylene and propylene glycol diesters subcategory since it also contains a propylene glycol diester as a major component.

Human health hazard analysis of chemicals in subcategory II can be based on the fact that glycol esters will be metabolized (hydrolyzed) *in vivo* to the corresponding fatty acids and free glycol alcohols, (triethylene glycol, CASRN 112-27-6, and tetraethylene glycol, CASRN 112-60-7, chemicals in the Ethylene Glycols category in the OECD SIDS Program <http://webnet.oecd.org/hpv/ui/Search.aspx>). The free fatty acids and glycols can undergo further metabolism or conjugation to polar products that are either excreted or used as nutrients.

Justification for Supporting Chemicals

The structures of the sponsored chemicals and supporting chemicals are consistent in that all contain at least one glycol moiety and at least one ester function. Additionally, all supporting chemicals have structures and molecular weights that span a range that is similar to that of the sponsored chemicals within the relevant subcategories. The estimated physicochemical data provided for supporting chemicals represents a wide range of values; however, these values indicate that the esters will typically have low vapor pressures and water solubilities and high octanol/water partition coefficients. Thus, compositional/structural similarities, based on carbon number and number of carbon units, as well as available physicochemical data, support the justification of all five supporting chemicals to their assigned subcategories.

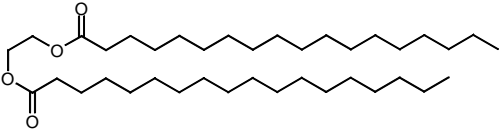
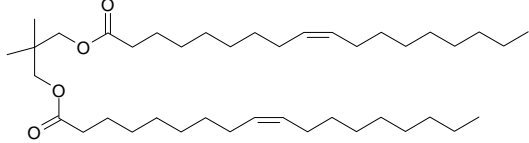
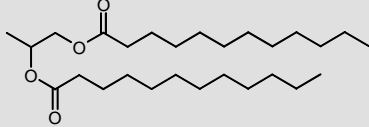
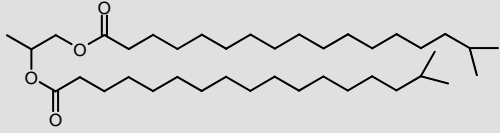
1. Chemical Identity

1.1 Identification and Purity

The following description is taken from the 2003 Test Plan and Robust Summary: The glycol esters category of the HPV aliphatic esters is comprised of aliphatic esters derived from a monocarboxylic acid (e.g., C6-C10 fatty acids, oleic, stearic and isostearic acids) and a dihydroxy alcohol (glycol or diol such as ethylene glycol, polyethylene glycol, propylene glycol, 2,2-dimethyl-1,3-propanediol). The purity, where mentioned, was 88% or greater.

Table 1 includes structures of the glycol esters and supporting chemicals included in the category.

Table 1. Chemical Structures for Glycol Esters		
CASRN	Chemical Name	Chemical Structure
Glycol Monoesters Subcategory		
111-60-4	Stearic acid, 2-hydroxyethyl ester	
67989-24-6 ¹	9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	<p>Major product (88%)</p> <p>Minor product (12%)</p>
71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol	
1323-39-3	Propylene glycol, monostearate	
Tri- and Tetraethylene Glycol Diesters Subcategory		
94-28-0	Hexanoic acid, 2-ethyl-, diester with triethylene glycol	
18268-70-7	Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	
68583-52-8	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	
70729-68-9	Heptanoic acid, oxybis(2,1-ethanediyl-2,1-ethanediyl) ester	
7434-40-4	Triethylene glycol, diheptanoate	
Ethylene and Propylene Glycol Esters Subcategory		
105-62-4	Oleic acid, propylene ester	

Table 1. Chemical Structures for Glycol Esters		
CASRN	Chemical Name	Chemical Structure
627-83-8	Stearic acid, ethylene ester	
42222-50-4	9-Octadecenoic acid (Z)-2,2-dimethyl-1,3-propanediyl ester	
22788-19-8	Propylene glycol, dilaurate	
68958-54-3	Propylene glycol, diisostearate	
¹ This composition may be listed in error by the sponsor due to the monoester structure being affiliated with CASRN 67989-24-6		

1.2 Physical-Chemical Properties

The physical-chemical properties are summarized in Table 2. The physical-chemical properties of the aliphatic ester category, Subcategories I, II, and III are summarized in Tables 2a, 2b and 2c, respectively.

The aliphatic ester category, Subcategories I, II, and III are both solids and liquids with negligible to low water solubility and negligible to low vapor pressures.

Property	Octadecanoic acid, 2-hydroxyethyl ester	9-Octadecenoic acid (9Z)-, ester with 2,2-dimethyl-1,3-propanediol²	Octadecanoic acid, monoester with 1,2-propanediol
CASRN	111-60-4	67989-24-6	1323-39-3
Molecular Weight	328.54	368.59	342.57
Physical State	Solid, (based on the melting point)	No data	Solid ³
Melting Point	60.5°C (measured)	No data	No data
Boiling Point	189–191°C at 3 mm Hg (measured); 360–362°C at 760 mm Hg (extrapolated) ⁴	>300°C (estimated) ⁵	>300°C (measured) ³
Vapor Pressure	1.2×10 ⁻⁶ mm Hg at 25°C (estimated) ⁴	1.0×10 ⁻⁹ mm Hg at 25°C (estimated) ⁵	1.1×10 ⁻⁸ mm Hg at 25°C (estimated) ⁵
Water Solubility	2.0×10 ⁻² mg/L at 25°C (estimated) ⁵	0.001 mg/L at 25°C (estimated) ⁵	6.2×10 ⁻³ mg/L at 25°C (estimated) ⁵
Dissociation Constant (pK _a)	Not applicable	Not applicable	Not applicable
Henry's Law Constant	4.6×10 ⁻⁷ atm-m ³ /mole (estimated) ⁵	4.1×10 ⁻⁷ atm-m ³ /mole (estimated) ⁵	1.1×10 ⁻⁶ atm-m ³ /mole (estimated) ⁵
Log K _{ow}	7.26 (estimated) ⁵	8.4 (estimated) ⁵	7.67 (estimated) ⁵

¹American Chemistry Council. December 24, 2003. Revised Robust Summary for the Glycol Esters Category of the Aliphatic Esters Chemicals. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm> as of April 16, 2010.

²The sponsor specifies CASRN 67989-24-6 is a mixture of two components; the diester (88%) and monoester (12%). Chemical nomenclature of CASRN 67989-24-6 assigned by the sponsor is ambiguous of the monoester/diester character although the CASRN is specifically associated with the monoester structure. The diester, CASRN 42222-50-4, is however indicated as the primary component in the mixture. This composition may be listed in error by the sponsor due to the monoester structure being affiliated with CASRN 67989-24-6. As a result of conflicting information, data is reported for only for the monoester in this table. Data for the diester, CASRN 42222-50-4 is also listed separately in Table 2c for Subcategory III: Ethylene and Propylene Glycol Esters.

³Aldrich Chemical Company. 2010. MSDS: Stearic Acid Monoester with Propane-1,2-Diol, CASRN 1323-39-3. Available online from: <http://www.sigmaaldrich.com/catalog/AdvancedSearchPage.do> as of April 30, 2010.

⁴NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.

⁵U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from:

<http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of April 16, 2010.

Property	Hexanoic acid, 2-ethyl-, 1,1'-[1,2-ethanediylbis(oxy-2,1-ethanediyl)] ester	Heptanoic acid, 1,1'-[oxybis(2,1-ethanediyl)oxy-2,1-ethanediyl] ester	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	Hexanoic acid, 2-ethyl-, 1,1'-[oxybis(2,1-ethanediyl)oxy-2,1-ethanediyl] ester
CASRN	94-28-0	70729-68-9	68583-52-8	18268-70-7
Molecular Weight	402.58	418.58	430.63	446.63
Physical State	Liquid	No data	No data	No data
Melting Point	<-40°C (measured)	No data	No data	No data
Boiling Point	344°C (measured)	180–188°C at 0.09 mm Hg (measured); >300°C at 760 mm Hg (estimated) ^{2,3}	>300°C (estimated) ³	>300°C (estimated) ³
Vapor Pressure	7.3×10 ⁻⁵ mm Hg at 25°C (estimated) ²	3.4×10 ⁻⁷ mm Hg at 25°C (estimated) ³	1.7×10 ⁻⁷ mm Hg at 25°C (estimated) ³	2.3×10 ⁻⁷ mm Hg at 25°C (estimated) ³
Water Solubility	0.45 mg/L at 25°C (estimated) ³	0.34 mg/L at 25°C (estimated) ³	3.5×10 ⁻³ mg/L at 25°C (estimated) ³	4.4×10 ⁻² mg/L at 25°C (estimated) ³
Dissociation Constant (pK _a)	Not applicable	Not applicable	Not applicable	Not applicable
Henry's Law Constant	<1.0×10 ⁻¹⁰ atm-m ³ /mole (estimated) ³	<1.0×10 ⁻¹⁰ atm-m ³ /mole (estimated) ³	<1.0×10 ⁻¹⁰ atm-m ³ /mole (estimated) ³	<1.0×10 ⁻¹⁰ atm-m ³ /mole (estimated) ³
Log K _{ow}	5.60 (estimated) ³	2.86 (measured) ^{1,4} ; 4.49 (estimated) ³	6.73 (estimated) ³	5.33 (estimated) ³

¹ American Chemistry Council. December 24, 2003. Revised Robust Summary for the Glycol Esters Category of the Aliphatic Esters Chemicals. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm> as of April 16, 2010.

² NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.

³ U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from:

<http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of April 16, 2010.

⁴ The test substance used for OECD 107 partition coefficient test was only 88% pure. The remainder of the test substance consisted of 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2-methylhexanoic acids, and 2% other mixed esters according to the sponsor.

Property	Octadecanoic acid, 1,1'-(1,2-ethanediyl) ester	9-Octadecenoic acid (9Z)-, 1,1'-(1-methyl-1,2-ethanediyl) ester	9-Octadecenoic acid (9Z)-, 1,1'-(2,2-dimethyl-1,3-propanediyl) ester
CASRN	627-83-8	105-62-4	42222-50-4
Molecular Weight	595.01	605.01	633.06
Physical State	Solid, leaves ²	Liquid (based on CASRN 42222-50-4)	Clear, amber, liquid ³
Melting Point	79°C (measured)	No data	<-25°C (measured) ³
Boiling Point	241°C at 20 mm Hg (measured); >300 °C at 760 mm Hg (estimated) ^{4,5}	>300°C (estimated) ⁵	>300°C (estimated) ⁵
Vapor Pressure	<1.0×10 ⁻¹⁰ mm Hg at 25°C (estimated) ⁵	<1.0×10 ⁻¹⁰ mm Hg at 25°C (estimated) ⁵	<1.0×10 ⁻¹⁰ mm Hg at 25°C (estimated) ⁵
Water Solubility	4.2×10 ⁻¹² mg/L at 25°C (estimated) ⁵	2.6×10 ⁻¹² mg/L at 25°C (estimated) ⁵	2.7×10 ⁻¹³ mg/L at 25°C (estimated) ⁵
Dissociation Constant (pK _a)	Not applicable	Not applicable	Not applicable
Henry's Law Constant	4.8×10 ⁻³ atm-m ³ /mole (estimated) ⁵	4.9×10 ⁻³ atm-m ³ /mole (estimated) ⁵	4.9×10 ⁻³ atm-m ³ /mole (estimated) ⁵
Log K _{ow}	16.1 (estimated) ⁵	16.1 (estimated) ⁵	17.1 (estimated) ⁵

¹ American Chemistry Council. December 24, 2003. Revised Robust Summary for the Glycol Esters Category of the Aliphatic Esters Chemicals. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm> as of April 16, 2010.

² Lide, D.R. (ed.). 2008. CRC Handbook of Chemistry and Physics. 81st Edition. CRC Press LLC, Boca Raton, FL, p. 3-232.

³ Chemical Associates. 2009. Material Safety Data Sheet, Neopentylglycol Dioleate, CASRN 42222-50-4, 99%+ purity, Available online from: <http://www.chemicalassociates.com/CA3600.pdf> as of April 20, 2010.

⁴ NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.

⁵ U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of April 16, 2010.

2.0. General Information on Exposure

2.1 Production Volume and Use Pattern

The Glycol Esters Category chemicals had aggregated production and/or import volume in the United States between 25 and 142 million pounds during calendar year 2005.

- CASRN 94-28-0: 10 to <50 million pounds;
- CASRN 105-62-4: 1 to <10 million pounds;

- CASRN 111-60-4: 1 to <10 million pounds;
- CASRN 627-83-8: 10 to <50 million pounds;
- CASRN 1323-39-3: 1 to 10 million pounds;
- CASRN 18268-70-7: 500,000 to <1 million pounds;
- CASRN 42222-50-4: 1 to <10 million pounds; and
- CASRN 68583-52-8: 500,000 to <1 million pounds;

CASRN 67989-24-6 and 70729-68-9 were not reported in the 2006 IUR.

CASRN 94-28-0:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include all other chemical product and preparation manufacturing as “other”; and other basic organic chemical manufacturing as “other”. Non-confidential commercial and consumer uses of this chemical include rubber and plastic products.

CASRN 105-62-4:

Industrial processing and uses for the chemical were claimed confidential. No commercial and consumer uses were reported.

CASRN 111-60-4 and 627-83-8:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemicals include soap and cleaning compound manufacturing as intermediates. Commercial and consumer uses were claimed confidential.

CASRN 1323-39-3, 18268-70-7 and 68583-52-8:

Industrial processing and uses and commercial and consumer uses for the chemicals were claimed confidential.

CASRN 42222-50-4:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include automobile and light duty motor vehicle manufacturing as lubricants; other petroleum and coal products manufacturing as lubricants; iron and steel mills and ferroalloy manufacturing as lubricants. Non-confidential commercial and consumer uses of this chemical include automotive care products.

2.2 Environmental Exposure and Fate

The environmental fate data are provided in Tables 3a, 3b and 3c. The glycol monoesters of Subcategory I are expected to have low mobility in soil. The tri- and tetraethylene glycol diesters of Subcategory II are expected to have low-to-moderate mobility in soil. The ethylene and propylene glycol esters of Subcategory III are expected to have low mobility in soil. Each subcategory has one member with experimental biodegradation data which was applied to the other members of the subcategory due to structural similarities. A mixture containing CASRN 67989-24-6 from Subcategory I (Glycol Monoesters) was readily biodegradable (73%

degradation in 28 days) by measuring CO₂ evolution using a modified Sturm test guideline, OECD 301B. Although the test was performed on a mixture, it is believed that the test substance used was predominately CASRN 67989-24-6. Structural similarities of CASRN 67989-24-6 9 and CASRN 111-60-4 suggest CASRN 111-60-4 and CASRN 1323-39-3, the other subcategory members, will also be readily biodegradable. A test substance of 95% pure CASRN 70729-68-9 from, Subcategory II, (Tri-and Tetraethylene Glycol Diesters), was readily biodegradable (98% degradation in 28 days) using a modified OECD Screening Test (OECD 301E) measuring dissolved organic carbon. These data suggest that the three other members of Subcategory II (Tri-and Tetraethylene Glycol Diesters) are also readily biodegradable due to structural similarities with CASRN 70729-68-9. CASRN 627-83-8 from Subcategory III (Ethylene and Propylene Glycol Esters) was readily biodegradable (73, 82, and 63% biodegradation in 28 days) using the modified MITI test OECD TG 301C. CASRN 627-83-8 was determined to be inherently biodegradable (94% degradation in 28 days) using a concentration of 30 mg/L, inoculated with 100 mg/L activated sludge as measured by HPLC. These data suggest that two other members of Subcategory III (Ethylene and Propylene Glycol Esters) are expected to be readily biodegradable based on their structural similarities with CASRN 627-83-8. The estimated rate of hydrolysis of the substances in the aliphatic esters category is expected to be negligible under environmental pH and temperature; however, these compounds are expected to be readily hydrolyzed via metabolic action of microbial esterases. The rate of volatilization is expected to be low for Subcategories I and II and moderate for Subcategory III based on the Henry's Law constants; however, adsorption may attenuate the rate of volatilization. The overall weight of evidence suggests that the glycol esters members of the aliphatic ester category are all expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	Octadecanoic acid, 2-hydroxyethyl ester	9-Octadecenoic acid (9Z)-, ester with 2,2-dimethyl-1,3-propanediol²	Octadecanoic acid, monoester with 1,2-propanediol
CASRN	111-60-4	67989-24-6	1323-39-3
Photodegradation Half-life	4.6 hours (estimated) ³	1.6 hours (estimated) ³	4.0 hours (estimated) ³
Hydrolysis Half-life	7.7 years at pH 7 and 281 days at pH 8 (estimated) ³	23.3 years at pH 7 and 2.3 years at pH 8 (estimated) ³	7.7 years at pH 7 and 281 days at pH 8 (estimated) ³
Biodegradation	No data	73% in 28 days (readily biodegradable) ^{1,4}	No data
Bioaccumulation Factor	BAF = 59.2 (estimated) ³	BAF = 153.3 (estimated) ³	BAF = 46.5 (estimated) ³
Log K _{oc}	3.9 (estimated) ³	4.5 (estimated) ³	4.1 (estimated) ³
Fugacity (Level III Model) ³			
Air (%)	0.7	0.1	0.5
Water (%)	22.2	23.5	21.3
Soil (%)	74.4	74.7	76
Sediment (%)	2.7	1.7	2.2
Persistence ⁵	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation ⁵	B1 (low)	B1 (low)	B1 (low)

¹ American Chemistry Council. December 24, 2003. Revised Robust Summary for the Glycol Esters Category of the Aliphatic Esters Chemicals. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm> as of April 16, 2010.

² The sponsor specifies CASRN 67989-24-6 is a mixture of two components; the diester (88%) and monoester (12%). Chemical nomenclature of CASRN 67989-24-6 assigned by the sponsor is ambiguous of the monoester/diester character although the CASRN is specifically associated with the monoester structure. The diester, CASRN 42222-50-4, is however indicated as the primary component in the mixture. This composition may be listed in error by the sponsor due to the monoester structure being affiliated with CASRN 67989-24-6. As a result of conflicting information, data is reported for only for the monoester in this table. Data for the diester, CASRN 42222-50-4 is also listed separately in Table 3c for Subcategory III: Ethylene and Propylene Glycol Esters.

³ U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from:

<http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of April 16, 2010

⁴ The experimental biodegradation data submitted by the sponsor states that the purity is not specified for the test substance, but it is a mixture containing CASRN 67989-24-6 and CASRN 70024-57-4. CASRN 70024-57 is not a valid CASRN so it is likely CASRN 70024-57-6, the product formed when CASRN 67989-24-6 undergoes olefin oxidation, followed by a nucleophilic attack of 2,2-dimethyl-1,3-propanediol.

⁵ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Property	Hexanoic acid, 2-ethyl-, 1,1'-[1,2-ethanediylbis(oxy-2,1-ethanediyl)] ester	Heptanoic acid, 1,1'-[oxybis(2,1-ethanediyl)oxy-2,1-ethanediyl] ester	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	Hexanoic acid, 2-ethyl-, 1,1'-[oxybis(2,1-ethanediyl)oxy-2,1-ethanediyl] ester
CASRN	94-28-0	70729-68-9	68583-52-8	18268-70-7
Photodegradation Half-life	2.9 hours (estimated) ²	2.2 hours (estimated) ²	2.6 hours (estimated) ²	2.2 hours (estimated) ²
Hydrolysis Half-life	30.8 years at pH 7 and 3.1 years at pH 8 (estimated) ²	294 days at pH 7 and 29 days at pH 8 (estimated) ²	1.1 years at pH 7 and 40 days at pH 8 (estimated) ²	30.8 years at pH 7 and 3.1 years at pH 8 (estimated) ²
Biodegradation	No data	98% in 28 days (readily biodegradable)	No data	No data
Bioaccumulation Factor	BAF = 16.2 (estimated) ²	BAF = 12.6 (estimated) ²	BAF = 16.7 (estimated) ²	BAF = 12.2 (estimated) ²
Log K _{oc}	3.4 (estimated) ²	2.8 (estimated) ²	3.9 (estimated) ²	3.3 (estimated) ²
Fugacity (Level III Model) ²				
Air (%)	<0.1	<0.1	<0.1	<0.1
Water (%)	15.9	16.5	15.4	16
Soil (%)	82.9	83.1	81.5	83
Sediment (%)	1.1	0.4	3.1	1.0
Persistence ³	P1 (low)	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation ³	B1 (low)	B1 (low)	B1 (low)	B1 (low)

¹American Chemistry Council. December 24, 2003. Revised Robust Summary for the Glycol Esters Category of the Aliphatic Esters Chemicals. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm> as of April 16, 2010.

²U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from:

<http://www.epa.gov/opptintr/exposure/pubs/episuitd.htm> as of April 16, 2010.

³Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Property	Octadecanoic acid, 1,1'-(1,2-ethanediyl) ester	9-Octadecenoic acid (9Z)-, 1,1'-(1-methyl-1,2-ethanediyl) ester	9-Octadecenoic acid (9Z)-, 1,1'-(2,2-dimethyl-1,3-propanediyl) ester
CASRN	627-83-8	105-62-4	42222-50-4
Photodegradation Half-life	4.3 hours (estimated) ²	0.8 hours (estimated) ²	0.8 hours (estimated) ²
Hydrolysis Half-life	14.1 years at pH 7 and 1.4 years at pH 8 (estimated) ²	2.6 years at pH 7 and 95 days at pH 8 (estimated) ²	11.7 years at pH 7 and 1.2 years at pH 8 (estimated) ²
Biodegradation	73, 82, 63% biodegradation in 28 days (readily biodegradable) ³ ; 94% in 28 days (inherently biodegradable) ³	No data	No data
Bioaccumulation Factor	BAF = 0.9 (estimated) ²	BAF = 0.9 (estimated) ²	BAF = 0.9 (estimated) ²
Log K _{oc}	8.8 (estimated) ²	9.0 (estimated) ²	9.4 (estimated) ²
Fugacity (Level III Model) ²			
Air (%)	0.5	<0.1	<0.1
Water (%)	24.6	17.6	17.6
Soil (%)	74.9	82.4	82.4
Sediment (%)	<0.1	<0.1	<0.1
Persistence ⁴	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation ⁴	B1 (low)	B1 (low)	B1 (low)

¹American Chemistry Council. December 24, 2003. Revised Robust Summary for the Glycol Esters Category of the Aliphatic Esters Chemicals. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/alipestr/c13466tc.htm> as of April 16, 2010.

²U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from:

<http://www.epa.gov/opptintr/exposure/pubs/episuitd1.htm> as of April 16, 2010.

³National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from:

http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html as of April 16, 2010.

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

Subcategory I: Glycol Monoesters

Stearic acid, 2-hydroxyethyl ester (CASRN 111-60-4)

Wistar rats (5/sex) were administered CASRN 111-60-4 (purity not specified) in corn oil via gavage at 5000 mg/kg and observed for 14 days following dosing. There were no mortalities.

LD₅₀ > 5000 mg/kg

Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentadiol (CASRN 71839-38-8, supporting chemical)

Crl:CD-BR rats (5/sex) were administered CASRN 71839-38-8 (100% purity) in corn oil via gavage at 2000 mg/kg and observed for 14 days. There were no mortalities.

LD₅₀ > 2000 mg/kg

Subcategory II: Tri- and Tetraethylene Glycol Diesters

Heptanoic acid, oxybis (2,1-ethanediylxy-2,1-ethanediyl) ester (CASRN 70729-68-9)

(1) Wistar rats (5/sex) were administered CASRN 70729-68-9 (94.5% purity and contained ~ 2% monoesters) via gavage at 2000 mg/kg and observed for 14 days. There were no mortalities.

LD₅₀ > 2000 mg/kg

(2) ChR:CD rats (10 males) were administered CASRN 70729-68-9 (88% purity with the remainder composed of 6% triethylene glycol di-n-heptanoate; 4% mixed ester of tetraethylene glycol with n-heptanoic and 2-methylhexanoic acids; and 2% other unspecified mixed esters) via gavage at 25,000 mg/kg and observed for 14 days. One mortality was noted within 1 day of dosing.

LD₅₀ > 25,000 mg/kg

(3) Crl:CD rats (10 females/dose) were administered CASRN 70729-68-9 (88% purity with the remainder composed of 6% triethylene glycol di-n-heptanoate; 4% mixed ester of tetraethylene glycol with n-heptanoic and 2-methylhexanoic acids; and 2% other unspecified mixed esters) in corn oil via gavage at 14,000, 19,000, 22,000, 23,000, 24,000, 24,500, 24,750, 24,900 or 25,000 mg/kg and observed for 14 days. At 24,000, 24,500, 24,750, 24,900 and 25,000 mg/kg, 4, 1, 1, 2 and 10 animals died within 2 days, respectively.

LD₅₀ = 24,000 – 25,000 mg/kg

Subcategory III: Ethylene and Propylene Glycol Esters

Stearic acid, ethylene ester (CASRN 627-83-8)

Rats of unspecified strain (5 males/dose) were administered CASRN 627-83-8 in corn oil (50% w/v) via gavage at 464, 1000, 2150, 4640 or 10,000 mg/kg and observed for 14 days. There were no mortalities.

LD₅₀ > 10,000 mg/kg

Repeated-Dose Toxicity

Subcategory I: Glycol Monoesters

Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentadiol (CASRN 71839-38-8, supporting chemical)

Crl:CD-BR rats (5/sex/dose) were exposed to CASRN 71839-38-8 (100% purity) in corn oil via gavage at 30 or 180 mg/kg-day for 28 days. Additional animals (10/sex) were exposed at 0 (vehicle control) or 1000 mg/kg-day. Five rats/sex from each of the control and high-dose groups were retained for a 14-day recovery period. No mortality or clinical signs of toxicity were observed. All treated females exhibited a decrease in body weight gain; however, the robust summary does not indicate if this was statistically different from controls or the magnitude of change. Slightly decreased platelet counts were noted in females of all treatment groups with 4 weeks. Decreased glucose levels were noted in animals at the highest dose and females of the 180 mg/kg-day group; however, glucose levels were increased in high-dose animals following the recovery period. Animals at the highest dose exhibited increased liver weights following treatment and recovery periods believed to be associated with the metabolism of the test material. There were no macroscopic findings at necropsy. Treatment-related histopathological effects were observed and included increased hyaline droplets and tubular basophilia in the kidneys of males at 1000 mg/kg-day. Partial reversal of these findings was noted in recovery animals. Examination of testes, epididymides and ovaries revealed no treatment-related macroscopic or histopathological effects.

LOAEL = 1000 mg/kg-day (based on hyaline droplet formation and tubular basophilia in male rats)⁴

NOAEL = 180 mg/kg-day

Subcategory II: Tri- and Tetraethylene Glycol Diesters

Heptanoic acid, oxybis (2,1-ethanedioxy-2,1-ethanediyl) ester (CASRN 70729-68-9)

Wistar rats (10/sex) were administered CASRN 70729-68-9 (88% purity with the remainder composed of 6% triethylene glycol di-n-heptanoate; 4% mixed ester of tetraethylene glycol with n-heptanoic and 2-methylhexanoic acids; and 2% other unspecified mixed esters) in corn oil as a 11 – 15% solution via gavage at 1000 mg/kg-day for 28 days. Five rats/sex at 1000 mg/kg-day were retained for a 14-day recovery period. Control animals (5/sex) were administered the vehicle. No mortality occurred. Body weight gains were decreased in both male and female animals of the dosed and recovery groups. Unspecified congestion was noted in dosed males only. Effects on hematology and clinical chemistry included increased leukocyte counts in dosed and recovery males, increased aspartate transaminase activity in dosed males, decreased alkaline phosphatase activity in dosed females and recovery males and females and increased bilirubin in control and dosed males. Although the sponsor considers these effects unrelated to treatment, adequate data including statistical significance and magnitude of the effects were not provided to support such a claim. Organ weights were not provided. No macroscopic effects were observed

⁴The nephropathy seen in males in this study may be occurring by an alpha 2 μ -globulin-mediated mechanism (which is male rat-specific and not considered relevant to humans). However, EPA's Risk Assessment Forum has outlined the key events and data that are necessary to demonstrate this mode of action (Alpha 2 μ -Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Rat, EPA/625/3-91/019F). The industry sponsor has not provided data to support these key events, and therefore, the effects in this study are considered potential human health hazards.

at necropsy. Histopathological effects were noted in all treatment and control groups and included lung lesions (pneumonitis, peribronchiolitis and/or perivascularitis). Other findings were considered to be incidental and included cysts in Kursteiner's duct of the thyroid, thyroid C-cell hyperplasia, periportal vacuolization, hepatitis, trachitis, nephritis, atrophy and degeneration of the seminiferous tubules of the testes as well as the epididymis. However, the robust summary did not indicate if these effects were observed in both control and treated animals or if a statistical analysis of incidence in control and treated animals was conducted.

LOAEL/NOAEL = Not established (one dose tested)

Subcategory III: Ethylene and Propylene Glycol Esters

No data were submitted for this endpoint. However, physicochemical properties including log K_{ow} , molecular weight, and water solubility can be used to predict the relative ability of a xenobiotic to be absorbed into the body. The high predicted log K_{ow} values (> 10), low predicted water solubility values ($< 1 \times 10^{-11}$ mg/L) and high molecular weights (> 500) of chemicals in subcategory III support the idea that these chemicals would be poorly absorbed, resulting in limited toxicity, into the body. The low acute oral toxicity for chemicals in subcategory III further supports their lack of mammalian toxicity.

Reproductive/Developmental Toxicity

Subcategory I: Glycol Monoesters

No data were submitted for this endpoint.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

No data were submitted for this endpoint. However, chemicals in subcategory II would have a low potential for reproductive and developmental toxicity. This conclusion is based on predicted metabolism of the subcategory II chemicals and also on the data for the supporting chemicals in the Ethylene Glycols category in the OECD SIDS Program (<http://webnet.oecd.org/hpv/ui/Search.aspx>). Hazard analysis of chemicals in this subcategory II can be based on the fact that glycol esters would be metabolized (hydrolyzed) *in vivo* to the corresponding fatty acids and free glycol alcohols. The free fatty acids and glycols can undergo further metabolism or conjugation to polar products that are either excreted or used as nutrients. The potential for reproductive and developmental toxicity for triethylene glycol CASRN 112-27-6, and tetraethylene glycol, CASRN 112-60-7 is low (NOAEL is above the limit dose of 1000 mg/kg.)

Subcategory III: Ethylene and Propylene Glycol Esters

No data were submitted for this endpoint. However, physicochemical properties including log K_{ow} , molecular weight, and water solubility can be used to predict the relative ability of a xenobiotic to be absorbed into the body. The high predicted log K_{ow} values (> 10), low predicted water solubility values ($< 1 \times 10^{-11}$ mg/L) and high molecular weights (> 500) of chemicals in subcategory III support the idea that these chemicals would be poorly absorbed, resulting in limited toxicity. The low acute oral toxicity for chemicals in subcategory III further supports their lack of mammalian toxicity.

Genetic Toxicity – Gene Mutations

In vitro

Subcategory I: Glycol Monoesters

Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentadiol (CASRN 71839-38-8, supporting chemical)

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* strain WP2uvrA were exposed to CASRN 71839-38-9 in DMSO at concentrations of 10, 33, 100, 333 or 1000 µg/plate in the absence and presence of metabolic activation. Positive controls responded appropriately. Cytotoxic concentrations were not specified.

CASRN 71839-38-9 was not mutagenic in this assay.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

Heptanoic acid, oxybis (2,1-ethanedioxy-2,1-ethanediyl) ester (CASRN 70729-68-9)

S. typhimurium strains TA98, TA100, TA1535 and TA1537 were exposed to CASRN 70729-68-9 (test material purity was 88% with the remainder comprised of 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2-methylhexanoic acids and 2% other unspecified mixed esters) in DMSO at concentrations of 500 – 10,000 or 100 – 2500 µg/plate in the presence and absence of metabolic activation. Positive controls responded appropriately. Cytotoxic concentrations were not specified.

CASRN 70729-68-9 was not mutagenic in this assay.

Subcategory III: Ethylene and Propylene Glycol Esters

No data were submitted for this endpoint. However, physicochemical properties including log K_{ow} , molecular weight, and water solubility can be used to predict the relative ability of a xenobiotic to be absorbed into the body. The high predicted log K_{ow} values (> 10), low predicted water solubility values ($< 1 \times 10^{-11}$ mg/L) and high molecular weights (> 500) of chemicals in subcategory III support the idea that these chemicals would be poorly absorbed, resulting in limited toxicity, into the body. The low acute oral toxicity for chemicals in subcategory III further supports their lack of mammalian toxicity.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Subcategory I: Glycol Monoesters

Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentadiol (CASRN 71839-38-8, supporting chemical)

Human lymphocytes were exposed to CASRN 71839-38-8 in ethanol at concentrations of 625, 1250, 2500 or 5000 µg/mL for 20 or 44 hours in the absence of metabolic activation or for 4 hours in the presence of metabolic activation. Positive controls responded appropriately. The cytotoxic concentration is > 5000 µg/mL.

CASRN 71839-38-8 did not induce chromosomal aberrations in this assay.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

No data were submitted for this endpoint. However, chemicals in subcategory II would have a low potential to induce *in vivo* genotoxicity. This conclusion is based on predicted metabolism

of the subcategory II chemicals and also on the data for the supporting chemicals in the Ethylene Glycols category in the OECD SIDS Program (<http://webnet.oecd.org/hpv/ui/Search.aspx>). Hazard analysis of chemicals in this subcategory II can be based on the fact that glycol esters would be metabolized (hydrolyzed) *in vivo* to the corresponding fatty acids and free glycol alcohols. The free fatty acids and glycols can undergo further metabolism or conjugation to polar products that are either excreted or used as nutrients. It is unlikely that triethylene glycol CASRN 112-27-6, and tetraethylene glycol, CASRN 112-60-7 can induce *in vivo* genotoxicity.

Subcategory III: Ethylene and Propylene Glycol Esters

Physicochemical properties including log K_{ow} , molecular weight, and water solubility can be used to predict the relative ability of a xenobiotic to be absorbed into the body. The high predicted log K_{ow} values (> 10), low predicted water solubility values ($< 1 \times 10^{-11}$ mg/L) and high molecular weights (> 500) of chemicals in subcategory III support the idea that these chemicals would be poorly absorbed, resulting in limited toxicity, into the body. The low acute oral toxicity for chemicals in subcategory III further supports their lack of mammalian toxicity.

Conclusions:

Subcategory I: Glycol Monoesters

The acute oral toxicity for glycol monoesters is low based on testing of the subcategory member, CASRN 111-60-4, and the supporting chemical, CASRN 71839-38-8. Following repeated administration of CASRN 71839-38-8 via gavage for 28 days, male rats exhibited increased hyaline droplets and tubular basophilia in the kidneys at 1000 mg/kg-day; the NOAEL for systemic toxicity is 180 mg/kg-day. No reproductive/developmental toxicity data were provided for glycol monoesters. The supporting chemical, CASRN 71839-38-8, did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells *in vitro*.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

The acute oral toxicity for tri- and tetraethylene glycol diesters is low based on testing of subcategory member, CASRN 70729-68-9. Following repeated administration of CASRN 70729-68-9 to rats via gavage for 28 days, increased leukocyte counts and aspartate transaminase activity in males and decreased alkaline phosphatase activity (both sexes) were seen at 1000 mg/kg-day, the only dose tested. No reproductive/developmental toxicity data were provided for tri- and tetraethylene glycol diesters. CASRN 70729-68-9 ester did not induce gene mutations in bacteria. No chromosomal aberration data were provided for tri- and tetraethylene glycol diesters. Members of the subcategory are predicted to be metabolized to triethylene glycol (CASRN 112-27-6) and tetraethylene glycol (CASRN 112-60-7), which can undergo further metabolism or conjugation into polar products that are either excreted or used as nutrients. Therefore, EPA considers the potential for reproductive and developmental toxicity of the metabolites, CASRN 112-27-6 and CASRN 112-60-7, to be low. These metabolites would also not likely induce *in vivo* genotoxicity. Therefore, EPA anticipates that no new information would be gained from further animal experimentation on subcategory II chemicals for the purposes of the HPV Challenge Program.

Subcategory III: Ethylene and Propylene Glycol Esters

The acute oral toxicity for ethylene and propylene glycol esters is low based on testing of subcategory member, CASRN 627-83-8. No repeated-dose, reproductive/developmental, gene mutation or chromosomal aberration data were provided for ethylene and propylene glycol esters. Based on physicochemical properties, absorption of the members of the subcategory is expected to be poor, resulting in limited toxicity. The low acute toxicity further supports their lack of mammalian toxicity. Therefore, EPA recommends no further testing of subcategory III for the purposes of the HPV Challenge Program.

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data					
Endpoints	Acute Oral Toxicity	Repeated-Dose Toxicity	Reproductive/Developmental Toxicity	Genetic Toxicity – Gene Mutation	Genetic Toxicity – Chromosomal Aberrations
	LD₅₀ (mg/kg-bw)	NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL/LOAEL Oral (mg/kg-bw/day)	Gene Mutation <i>in vitro</i>	<i>in vitro</i>
Subcategory I: Glycol Monoesters					
Stearic acid, 2-hydroxyethyl ester (111-60-4)	> 5000	No Data NOAEL = 180 (RA)	No Data	No Data Negative (RA)	No Data Negative (RA)
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (67989-24-6)^a	No Data 2000 – 5000 (RA)	No Data NOAEL = 180 (RA)	No Data	No Data Negative (RA)	No Data Negative (RA)
Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (71839-38-8)	> 2000	NOAEL = 180	—	Negative	Negative
Propylene glycol, monostearate (1323-39-3)	—	—	—	—	—
Subcategory II: Tri- and Tetraethylene Glycol Diesters					
Hexanoic acid, 2-ethyl-, diester with triethylene glycol (94-28-0)	No Data > 2000 (RA)	No Data NOAEL = NE LOAEL = 1000	No Data	No Data Negative (RA)	No Data

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data					
Endpoints	Acute Oral Toxicity LD₅₀ (mg/kg-bw)	Repeated-Dose Toxicity NOAEL/LOAEL Oral(mg/kg-bw/day)	Reproductive/Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Genetic Toxicity – Gene Mutation <i>in vitro</i>	Genetic Toxicity – Chromosomal Aberrations <i>in vitro</i>
		(RA)			
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol (18268-70-7)	No Data > 2000 (RA)	No Data NOAEL = NE LOAEL = 1000 (RA)	No Data	No Data Negative (RA)	No Data
Decanoic acid, mixed diester with octanoic acid and triethylene glycol (68583-52-8)	No Data > 2000 (RA)	No Data NOAEL = NE LOAEL = 1000 (RA)	No Data	No Data Negative (RA)	No Data
Heptanoic acid, oxybis(2,1-ethanedioxy-2,1-ethanediyl) ester (70729-68-9)	> 2000	NOAEL = NE LOAEL = 1000	No Data	Negative	No Data
Triethylene glycol, diheptanoate (7434-40-4)	—	—	—	—	—
Subcategory III: Ethylene and Propylene Glycol Esters					
Oleic acid, propylene ester (105-62-4)	No Data > 10,000 (RA)	No Data	No Data	No Data	No Data
Stearic acid, ethylene ester (627-83-8)	> 10,000	No Data	No Data	No Data	No Data
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (42222-50-4)	No Data > 10,000 (RA)	No Data	No Data	No Data	No Data

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

Endpoints	Acute Oral Toxicity LD₅₀ (mg/kg-bw)	Repeated-Dose Toxicity NOAEL/LOAEL Oral(mg/kg-bw/day)	Reproductive/Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	Genetic Toxicity – Gene Mutation <i>in vitro</i>	Genetic Toxicity – Chromosomal Aberrations <i>in vitro</i>
Propylene glycol, dilaurate (22788-19-8)	—	—	—	—	—
Propylene glycol, diisostearate (68958-54-3)	—	—	—	—	—

Measured data in bold text; (RA) = Read Across; – indicates that endpoint not addressed for the chemical; Shaded cells = supporting chemicals; NE = Not established

4. Hazard to the Environment

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

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

Subcategory I: Glycol Monoesters

Data were submitted for the acute toxicity to fish, daphnia and algae endpoints for the supporting chemical CASRN 71839-38-8 and data for the acute toxicity to fish endpoint for the sponsored chemical, CASRN 67989-24-6. EPA has determined that these data are inadequate because the results are provided using nominal loading rates without accompanying analytical data. EPA has determined that additional testing is not required because members of the subcategory have high estimated Log K_{ow} values (7.26 – 8.40) and low estimated water solubility.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

Data were submitted for the acute toxicity to fish daphnia and algae endpoints for the supporting chemical, CASRN 7424-40-4 and the sponsored chemical, CASRN 70729-68-9 and acute toxicity to fish and daphnia endpoints for the sponsored chemical, CASRN 93-28-0. EPA has determined that these data are inadequate because the sponsor considered reliabilities to be low and experimental information provided in the studies was limited. Testing for these endpoints is recommended for one representative member of the subcategory. Chronic testing is recommended because the sponsored chemicals in this subgroup have low Log K_{ow} values

ranging from 2.86 to 6.73 (measured and estimated) and they are soluble or miscible in water at concentrations that could cause chronic effects.

Subcategory III: Ethylene and Propylene Glycol Esters

No data were submitted for these endpoints. Additional testing is not required because the sponsored chemicals in this subcategory have high estimated Log K_{ow} values ranging from 16.11 to 17.05 and are therefore considered to have no effects at saturation.

Conclusions:

Subcategory I: Glycol Monoesters

The Log K_{ow} values of the two subcategory members indicate that their potential to bioaccumulate is expected to be high. The subcategory member, CASRN 67989-24-6 and the supporting chemical, CASRN 71839-38-8, are not readily biodegradable, indicating that members of the glycol monoesters subcategory are expected to persist in the environment.

No adequate data were available to evaluate the potential acute hazard to fish, aquatic invertebrates and aquatic plants. Chronic toxicity testing is requested for the subcategory member CASRN 111-60-4 because of the Log K_{ow} value of 7.26.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

No adequate data were submitted for the aquatic toxicity endpoints. Because the sponsored substances in this group have low Log K_{ow} values ranging from 2.86 to 6.73 (measured and estimated), the potential acute hazard to aquatic organisms cannot be estimated without experimental data.

Data gaps for acute toxicity to fish, acute toxicity to aquatic invertebrates, toxicity to aquatic plants and chronic aquatic toxicity endpoints were identified for Subcategory II: tri- and tetraethylene glycol diesters under the HPV Challenge Program.

Subcategory III: Ethylene and Propylene Glycol Esters

The Log K_{ow} values of the three subcategory members (CASRNs 105-62-4, 627-83-8, 42222-50-4) indicate that their potential to bioaccumulate is expected to be high. Biodegradation data for this subcategory are not available; however, based on data for a member of the glycol monoesters subcategory, which also contains a propylene glycol ester as a major component, the members of the ethylene and propylene glycol esters subcategory are expected to persist in the environment.

No data were available to evaluate the potential acute hazard to fish, aquatic invertebrates and aquatic plants. However, because the Log K_{ow} values for the members of this subcategory are estimated to be > 8 , the toxicity is expected to be no effects at saturation.

No data gaps were identified for Subcategory III: Ethylene and propylene glycol esters under the HPV Challenge Program.

Subcategory I: Glycol Monoesters

The Log K_{ow} values of the two subcategory members indicate that their potential to bioaccumulate is expected to be high. The subcategory member, CASRN 67989-24-6 and the supporting chemical, CASRN 71839-38-8, are not readily biodegradable, indicating that members of the glycol monoesters subcategory are expected to persist in the environment.

No adequate data were available to evaluate the potential acute hazard to fish, aquatic invertebrates and aquatic plants. Chronic toxicity testing is requested for the subcategory member CASRN 111-60-4 because of the Log K_{ow} value of 7.26.

Subcategory II: Tri- and Tetraethylene Glycol Diesters

No adequate data were submitted for the aquatic toxicity endpoints. Because the sponsored substances in this group have low Log K_{ow} values ranging from 2.86 to 6.73 (measured and estimated), the potential acute hazard to aquatic organisms cannot be estimated without experimental data.

Data gaps for acute toxicity to fish, acute toxicity to aquatic invertebrates, toxicity to aquatic plants and chronic aquatic toxicity endpoints were identified for Subcategory II: tri- and tetraethylene glycol diesters under the HPV Challenge Program.

Subcategory III: Ethylene and Propylene Glycol Esters

The Log K_{ow} values of the three subcategory members (CASRNs 105-62-4, 627-83-8, 42222-50-4) indicate that their potential to bioaccumulate is expected to be high. Biodegradation data for this subcategory are not available; however, based on data for a member of the glycol monoesters subcategory, which also contains a propylene glycol ester as a major component, the members of the ethylene and propylene glycol esters subcategory are expected to persist in the environment.

No data were available to evaluate the potential acute hazard to fish, aquatic invertebrates and aquatic plants. However, because the Log K_{ow} values for the members of this subcategory are estimated to be > 8 , the toxicity is expected to be no effects at saturation.

No data gaps were identified for Subcategory III: Ethylene and propylene glycol esters under the HPV Challenge Program.

Table 5. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data			
Chemical name (CASRN)	Fish 96-h LC₅₀ (mg/L)	Aquatic Invertebrates 48-h EC₅₀ (mg/L)	Aquatic Plants 72-h EC₅₀ (mg/L)
Subcategory I: Glycol Monoesters			
Stearic acid, 2-hydroxyethyl ester (111-60-4)	No data.	No data.	No data.
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (67989-24-6)^a	NES	NES	NES
Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentane-1,3-diol (71839-38-8)	—	—	—
Propylene glycol, monostearate (1323-39-3)	—	—	—
Subcategory II: Tri- and Tetraethylene Glycol Diesters			
Hexanoic acid, 2-ethyl-, diester with triethylene glycol (94-28-0)	No data	No data	No data.

Table 5. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data			
Chemical name (CASRN)	Fish 96-h LC₅₀ (mg/L)	Aquatic Invertebrates 48-h EC₅₀ (mg/L)	Aquatic Plants 72-h EC₅₀ (mg/L)
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol (18268-70-7)	No data.	No data.	No data.
Decanoic acid, mixed diester with octanoic acid and triethylene glycol (68583-52-8)	No data.	No data.	No data.
Heptanoic acid, oxybis(2,1-ethanediyl-oxy-2,1-ethanediyl) ester (70729-68-9)	No data	No data	No Data
Triethylene glycol, diheptanoate (7434-40-4)	—	—	—
Subcategory III: Ethylene and Propylene Glycol Esters			
Oleic acid, propylene ester (105-62-4)	No data. NES	No data. NES	No data. NES
Stearic acid, ethylene ester (627-83-8)	No data. NES	No data. NES	No data. NES
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (42222-50-4)	No data. NES	No data. NES	No data. NES
Propylene glycol, dilaurate (22788-19-8)	—	—	—

Table 5. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data			
Chemical name (CASRN)	Fish 96-h LC₅₀ (mg/L)	Aquatic Invertebrates 48-h EC₅₀ (mg/L)	Aquatic Plants 72-h EC₅₀ (mg/L)
Propylene glycol, diisostearate (68958-54-3)	—	—	—

Shaded cells = supporting chemicals; NES = no effects at saturation; (—) = no data