

201-14977A

**HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM**

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**TEST PLAN
FOR THE GLYCOL ESTERS CATEGORY OF THE
ALIPHATIC ESTERS CHEMICALS**

Prepared by:

American Chemistry Council's
Aliphatic Esters Panel

December 24, 2003

(With corrected text and pagination)

GLYCOL ESTERS HPV Test Plan

EXECUTIVE SUMMARY

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) hereby submits the revised test plan for the "glycol esters" category of the "aliphatic esters" chemicals, under the High Production Volume (HPV) Chemical Challenge Program. The Panel has used existing available public and company data in conjunction with scientific judgment/analysis to characterize the Screening Information Data Set (SIDS) of human health, environmental fate and effects, and physicochemical property endpoints for the glycol esters category.

This test plan addresses the nine HPV glycol esters chemicals listed in Table 1A. The distinguishing feature of this category of chemicals is that they are ester derivatives of ethylene glycol and propylene glycol (the alcohol portion of the ester molecule). Fatty acids (C6-C18) make up the carboxylic acid portion of the ester molecule and include the naturally occurring fatty acids, oleic and stearic acids. The HPV glycol esters cover the C20-C41 carbon number range. The commonalities of the ethylene glycol or propylene glycol substructure and the fatty acids (e.g., C6-10 fatty acids, oleic, stearic and isostearic acids) are the main reason for grouping these HPV glycol esters together. The glycol esters in this category find commercial use as lubricants, cosmetic ingredients, emulsifiers or solvents.

The chemical and structural similarities of the glycol esters listed in Table 1A justify grouping these nine HPV chemicals collectively together under the glycol esters category of the aliphatic esters. They have close commonalities in their physicochemical properties, chemical characteristics and biological/toxicological activities as a result of the structural glycol ester similarities in their molecules. Grouping these glycol esters together also represents a rational structural approach: (1) to systematically compare existing data; (2) to justify read-across assessments for structurally related or analogous glycol esters, and (3) to develop a stepwise strategy test plan for the glycol esters substances based on their ester group type. The glycol esters as an ester group type are structurally differentiated from other aliphatic ester types such as diacid esters, polyol esters, and sorbitan esters.

There was published information for five structurally analogous surrogate glycol esters, which provided useful supplementary data to help bridge the toxicity data for the HPV glycol esters. The five structurally analogous surrogate glycol esters are: [1] heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8); [2] triethylene glycol, diheptanoate (CAS 7434-40-4); [3] propylene glycol, monostearate (CAS 1323-39-3); [4] propylene glycol, dilaurate (CAS 22788-19-8); and [5] propylene glycol, diisostearate (CAS 68958-54-3). It should be pointed out that the propylene glycol stearates, oleates and laurates as well as polyethylene glycol (PEG) fatty acid esters [which are commonly used in many cosmetics] are very structurally similar to many of the HPV glycol esters substances and have low degrees of toxicity. (For example, it is noteworthy that propylene glycol stearate has been used in many pharmaceutical applications and is "Generally Recognized as Safe" (GRAS) in food applications.) Thus, the surrogate glycol esters provided useful toxicity information for read-across assessments of the HPV glycol esters.

Measured physicochemical property data were available for the HPV and surrogate glycol esters. Computer estimation models were used to calculate physicochemical property and environmental fate data for the glycol esters. The calculated data were obtained using the EPIWIN and EQC (Level III) models that the EPA has cited for use in the HPV Chemical Challenge Program. Use of

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the calculated and experimental values for HPV substances and for the surrogate glycol esters provided the information on the physicochemical and environmental fate properties of the chemicals in the glycol esters category to satisfy HPV program requirements. No additional testing for physicochemical and environmental fate properties is proposed.

Aquatic toxicity and biodegradation data exist for both the HPV glycol esters and the structurally analogous surrogate glycol esters to sufficiently allow for read-across assessments of the HPV substances and for bridging data. In addition, there are published data which indicate that the constituent free ethylene and propylene glycols and free fatty acids, generated from enzymatic ester cleavage of the parent glycol esters, are expected to be extensively biodegraded and to have low degrees of aquatic toxicity. No further aquatic toxicity and biodegradation testing is proposed for glycol esters category of the aliphatic esters.

There were sufficient existing toxicity data for the HPV and structurally related surrogate glycol esters to make hazard assessments for mammalian health effects (SIDS data endpoints) for the HPV glycol esters substances. Given the similar chemical and structural features between the HPV and surrogate glycol esters (including the structurally analogous polyethylene glycol or propylene glycol fatty acid esters), it was justifiable to utilize the available existing data to make read-across assessments on potential toxicity and to bridge toxicity data for the HPV substances. No additional mammalian toxicity testing is proposed for substances in the glycol esters category. This resourceful use of existing data will help minimize the use of animals for testing while assessing the potential hazards in the glycol esters category of the aliphatic esters. Taken into consideration in the assessment were the published health safety assessments for thirteen propylene glycol fatty acid esters [Andersen, 1999a] as well as the multigeneration feeding studies for several polyethylene glycol fatty acid esters [Oser *et al.* (1956b), Elder (1983b)]. A technical discussion was provided to address the reproductive/developmental potential of the HPV glycol esters, based on the published data that have been reported for related polyethylene glycol monostearates.

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The following member companies of the American Chemistry Council's Aliphatic Esters Panel are sponsoring the Glycol Esters category:

LIST OF MEMBER COMPANIES

BASF Corporation

Cognis Corporation

C.P. Hall Company

Crompton Corporation

E.I. duPont de Nemours & Company, Inc.

Goldschmidt Chemical Corporation

Inolex Chemical Company

Kaufman Holdings Corporation

Quaker Chemical Company

Stepan Company

Uniqema

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Appendix - Robust Summaries for Glycol Esters

- Part I. HPV Substances in the Glycol Esters Category Test Plan
- Part II. Surrogate Glycol Esters

TEST PLAN FOR THE GLYCOL ESTERS CATEGORY
OF THE ALIPHATIC ESTERS

1.0 INTRODUCTION

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) has committed voluntarily to develop a Screening Information Data Set (SIDS) (i.e., physicochemical data, environmental fate and effects, and human health effects) for the "glycol esters" category of aliphatic esters chemicals, listed under the High Production Volume (HPV) Chemical Challenge Program. This test plan sets forth how the Aliphatic Esters Panel intends to address the testing information for the nine glycol esters listed in Table 1A (organized by CAS Numbers in ascending order).

The Panel added one chemical, Hexanoic acid, 2-ethyl, diester with triethylene glycol (94-28-0), to the original glycol esters group of chemicals. The other chemicals in this test plan were originally part of a larger test plan submitted on December 20, 2001. As a result of comments, the Panel has revised the original test plan for these chemicals, and the revised approach follows below.

The chemical structures of the glycol esters are given in Figure 1. The test plan identifies the CAS numbers used to characterize the SIDS endpoints for the glycol esters in this category, describes the chemical and structural features/similarities of the glycol esters, identifies existing data of adequate quality for substances in the glycol esters category and provides the Panel's rationale for applying the available SIDS data to characterize the hazards of the category members. The primary objective of this effort is to identify and to characterize the physicochemical properties, mammalian health and environmental fate and effects for the glycol esters category of the aliphatic esters consistent with the EPA HPV Program.

The data from this HPV category will be used to inform the public about the potential health effects of the glycol esters category of the aliphatic esters. Developing a data matrix with reliable studies and applying justifiable read-across assessments will help provide a sufficiently robust data set to characterize the endpoints in the HPV Chemical Challenge Program. This approach to the resourceful use of existing data will help minimize the use of animals for testing while assessing the potential hazards in the glycol esters category of the aliphatic esters.

Table 1A: List of Individual Substances in the Glycol Esters Category
(by ascending CAS Numbers and designated TSCA HPV chemical name)

Chemical Name (designated TSCA HPV chemical name)	CAS Number
Hexanoic acid, 2-ethyl-, diester with triethyl ene glycol *	94-28-0
Oleic acid, propylene ester	105-62-4
Stearic acid, 2-hydroxyethyl ester	111-60-4
Stearic acid, ethylene ester	627-83-8
Hexanoic acid, 2-ethyl-, diester with tetraethyl ene glycol	18268-70-7
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	42222-50-4
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	67989-24-6
Decanoic acid, mixed diesters with octanoic acid and triethyl-ene glycol	68583-52-8
Heptanoic acid, oxybis(2,1-ethanediyl-oxo-2,1-ethanediyl) ester	70729-68-9

*This chemical was added to glycol esters category.

2.0 DESCRIPTION OF THE GLYCOL ESTERS CATEGORY

Nine CAS Numbers are used to describe the glycol esters in this HPV category of the aliphatic esters (Table 1A). 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). These esters are often referred to as "glycol or diol esters" or as "alkylidene or alkanediyl esters."

The rationale for grouping the glycol or diol esters is that they represent structurally similar ethylene/propylene glycol esters in which the hydroxyl groups in the glycol are functionalized with fatty acids as ester derivatives. Esterification of the glycol with fatty acids such as stearic and oleic acid can provide glycol diesters in the 38 to 41 carbon number range, which typically make them relatively non-volatile and high boiling liquids with limited water solubility and with sufficient polar characteristics to make them useful as lubricants and solvents. In the case of the tri- and tetraethylene glycol diesters, the ether linkage in the polyalkylene portion of the glycol also imparts additional polar character to these glycol esters (Reck, 1999).

Metabolism of the HPV glycol esters in animals would be expected to occur initially via enzymatic hydrolysis leading to the corresponding free fatty acids and free glycol alcohols (e.g., ethylene glycol, propylene glycol, 2,2-dimethyl-1,3-propanediol, polyethylene glycol) [Long *et al.* (1958b); Elder (1982; 1983a); Andersen (1999a)]. These free fatty acids and glycols can be further metabolized or conjugated (e.g., glucuronides, sulfates, etc.) to polar products that are excreted in the urine [Long *et al.* (1958a); Bisesi (2001); Cragg (2001a,b); Bevan (2001b); Thurman (1992)]. The fatty acids, especially the natural occurring ones such as stearic and oleic acids, have low degrees of toxicity [Cragg (2001a,b); Elder (1986, 1987); Chow (1999)]. The toxicity of the alkylidene or alkanediyl glycols has been extensively reviewed, especially in case of ethylene glycol [ATSDR (1997); Cavender (2001); Andersen (1999b)] and propylene glycol [Andersen (1994); Hardman *et al.* (2001); NTIS (1973)].

Metabolic hydrolytic reactions of esters have been extensively reviewed in the literature [Testa and Mayer (2003); Bisesi (2001); Buchwald (2001); Parkinson (2001); Heyman (1982); Long *et al.* 1958a,b)]. It is beyond the scope of this test plan to discuss or review this topic in more detail except to mention its contribution in the general metabolism scheme for ester linkages.

Organization of HPV Glycol Esters and Surrogate Glycol Esters

Due to the number of substances in this category, it is useful to organize the nine HPV glycol esters on the basis of total carbon numbers rather than in the order of their CAS numbers as in Table 1A. Hence, Table 1B below has been organized in that manner.

Table 1B. Organization of the Nine HPV Glycol Esters according to Total Carbon Number in the Glycol Ester

Individual Glycol Ester (organized according to total carbon number) Chemical Name (designated TSCA HPV names)	CAS Number	Carbon Number in Acid	Carbon Number in dihydroxy alcohol	Total Carbons in Glycol Ester	MW
Stearic acid, 2-hydroxyethyl ester	111-60-4	C18	C2	C20	329
Hexanoic acid, 2-ethyl-, diester with triethylene glycol	94-28-0	C8	C6	C22	403
Heptanoic acid, oxybis(2,1-ethanediyl-2,1-ethanediyl) ester	70729-68-9	C7	C8	C22	419
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	67989-24-6	C18	C5	C23	368
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol (use average of C9*)	68583-52-8	C9 *	C6	C24	431
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	18268-70-7	C8	C8	C24	447
Stearic acid, ethylene ester	627-83-8	C18	C2	C38	595
Oleic acid, propylene ester	105-62-4	C18	C3	C39	605
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	42222-50-4	C18	C5	C41	633

* An average of C9 carbon atoms was used for the fatty acid in the mixed diester of decanoic and octanoic acids of triethylene glycol (CAS 68583-52-8)

There are relevant published or unpublished toxicity data that also exist for five structurally homologous or analogous glycol esters (denoted as "surrogate glycol esters") which provide very useful read-across information to help bridge the toxicity data for the HPV substances.

The five structurally analogous surrogate glycol esters are:

- Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8)
- Triethylene glycol, diheptanoate (CAS 7434-40-4)
- Propylene glycol, monostearate (CAS 1323-39-3)
- Propylene glycol, dilaurate (CAS 22788-19-8)
- Propylene glycol, diisostearate (CAS 68958-54-3)

Incorporation of these five surrogate glycol esters into Table 1B leads to Table 1C below, which is useful in the overall HPV data review and test plan evaluation and provides reasonable justification (based on total carbon number, structural or MW similarities, etc.) to support read-across health effects and environmental fate/toxicity assessments.

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Table 1C. Organization of the Nine HPV Glycol Esters and Five Surrogate Glycol Esters According to Total Carbon Number for Use in HPV Data Assessment and Testing Rationale**

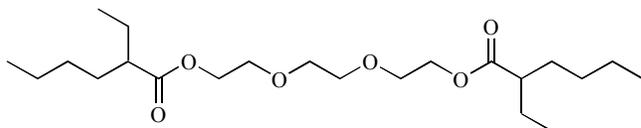
Individual Glycol Ester (organized according to total carbon number) Chemical Name (designated TSCA HPV names)	CAS Number	Carbon Number in Acid	Carbon Number in dihydroxy alcohol	Total Carbons in Glycol Ester	MW
Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol **	71839-38-8	C7	C8	C15	258
Stearic acid, 2-hydroxyethyl ester	111-60-4	C18	C2	C20	329
Triethylene glycol, diheptanoate **	7434-40-4	C7	C6	C20	375
Propylene glycol, monostearate **	1323-39-3	C18	C3	C21	343
Hexanoic acid, 2-ethyl-, diester with triethylene glycol	94-28-0	C8	C6	C22	403
Heptanoic acid, oxybis(2,1-ethanedioxy-2,1-ethanediyl) ester	70729-68-9	C7	C8	C22	419
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	67989-24-6	C18	C5	C23	368
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	68583-52-8	C9	C6	C24	431
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	18268-70-7	C8	C8	C24	447
Propylene glycol dilaurate**	22788-19-8	C12	C3	C27	441
Stearic acid, ethylene ester	627-83-8	C18	C2	C38	595
Oleic acid, propylene ester	105-62-4	C18	C3	C39	605
Propylene glycol diisostearate**	68958-54-3	C18	C3	C39	609
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	42222-50-4	C18	C5	C41	633

** The five surrogate glycol esters (highlighted or shaded) are not part of the present HPV glycol esters category test plan. They are included in this matrix table since existing toxicity data for these materials can be used for read-across assessment or for bridging data to the HPV glycol esters category members based on chemical /structural similarities.

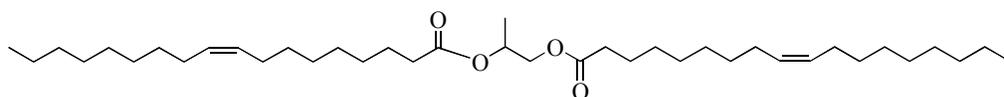
Figure 1. Chemical Structure of the Glycol Esters Listed in Table 1A

The structures of the HPV glycol esters are given in the order listed in Table 1A, which is organized according to ascending CAS Numbers. The chemical structure depicted for each HPV substance is consistent with the designated CAS Number and is considered representative of the commercial product evaluated.

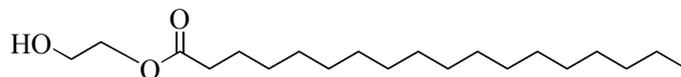
Hexanoic acid, 2-ethyl-, diester with triethylene glycol (CAS 94-28-0)



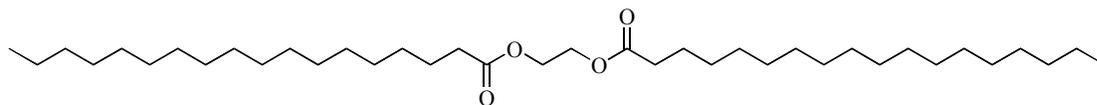
Oleic acid, propylene ester (CAS 105-62-4)



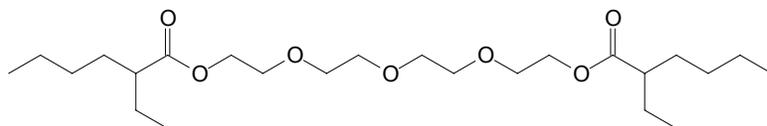
Stearic acid, 2-hydroxyethyl ester (CAS 111-60-4)



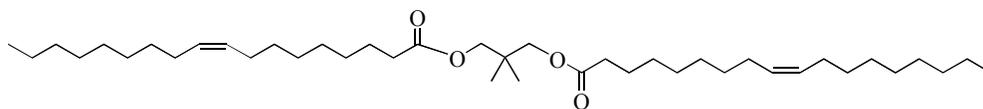
Stearic acid, ethylene ester (CAS 627-83-8)



Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol (CAS 18268-70-7)

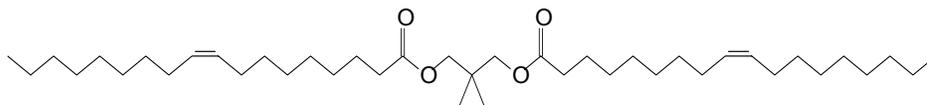


9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (CAS 42222-50-4)

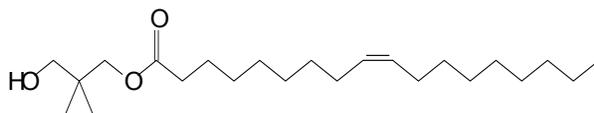


9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6)

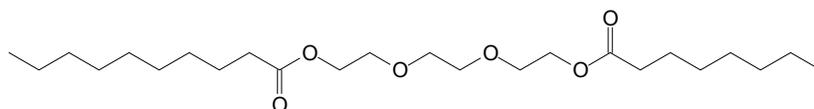
Major (88%)



Minor (12%)



Decanoic acid, mixed diesters with octanoic acid and triethylene glycol (CAS 68583-52-8)



Heptanoic acid, oxybis(2,1-ethanediyl)oxy-2,1-ethanediyl ester (CAS 70729-68-9)

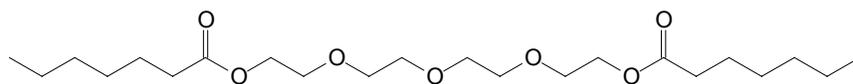
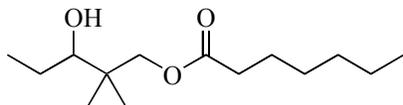
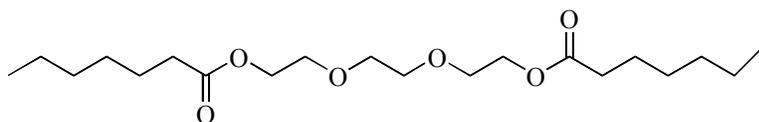


Figure 2. Chemical Structure of Surrogate Glycol Esters

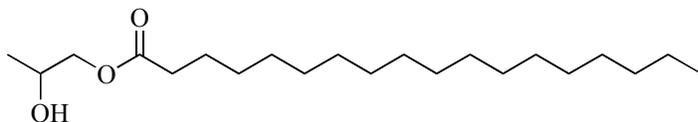
Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8)



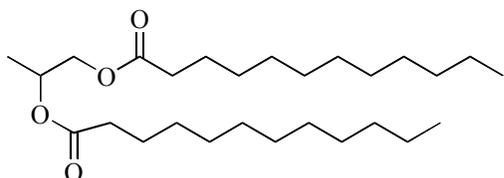
Triethylene glycol, diheptanoate (CAS 7434-40-4)



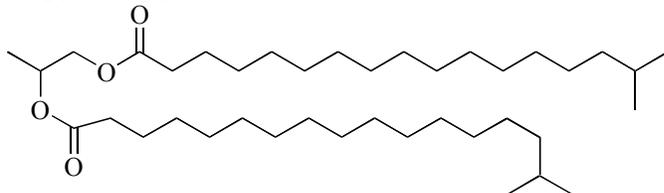
Propylene glycol, monostearate (CAS 1323-39-3)



Propylene glycol, dilaurate (CAS 22788-19-8)



Propylene glycol, diisostearate (CAS 68958-54-3)



3.0 DESCRIPTION OF AVAILABLE PUBLIC AND COMPANY DATA

A review of the literature and confidential company data was conducted on the physicochemical properties, mammalian toxicity endpoints, and environmental fate and effects for the nine glycol esters using CAS numbers and chemical names. Searches included the following sources: MEDLINE and TOXLINE databases; the TSCATS database for relevant unpublished studies on these chemicals; and standard handbooks and databases (e.g., Sax, CRC Handbook of Chemistry and Physics, IUCLID, Merck Index, and other references) for physicochemical properties.

The reports were selected for review based on the following criteria: relevant SIDS endpoint, relevant CAS number, final report of company study (TSCATS), peer reviewed journal, or comprehensive reviews. Safety assessment reviews for various ethylene glycol or propylene glycol fatty acid esters and related polyethylene glycol (PEG) fatty acid esters have been carried out by the Cosmetic Ingredient Review Expert Panel in the Journal of the American College of Toxicology [Elder (1982, 1983a, 1983b); Andersen (1994)] and in the International Journal of Toxicology [Andersen (1999a); Andersen (2000)]. Five surrogate glycol esters that were chemically or structurally-related or analogous to the HPV glycol esters were also reviewed to identify available published or unpublished data to help bridge data for environmental fate, aquatic toxicity or mammalian toxicity.

3.1 Physicochemical Properties Data

Physicochemical data [i.e., melting point, boiling point, vapor pressure, water solubility and octanol-water partition coefficient] for the HPV glycol esters and surrogate glycol esters were obtained from the searches and sources described above. In addition to available experimental and measured data, calculated physicochemical values were also incorporated into a summary table for all these physical and chemical properties. There are a number of reasons for this approach:

- The EPA guidance (www.epa.gov/chmrtk/robsumgd.htm) allows inclusion of calculated values in the robust summaries for physicochemical elements.
- A complete set of physical property data was a prerequisite to calculate fugacity or the chemical distribution in the environment (see below)
- Physicochemical properties data had yet to be developed for some of the glycol esters.

The physicochemical properties were also modeled using the Syracuse Research Corp./EPA computer program EPIWIN, a modeling package that includes a number of algorithms developed for the EPA [EPIWIN (1999); US EPA (1999b)]. EPIWIN is the program used and advocated by the EPA. Because the model is a structure-property model, a specific discreet structure is required. EPIWIN contains a CAS number database, which contains the structures for a large number of chemicals. For mixtures, a single representative structure is contained in the database, and in this test plan these surrogate chemical structures were accepted for further modeling.

3.2 Environmental Fate and Biodegradability Data

Environmental fate data including biodegradability, photodegradation, stability in water (i.e., hydrolysis) and fugacity (chemical distribution in the environment) data were primarily obtained through the literature, from unpublished confidential company data, or from modeling [e.g., EPIWIN, EQC (Level III) - Mackay et al. (1996)]. When relevant studies (particularly biodegradability endpoints) were identified, the study reports were reviewed, robust summaries were prepared and the reliability of the data was assessed. The method of Klimisch *et al.* (1997) was utilized to evaluate the data quality of the studies.

3.3 Aquatic Toxicity Data

Existing data for aquatic toxicity studies (e.g., fish, invertebrate and algae) for the HPV and surrogate glycol esters were obtained primarily from the literature or from unpublished confidential proprietary studies. When relevant studies were identified, the study reports were reviewed, robust summaries were prepared and the reliability of the data was assessed. The method of Klimisch *et al.* (1997) was utilized to evaluate the data quality of the aquatic toxicity studies.

3.4 Mammalian Toxicity Data

The existing data for the mammalian toxicity endpoints for the HPV and surrogate glycol esters were reviewed using the literature searches to identify the most relevant studies for the substances in the glycol esters category. For some substances, there may have been no relevant studies identified in the searches. For the HPV glycol esters that contained relevant data, the available studies were reviewed using the criteria outlined in the EPA's methods for determining the data quality and adequacy of the existing data and the reliability ranking method of Klimisch *et al.* (1997). Relevant studies that were available for the mammalian toxicity endpoints are summarized in the HPV test plan and presented in greater detail in the robust summaries in the Appendix.

Studies that were selected for the robust summaries generally represented the most relevant or reliable data for a particular SIDS endpoint. Published studies from the general literature as well as from a number of unpublished confidential company reports were obtained and summarized. Some of the reported studies (particularly older acute data) could not be summarized because of limited experimental details to assess their quality (i.e., not assignable, Klimisch reliability code 4) or only were reported as LD₅₀ values from secondary sources. These studies were included in the summary data table and may be included in the robust summaries with reference to the secondary literature source.

4.0 EVALUATION OF EXISTING DATA

The nine HPV substances in Table 1A were grouped together under the glycol esters category of aliphatic esters because of the presence of the diol or glycol functionality that was common to all the HPV glycol esters. The HPV substances were fatty acid (i.e., C6-18 fatty acids which include the naturally occurring fatty acids, stearic and oleic acids) ester derivatives of ethylene glycols (EG), propylene glycols (PG) or polyethylene glycols (PEG). In addition to the existing data for the HPV substances, there were read-across data for five surrogate glycol esters not on the HPV list in this category. Because of their structural similarities, these five surrogate glycol esters provided useful data for bridging toxicity information for structurally analogous HPV glycol esters in regards to mammalian toxicity, aquatic toxicity and biodegradability endpoints.

The five surrogate glycol esters were:

- Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8)
- Triethylene glycol, diheptanoate (CAS 7434-40-4)
- Propylene glycol, monostearate (CAS 1323-39-3)
- Propylene glycol, dilaurate (CAS 22788-19-8)
- Propylene glycol, diisostearate (CAS 68958-54-3)

The existing data for the HPV glycol esters and for the surrogate glycol esters have been reviewed. Discussion will be provided in this section regarding the available data for SIDS toxicity endpoints, an assessment and summary of the data, and comments on HPV test plan as to whether the existing data are adequate and whether further testing is needed or planned. The order of discussion of endpoints will be: (1) physicochemical properties; (2) environmental fate and biodegradability; (3) aquatic toxicity; and (4) mammalian health effects.

4.1 Physicochemical Properties Data

Summary of Physicochemical Properties Data

The physicochemical properties for the HPV glycol esters and surrogate glycol esters are summarized in Table 2. EPIWIN was used to calculate the physicochemical properties for the nine HPV glycol esters as well as for the five surrogate glycol esters. The experimental data and calculated (EPIWIN) data for the physicochemical properties of the glycol esters are summarized in Table 2.

Data Assessment and Test Plan for Physicochemical Properties

In general, the glycol monoesters with shorter carbon-number fatty acids (C6-C7) were predicted to be more water-soluble and less lipophilic than the corresponding glycol monoesters containing long-chain fatty acids such as stearic and oleic acids. The glycol diesters were predicted to be more lipophilic and less water-soluble than the corresponding glycol monoesters [e.g., ethylene glycol distearate (CAS 627-83-8) *versus* its monostearate (CAS 111-60-4); 2,2-dimethyl-1,3-propanediol dioleate (CAS 42222-50-4) *versus* its monooleate (CAS 67989-24-6)]. In addition, the glycol diesters have higher boiling points than the corresponding monoesters.

Polyethylene glycol (or polyoxyethylene) esters, that contain more than one repeating ethylene glycol unit, generally showed greater water solubility than the corresponding monoethylene glycol esters, owing to the increased polarity of multiple ether linkages; this was consistent with what would be expected (Reck, 1999). The greater degree of ether linkage was also consistent with the lower lipophilicity (log P) values predicted by EPIWIN.

Most of the glycol esters on the HPV list have molecular weights of greater than 300, have high boiling points (>400 °C) and showed very low water solubility and high lipophilic characteristics (log P >4 or 5). The glycol distearates and dioleates had total carbon numbers above C38 and high predicted boiling points (>550 °C) (Table 2).

The five surrogate glycol esters were selected because they were structurally similar to the nine HPV glycol esters. These surrogate glycol esters were examined and their experimental and calculated (EPIWIN) data were used to help assess the physicochemical properties expected for the HPV glycol esters.

Based on the summarized data in Table 2, there are sufficient physicochemical data to characterize the substances in the glycol esters category and no additional testing is proposed.

4.2 Environmental Fate and Biodegradability Data

Summary of Environmental Fate and Biodegradability Data

The environmental fate and biodegradability data relevant to the glycol esters category are summarized in Table 2 and Table 3, respectively. Biodegradation testing has been carried out for two HPV glycol esters [heptanoic acid, oxybis(2,1-ethanediyl-2,1-ethanediyl) ester (CAS 70729-68-9) and 9-octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6)] and for two surrogate glycol esters [heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8) and triethylene glycol, diheptanoate (CAS 7434-40-4)].

Other environmental fate endpoints such as photodegradation, stability in water (hydrolysis), and chemical distribution (transport) in the environment (fugacity modeling) have been calculated for the glycol esters using EPIWIN. Calculated hydrolysis half-lives and atmospheric photodegradation rates for the glycol esters using EPIWIN are summarized in Table 2.

Chemical distribution of the glycol esters in the environment has been determined using the EQC (Level III) fugacity-based multimedia model [Mackay *et al.* (1996)]. The calculated values for the transport (or distribution) in the soil, air, water and sediment environmental compartments are summarized in Table 2.

Data Assessment and Test Plan for Environmental Fate and Biodegradability

Biodegradation studies with two HPV and two surrogate glycol esters have been reported. The extent of biodegradation has been reported to range from 65% to 98% in 28 days for the four glycol esters. These results indicate that the glycol esters are rapidly and extensively biodegraded. The tested substances covered the C15-C23 carbon range for the glycol esters. Glycol esters above C30 appear to be mainly comprised of the glycol diesters such as the dioleates and distearates, and several of the HPV substances are simply to be diester homologs of the corresponding monooleate or monostearate esters. These diesters are expected to be microbio-

ally metabolized in the environment to the corresponding monoesters, some of which have been reported to be extensively biodegraded. For example, the glycol monooleate ester, 9-octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6) has been demonstrated to be readily biodegradable in the OECD 301B modified Sturm test. Since 9-octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl (di)ester (CAS 4222-50-4) is the corresponding diester derivative of the above glycol monooleate (i.e., CAS 67989-24-6), it is not unexpected that the dioleate would be extensively biodegraded as well. This is based on the premise that the dioleate would be expected to be microbially metabolized (hydrolyzed) to the monooleate, which has already been found to be readily biodegradable.

Biodegradation or enzymatic (microbial) breakdown of the glycol esters would be expected to ultimately lead to the free glycol such as propylene glycol, ethylene glycol, polyethylene glycol and to the corresponding free fatty acids, including stearic acid and oleic acid. There are adequate biodegradability data in the scientific literature to support the premise that these constituent components, namely, the free glycols and the free fatty acids, would be expected to be rapidly and extensively biodegraded in aerobic systems (e.g., sewage, activated sludge, wastewater) in the environment [Swisher (1987); Vershueren (1996); IUCLID (1996); ASTDR (1997); Howard (1990)].

Based on the above discussion and the existing data for the four glycol esters and published biodegradability data for constituent free glycols (e.g., ethylene glycol, propylene glycol and polyethylene glycol) and free fatty acids (e.g., stearic acid, oleic acid), it is expected that the HPV glycol esters would be rapidly and extensively biodegraded in the environment. Further biodegradation testing for substances in this group is not proposed at the present time given that sufficient existing data are available to assess the biodegradability potential of the structurally related HPV glycol esters substances.

In addition, hydrolysis half-lives and atmospheric photodegradation rates have been calculated using EPIWIN. Environmental distribution was determined using the EQC (Level III) model (Mackay, et al. 1996). The distribution between the environmental compartments for glycol esters in this category appears to be influenced by lipophilicity or water solubility. For lipophilic glycol esters with calculated log Pow >7, the EQC (Level III) model predicted a greater chemical distribution in the sediment and soil compartment (see Table 2). Conversely, for glycol esters with greater water solubility characteristics [e.g., heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8); triethylene glycol, diheptanoate (CAS 7434-40-4); heptanoic acid, oxybis(2,1-ethanediyl) ester (CAS 70729-68-9)], the EQC Level III model predicted greater distribution in the water compartment, in comparison to other very water-insoluble glycol esters (Table 2). Based on the calculated data for these environmental fate endpoints in Table 2, sufficient data exist and that no additional testing is proposed for the substances in the glycol esters category.

4.3 Aquatic Toxicity Data

Summary of Aquatic Toxicity Data

Twelve acute aquatic toxicity studies (e.g., fish, invertebrates, algae) relevant to the glycol esters category are summarized in Table 3. Aquatic toxicity testing have been reported for three HPV glycol esters [hexanoic acid, 2-ethyl-, diester with triethylene glycol (CAS 94-28-0); heptanoic acid, oxybis(2,1-ethanediyl) ester (CAS 70729-68-9); 9-

octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6)] and for two structurally analogous surrogate glycol ester [heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8); triethylene glycol diheptanoate (CAS 7434-40-4)]. The existing acute aquatic toxicity data for these structurally related glycol esters provides sufficient information to help assess the potential aquatic toxicity for the substances in the glycol esters category.

Data Assessment and Test Plan for Aquatic Toxicity

Acute aquatic toxicity data have been reported for the HPV and surrogate glycol esters. Three HPV substances [hexanoic acid, 2-ethyl-, diester with triethylene glycol (CAS 94-28-0); heptanoic acid, oxybis(2,1-ethanediyl-2,1-ethanediyl) ester (CAS 70729-68-9); and 9-octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6)] have been tested. Hexanoic acid, 2-ethyl-, diester with triethylene glycol (CAS 94-28-0) was shown to have LC50 and EC50 values of > 97 mg/L in both fish and daphnids. Heptanoic acid, oxybis(2,1-ethanediyl-2,1-ethanediyl) ester (CAS 70729-68-9) was shown to have LC50 and EC50 values of 720-4800 mg/L and 3800 mg/L, in fish and daphnids, respectively. It also had an EC50 value of 25 mg/L in algae. On the other hand, 9-octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6) was reported to have an EC50 of ~2000 mg/L in daphnia. The two surrogate glycol esters, heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8) and triethylene glycol diheptanoate (CAS 7434-40-4), have also been tested in three aquatic species (fish, invertebrates, algae) and the results are summarized in Table 3. The available data for the tested HPV and surrogate glycol esters indicate that acute aquatic toxicity would not be expected at the water solubility limit or water saturation levels (WSL) of the tested glycol ester materials.

While the higher molecular weight glycol esters (>C38, MW ~600) have not been evaluated, they are probably expected to have low degrees of aquatic toxicity due to their very low water solubility. It should be noted that several substances on the HPV list are simply the diester analogs of the corresponding HPV ethylene or propylene glycol monoesters. One example is that stearic acid, ethylene ester (CAS 627-83-8) is simply the diester analog of stearic acid, 2-hydroxyethyl ester (CAS 111-60-4). Another example is that 9-octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl (di)ester (CAS 4222-50-4) is simply the diester analog of 9-octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6). Interestingly, the latter HPV substance (i.e., monooleate ester: CAS 67989-24-6) has been tested and has been shown not to be acutely toxic to fish (LC50 ~2000 ppm). Therefore, the dioleate HPV substance (CAS 4222-50-4), would be expected to show a similar low degree of aquatic toxicity because of its very low water solubility and the fact that it can be enzymatically hydrolyzed to the monooleate substance, which already has been tested and found not to be acutely toxic. It is of interest to note that ethylene glycol and propylene glycol are not acutely toxic to aquatic organisms [Verschueren (1996); ATSDR (1997); IUCLID (1996)]. In addition, free fatty acids (e.g., stearic and oleic acids) that may be generated from enzymatic metabolism of the glycol esters are expected to have low degrees of aquatic toxicity [Verschueren (1996); IUCLID (1996)]

Based on the above findings/discussion and on the structural similarities between the tested HPV and surrogate glycol esters, the existing aquatic toxicity data for the glycol esters, free glycols and free fatty acids, is sufficient to address the potential aquatic toxicity of the HPV substances in glycol esters category and, therefore, no further aquatic testing is proposed.

The acute aquatic studies followed generally accepted test guidelines in which water solutions or water accommodated fractions (WAFs) were generated for poorly water-soluble lubricant test materials at nominal loading rates and then evaluated for toxicity. However, the ACC Panel believes that in cases where the LC50 or EC50 values (based on nominal loading rates to generate the test solutions or WAFs) clearly exceeded the water solubility of the glycol esters and appear exceedingly improbable (e.g., 3800 mg/L, 4800 mg/L, >1000, >2000 mg/L), it would be more appropriate to note (as in Table 3) that the toxicity endpoint (LC50 or EC50 value) greatly exceeded the maximum water solubility limit (WSL) of the test material. For very water insoluble test materials such as for the glycol esters (Table 2), the existing data suggest that aquatic toxicity would not be expected at or close to the maximum water solubility limit (WSL) or at water saturated levels, typical of water solutions or WAFs generated using high nominal loading rates.

4.4 Mammalian Toxicity Data

A) Acute Mammalian Toxicity

Summary of Available Acute Oral Toxicity Data

Acute oral toxicity data relevant to the glycol esters category are summarized in Table 3 and have been reported for five of the nine HPV substances as well as for the surrogate glycol esters. Overall, the acute oral LD₅₀ values for these substances was greater than the 2000 mg/kg, indicating a very low order of toxicity for the glycol esters. It should be mentioned that acute dermal toxicity studies have also been carried out and reported for the various propylene glycol fatty acid esters and polyethylene glycol fatty acid esters, particularly those used in cosmetic applications [see reviews by Elder (1982; 1983a; 1983b); Andersen (1994; 1999a; 2000)] but will not be discussed in any depth here. Overall, the glycol fatty acids exhibit very low degrees of acute oral and dermal toxicity.

Data Assessment and Test Plan for Acute Mammalian Toxicity

Adequate acute oral toxicity studies have been located for five of the nine HPV glycol esters and for the structurally analogous surrogate glycol esters. There were no deaths when the HPV glycol esters and the surrogate glycol esters were administered at oral doses of >2000 mg/kg in rodents. The reported oral rat LD50 values ranged from > 2g/kg to >34.6 g/kg for the HPV substances and the surrogate glycol esters tested (Table 3). Hence, the existing data (covering C15-C39 carbon number range) consistently demonstrated a very low order of acute oral toxicity for the glycol esters and, overall, covered the carbon number range for the HPV substances (C20-C41). No additional acute toxicity testing is proposed for HPV substances in the glycol esters category.

As mentioned above, the ethylene glycol fatty acid esters, propylene glycol fatty acid esters and the PEG fatty acid esters have been extensively studied and their health safety evaluated [Andersen (1999a); Elder (1982; 1983a)]. For example, propylene glycol monostearate (CAS 1323-39-3) has an acute oral LD50 of 25.8 g/kg in rats. In addition, propylene glycol stearate is extensively used in many pharmaceuticals and is considered as "Generally Recognized as Safe" (GRAS) for food applications [Elder (1983a); Andersen (1999a)]. Numerous other propylene glycol fatty acid monoesters and diesters as well as polyethylene glycol (PEG) fatty acid monoesters and diesters,

have been demonstrated also to have very low degrees of acute oral and dermal toxicity [Andersen (1999a,c); Elder (1983b)].

B) Mutagenicity and Genotoxicity

Summary of Mutagenicity and Genotoxicity Data

A summary of the mutagenicity and genotoxicity data for the HPV substances in the glycol esters category and structurally analogous surrogate substances is presented in Table 3. Bacterial gene mutation assays have been conducted with one HPV glycol ester [heptanoic acid, oxybis(2,1-ethanedioxy-2,1-ethanediyl) ester, (CAS 70729-68-9)] and three surrogate glycol esters [heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8); triethylene glycol diheptanoate (CAS 7434-40-4); and propylene glycol monostearate (CAS 1323-39-3)]. In addition, the HPV substance, heptanoic acid, oxybis[2,1-ethanedioxy-2,1-ethanediyl] ester (CAS 70729-68-9) has been evaluated for mutagenicity in the Chinese hamster ovary cell forward mutation assay on the HGPRT locus. The surrogate glycol ester, heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8), has been evaluated for *in vitro* genotoxicity using human peripheral lymphocytes.

Mutation Assay

One HPV substance, heptanoic acid, oxybis[2,1-ethanedioxy-2,1-ethanediyl] ester (CAS 70729-68-9), has been shown to be negative for mutagenic activity in the Ames assay and in the Chinese ovary cell forward mutation assay on the HGPRT locus, with and without metabolic activation. In addition, three surrogate glycol esters [heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8); triethylene glycol diheptanoate (CAS 7434-40-4); and propylene glycol monostearate (CAS 1323-39-3)] have been evaluated in the bacterial reverse mutation test. All three surrogate glycol esters were shown to be negative for mutagenic activity, with and without metabolic activation.

Chromosomal Aberration Genotoxicity Assay

The surrogate glycol ester, heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8), has been evaluated in the *in vitro* cytogenetics test using human peripheral lymphocytes. The results were negative for chromosomal aberrations. The genotoxicity data for this surrogate suggest that glycol esters are not likely to cause chromosomal aberrations. This is consistent with the chemistry of the glycol esters, which does not suggest the likelihood that these substances, or their constituent glycols or fatty acids, are electrophilic or reactive in nature. Therefore, the likelihood that the glycol esters may cause chromosomal aberration is expected to be very low.

Data Assessment and Test Plan for Mutagenicity and Genotoxicity

Due to the close structural and chemical similarities (i.e., glycol and fatty acids constituents) between the three surrogate glycol esters and the HPV glycol esters, read-across assessment for mutagenic toxicity is justifiable. Based on the existing data for the four glycol esters that were tested, the HPV glycol esters would not be expected to be mutagenic, with or without metabolic activation. These findings indicate that the glycol esters are not expected to cause point mutations. The existing data are sufficient to address the mutagenic potential for members of the glycol esters category and therefore, no further mutagenicity testing is proposed.

One surrogate glycol ester substance has been evaluated for mammalian cell genotoxicity and the negative findings, with and without metabolic activation, suggest that members of the glycol esters category and related structural analogs are not expected to be genotoxic. This is consistent with the chemistry of the glycol esters which does not suggest the likelihood that these substances, or their constituent glycols or fatty acids, are electrophilic or inherently reactive in nature. The available data adequately address the genotoxicity potential of the HPV substances in the glycol esters category and, therefore, no additional testing for genetic toxicity (e.g., chromosomal aberration) is proposed at this time.

In addition, the existing data for ethylene glycol, propylene glycol and natural fatty acids, do not indicate that these constituents are mutagenic or genotoxic [see reviews by ATSDR (1997); Andersen (1999a,b), Andersen (1994); WHO (2003); Elder (1986; 1987)].

C) Repeated-Dose Toxicity

Summary of Repeated-Dose Toxicity Data

Repeated-dose oral toxicity studies have been reported for two substances in the HPV glycol esters category [hexanoic acid, 2-ethyl-, diester with triethylene glycol (CAS 94-28-0); heptanoic acid, oxybis (2,1-ethanediyl-2,1-ethanediyl) ester (CAS 70729-68-9)] and for two surrogate glycol esters [propylene glycol monostearate (CAS 1323-39-3); heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8)]. The results are summarized in Table 3. It should be noted that repeated-dose dermal toxicity studies have also been carried out for various propylene glycol fatty acid esters and polyethylene glycol esters [see reviews by Elder (1982; 1983a; 1983b); Andersen (1994; 1999a; 2000)].

Repeated-Dose Oral Toxicity

In a 12-day rat oral feeding study with 0.1% or 1% in the diet, the HPV substance, hexanoic acid, 2-ethyl-, diester with triethylene glycol (CAS 94-28-0), did not cause any systemic toxicity. No adverse effects were observed with respect to food consumption, body weight gain, behavior, hematology, clinical chemistry, liver or kidney weight, gross or microscopic examination of the organs. Subchronic studies have also been carried out with another HPV substance, heptanoic acid, oxybis[2,1-ethanediyl-2,1-ethanediyl] ester (CAS 70729-68-9). In 28-day oral gavage studies in rats, the NOAEL was determined to be 1000 mg/kg for this material. No signs of toxicity were observed and no treatment-related changes in hematology and clinical chemistry were reported.

Two surrogate glycol esters have also been evaluated in repeated dose toxicity studies. Propylene glycol monostearate (CAS 1323-39-3), which was administered for 13 weeks at dietary concentrations of 0, 1.5%, 3.36% and 7.52%, showed no signs of toxicity in rats. Elder (1983a) in his review of these studies noted that the dosed groups showed no significant differences from the control group with respect to growth, relative organ weights, histopathology, blood chemistry, hematocrit, hemoglobin, white cell count, white cell differential count, clotting time, or urinalyses. Similarly, in 6-month oral studies, no signs of toxicity, gross or histological pathology were observed in rats and dogs fed diets containing up to 1.7% propylene glycol stearate (Elder, 1983a). For the surrogate glycol ester, heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8), doses up to 1000 mg/kg/day were well tolerated in rats that were orally gavaged daily with the test material for 28 days. Signs of

toxicity were minor, reversible or sex/species specific. Increased liver weights observed at 1000 mg/kg/day regimen were believed to be associated with adaptive changes associated with metabolism (e.g., enzyme induction) and were considered not toxic as such. Hyaline droplet formation observed in the male kidneys was believed to be a sex/species condition specific to only male rats, which has little relevance to humans.

Data Assessment and Test Plan for Repeated-Dose Toxicity

Sufficient read-across data for the two surrogate esters, especially the data reported for propylene glycol monostearate (CAS 1323-39-3) as well as the data for two HPV substances, suggest that members of the glycol esters category would be expected to exhibit a low order of toxicity following repeated oral administration. Additional support data that glycol esters are likely to have low orders of repeated-dose toxicity are based on a number of feeding studies conducted in rats, dogs, mice, rabbits and monkeys for PEG-8 stearate [polyethylene glycol stearate ester in which there are 8 repeating oxyethylene units in the polyethylene glycol (PEG-8) giving total of 34 carbon atoms in the PEG ester structure] (Elder 1983b). The Cosmetic Ingredient Review expert panel has reviewed these studies and has reported that PEG-8 stearate produced no significant changes in growth mortality rates, histopathological observations or hematology values in long-term feeding studies in rats (i.e., 8-week feeding study at 2% in diet; 9-week feeding study at 4% in diet and 2-year 3-generation feeding studies at 4% in the diet)(Elder, 1983b). Repeated-dose toxicity studies carried out with PEG-40 stearate and PEG-100 stearate also have been reported to demonstrate low degrees of toxicity [Elder (1983b)].

Since the HPV glycol esters and surrogate glycol esters are structurally analogous and have essentially similar constituent ethylene glycol or propylene glycol substructures and fatty acids, the available repeated-dose oral toxicity data are considered adequate for read-across assessment and for bridging data. The propylene glycol stearate repeated-dose toxicity data would be justified for read-across assessment of the lower carbon range glycol monoesters (covering the C20-C24 range of the HPV substances) while the PEG-8 stearate repeated-dose toxicity data would be justified for read-across assessment of the higher carbon range HPV glycol esters (i.e., C38-C41). Therefore, no further testing for repeated dose toxicity is proposed.

Overall, the ACC Aliphatic Esters panel believes that extensive subchronic toxicity data exist for numerous propylene glycol fatty acid esters and polyethylene glycol fatty acid esters to adequately address the repeated-dose toxicity of the HPV glycol esters [see reviews by Elder (1982; 1983a,b); Andersen (1994; 1999a,c; 2000; 2001)].

D) Reproductive/Developmental Toxicity

Summary of Reproductive/Developmental Toxicity Data

No adequate studies were located regarding reproductive and developmental effects in animals exposed to members of the HPV glycol esters category. Since members of this category are ester derivatives (e.g., C6-C18 fatty acids) of mainly, ethylene glycols or propylene glycols, chemically related glycol esters (e.g., polyethylene glycol fatty acid esters) were reviewed to identify available useful data to address potential reproductive/developmental effects.

Reproductive Toxicity

Although no adequate reproductive toxicity studies were located on members of the glycol esters category, numerous regulatory bodies have determined that these substances do not pose a reproductive hazard. These hazard and/or risk assessments are based on the fact that glycol esters would be metabolized (hydrolyzed) *in vivo* to the corresponding fatty acids and free glycol alcohols (e.g., ethylene glycol, propylene glycol) [WHO (2003)]. The free fatty acids and glycols can undergo further metabolism or conjugation to polar products that are either excreted or can be used as nutrients. In most cases, the parent fatty acids derived from the glycol esters are comprised of natural fatty acids that are typical of those (e.g., oleic, stearic acid) found in edible oils and fats.

For example, the FDA has determined that propylene glycol mono- and diesters of fats and fatty acids can be used safely in food, provided they are produced from edible fats and used in amounts not in excess of the reasonably required to produce their intended effect. The FDA and FAO/WHO Expert Committee on Food Additives have approved propylene glycol stearate (PGS), a mixture of mono- and diesters of stearic acid and propylene glycol, as a food additive. PGS is considered to be Generally Recognized as Safe (GRAS) for food use and has been approved for a variety of uses in the pharmaceutical industry and personal care (cosmetic) industry. Studies have demonstrated PGS to be readily hydrolyzed *in vivo*, and the resulting propylene glycol (PG) and stearic acid constituents enter their respective metabolic pathways. Propylene glycol distearate (PGDS) is similarly metabolized to PGS, PG and stearic acid in the gut. The mechanism, by which PG is utilized, by oxidation to lactic acid, has been thoroughly described in the literature (Elder, 1983a). The metabolism of stearic acid, a fatty acid constituent found in vegetable oils and in the fats and oils of animals, has also been thoroughly described in the literature.

Although reproductive studies have not been reported for PGS, a continuous breeding reproduction study in mice has been conducted by Morrissey *et al.* (1989) to evaluate the reproductive and developmental effects of its corresponding glycol alcohol, namely, propylene glycol (PG). Three experimental groups of mice were administered either 1.0% PG (daily dose of 1.82 g/kg), 2.5% PG (daily dose of 4.8 g/kg), or 5.0% PG (daily dose of 10.10 g/kg) during a 7-day pre-mating period in feed and water. The mice were then randomly grouped as mating pairs, cohabitated, and treated continuously for 98 days. There were no significant differences between control and experimental groups of mice with respect to mating index, mean number of live pups per litter, proportion of pups born alive, and sex of pups born alive. In addition, PG had no significant effects on gonads in rats given doses of 0%, 0.625%, 1.25%, 2.5% and 5% PG in a long-term feeding study (2-years). On the basis of these data, propylene glycol esters would not be expected to demonstrate reproductive effects.

Additional supporting data that glycol esters are unlikely to be reproductive toxicants are based on a multiple generation feeding of polyethylene glycol-8 stearate [PEG-8 stearate; a "related chemical" in which there are 8 repeating oxyethylene units in polyethylene glycol molecule giving a total of 34 carbon atoms in the PEG ester structure] in rats (Elder, 1983b). Animals receiving 4% PEG-8 stearate in their diet for three successive generations did not affect growth or fecundity. In another three-generation study in rats receiving diets containing 5%, 10%, or 20% PEG-8 stearate, reproduction and lactation responses were no different from controls at the 5% dose level. Newborn litter survival times were diminished most likely due to maternal neglect at the 10% and 20% dose levels. The overall level of reproductive performance (e.g., greater mortality rate of nurslings, impairment of lactation efficiency) was lower in animals fed the 20% PEG-8 stearate diet [Oser *et al.* (1956b); Elder (1983b)].

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Results from these studies showed a low order of reproductive/developmental toxicity. PEG stearates (including PEG-8 stearate) have been approved by the FDA for use in the bakery and pharmaceutical industries.

Although adequate reproductive and developmental studies have not been reported for ethylene glycol stearates or other ethylene glycol fatty acid esters, numerous studies have been conducted to evaluate reproductive and developmental effects of the parent glycol alcohol, namely, ethylene glycol (EG). EG itself is considered to have a relatively low order of toxicity; however, it is oxidized to more toxic metabolites such as glycolic acid, glycolaldehyde, glyoxalic acid, and oxalic acid. Accumulation of these C2 acid products leads to metabolic acidosis which is the underlying cause of EG systemic toxicity. The Cosmetic Ingredient Review (CIR) expert panel has reviewed these reproductive and developmental studies [Andersen, 1999b] as have many regulatory organizations. The Lowest Observed Adverse Effect Levels (LOAELs) and No Observed Adverse Effect Levels (NOAELs) for EG have been reported [see review by Andersen (1999b)]. The CIR report [Andersen, 1999b], have concluded along with other investigators, "... that normal human uses of EG would result in negligible plasma concentrations of EG that were well below the threshold limits for reproductive and developmental toxicity."

Developmental Toxicity/Teratogenicity

Although no adequate developmental toxicity studies were located on members of the glycol esters category, numerous regulatory bodies have determined that these substances do not pose a reproductive/developmental hazard. This is based on the previously discussed reproductive effects of related substances in the section above.

In addition to the above discussion, two developmental studies were located in the literature for propylene glycol (PG). PG was found not to be teratogenic in female mice given single oral doses of 10,000 ppm PG during gestation days 8-12. Fertility rates and all other parameters measured in mice given PG were not significantly different from controls (Kavlock, et al. 1987). However, Nomura (1977) observed malformations in 5 of 226 living fetuses from female mice injected subcutaneously with PG (0.01 ml/g body weight on day 9, 10, 11 of gestation). The water control group (0.01 ml/g body weight on day 9, 10, 11 of gestation) only had one (1) malformation of 320 living fetuses. The incidence of malformations in historical untreated controls was 3 fetuses of 1,026 living fetuses. From these findings, it appears unlikely that glycol esters, as a category would pose developmental toxicity concerns.

Although NOAELs and LOAELs have been reported for EG, exposure to EG would result in negligible plasma concentrations of ethylene glycol that were well below the threshold limits for reproductive and developmental toxicity [Andersen, 1999b].

Data Assessment and Test Plan for Reproductive/Developmental Toxicity

No adequate data were available on the reproductive or developmental toxicity of members of the HPV glycol esters category. It is unlikely that the glycol esters would cause reproductive and developmental effects based on their structural characteristics and *in vivo* metabolic processes. In addition, repeated-dose toxicity studies with glycol esters and related substances have not been reported to adversely affect the reproductive organs.

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The PEG esters are not considered to produce reproductive or developmental toxicity in sub-chronic or chronic toxicity studies. These available reproductive/developmental toxicity data, in conjunction with reproductive/developmental data for ethylene glycol, propylene glycol, propylene glycol stearate, PEG-8 stearate and natural fatty acids support no additional reproductive/developmental toxicity testing for the HPV glycol esters.

5.0 TEST PLAN SUMMARY

The American Chemistry Council's Aliphatic Esters Panel believes that sufficient health effects and toxicity data exist for the glycol esters category of the aliphatic esters [taking into account data available for structurally related and analogous surrogate glycol esters] to substantially characterize the mammalian health effects, aquatic toxicity and biodegradation endpoints for the members of this category under the HPV program (Table 4). No additional toxicity tests are proposed for the glycol esters category of the aliphatic esters. This approach to the resourceful use of existing data will help minimize the use of animals for testing and at the same time assess the potential hazards in the glycol esters category of the aliphatic esters.

Table 4. Assessment Plan for Substances in the Glycol Esters Category under the HPV Program

Glycol Ester	Total Carbon No. MW	Mammalian Health Effects						Ecotoxicity - Biodegradability			
		Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol *	C15 258	☐☐	☐☐	☐☐	☐☐			☐☐	☐☐	☐☐	☐☐
Stearic acid, 2-hydroxyethyl ester	C20 329	☐☐	R	R	R	TD	TD	R	R	R	R
Triethylene glycol, diheptanoate *	C20 375			☐☐				☐☐	☐☐	☐☐	☐☐
Propylene glycol, mono-stearate *	C21 343	☐☐	☐☐	☐☐							
Hexanoic acid, 2-ethyl-, diester with triethylene glycol	C22 403	☐☐	☐☐	R	R	TD	TD	☐☐	☐☐	R	R
Heptanoic acid, oxybis (2,1-ethanedioxy-2,1-ethanedioyl) ester	C22 419	☐☐	☐☐	☐☐	R	TD	TD	☐☐	☐☐	☐☐	☐☐
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	C23 368	☐☐	R	R	R	TD	TD	☐☐	R	R	☐☐
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	C24 431	R	R	R	R	TD	TD	R	R	R	R
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	C24 447	R	R	R	R	TD	TD	R	R	R	R
Propylene glycol dilaurate*	C27 441	☐☐									
Stearic acid, ethylene ester	C38 595	☐☐	R	R	R	TD	TD	R	R	R	R
Oleic acid, propylene ester	C39 605	R	R	R	R	TD	TD	R	R	R	R
Propylene glycol diisostearate*	C39 609	☐☐									
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	C41 633	R	R	R	R	TD	TD	R	R	R	R

* Shaded (highlighted) areas denote surrogate glycol ester substances - their data are included in table to help bridge data for structurally analogous HPV glycol esters.

Abbreviations in table:

☐ = adequate existing data available,

R = read-across data from structurally analogous glycol esters

-- denotes that no data for specific toxicity endpoint heading available for this surrogate glycol ester

TD = Technical discussion on reproductive/developmental toxicity potential for the glycol esters [see Section 4.4 (D)]

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Adequate experimental and calculated data for physicochemical properties (i.e., melting point, boiling point, vapor pressure, water solubility and octanol-water partition coefficient) exist for the glycol esters and surrogates in this category. No further testing is proposed for these endpoints for the glycol esters category of the aliphatic esters.

In addition, there are adequate calculated and experimental data for environmental fate endpoints such as photodegradation, hydrolysis, biodegradability (see below) and chemical distribution in the environment (via fugacity modeling) for the glycol esters in this category. No further testing is proposed for these endpoints for the glycol esters category.

Aquatic toxicity and biodegradation data exist for both the HPV glycol esters and the structurally analogous surrogate glycol esters to sufficiently allow for read-across assessments for the HPV substances and for bridging data. In addition, there are published data which indicate that the constituent free ethylene and propylene glycols and free fatty acids, generated from enzymatic ester cleavage of the parent glycol esters, are expected to be extensively biodegraded and to have low degrees of aquatic toxicity. No further aquatic toxicity and biodegradation testing are proposed for glycol esters category of the aliphatic esters.

There were existing toxicity data for the HPV and structurally related surrogate glycol esters to sufficiently make hazard assessments for mammalian health effects (SIDS data endpoints) for the HPV glycol esters substances. Given the similar chemical and structural features between the HPV and surrogate glycol esters (including the structurally analogous polyethylene or propylene glycol fatty acid esters), it was justifiable to utilize the available existing data to make read-across assessments on potential toxicity and to bridge toxicity data for the HPV substances. No additional mammalian toxicity testing is proposed for substances in the glycol esters category. A technical discussion was provided to address the reproductive/developmental potential of the HPV glycol esters, based on the published data that have been reported for related polyethylene glycol monostearates.

It should be noted that the propylene glycol (PG) stearates, oleates and laurates as well as polyethylene glycol (PEG) fatty acid esters (which are commonly used as nonionic surfactants, emulsifiers, emollients in many cosmetic applications) are very structurally similar to many of the HPV glycol esters substances and have low degrees of toxicity. It is important to point out that there is a large body of existing toxicity and health safety data for these structurally related PG and PEG fatty acid esters. It should be noted that propylene glycol stearate has been used in many pharmaceutical applications and is "Generally Recognized as Safe" (GRAS) in food applications. Thus, the surrogate glycol esters provided useful toxicity information for read-across assessments of the HPV glycol esters. Taken into consideration in the assessment were the published health safety assessments for thirteen propylene glycol fatty acid esters [Andersen, 1999a] as well as the multi-generation feeding studies for several polyethylene glycol fatty acid esters [Oser *et al.* (1956b), Elder (1983b)].

Robust summaries of existing health effects, environmental fate and effects, and physicochemical properties data are attached in the Appendix. Summaries of other environmental fate endpoints are also included. Existing data for the HPV and structurally analogous surrogate glycol esters are either included in robust summaries or are referenced in the Appendix should they have been reviewed or summarized elsewhere (such as existing SIDS, HPV test plans, other peer reviews) in the literature/public domain. This test plan is expected to provide adequate information to substantially characterize the mammalian health effects, physicochemical properties and environmental

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fate and effects (including aquatic toxicity, biodegradability) endpoints for the glycol esters category of the aliphatic esters under the HPV Chemical Challenge Program.

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Table 2. Summary Table of Physicochemical Properties and Environmental Fate Data for the Glycol Esters

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (mm Hg@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Chemical Distribution (Transport) within Environmental Compartments- Fugacity Model			
											Soil %	Air %	Water %	Sediment %
15	258	71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol	-50 75 c	>300 322 c	2.8 E-05 Pa at 25 C 1.08 E-05 c	>6.3 4.6 c	2.7 7.84 c	0.50 c	10.6 c	58.7 c	1.1 c	32.2 c	7.9 c
20	329	111-60-4	Stearic acid, 2-hydroxyethyl ester	60.5 138 c	189-191 (3 mm Hg) 404c	6.58 E-08 c	7.26 c	0.01711 c	0.39 c	7.7 c	31.0 c	0.5 c	7.5 c	61 c
20	375	7434-40-4	Triethylene glycol, diheptanoate	-24 54 c	decomp >250 394 c	6.29 E-06 c	4.77 c	30 0.3732 c	0.25 c	0.81 c	67.4 c	0.0 c	24.3 c	8.3 c
21	343	1323-39-3	Propylene glycol, monostearate	132 c	405 c	1.12 E-08 c	7.67 c	0.0062 c	0.34 c	7.7 c	31.3 c	0.4 c	7.1 c	61.2 c
22	403	94-28-0	Hexanoic acid, 2-ethyl-, diester with triethylene glycol	<40 48 c	344 403 c	4.22 E-06 c	5.60 c	0.04851 c	0.24 c	30.8 c	54.7 c	0.0 c	15.8 c	29.5 c
22	419	70729-68-9	Heptanoic acid, oxybis(2,1-ethanedioxy)-2,1-ethanedioyl ester	94 c	429 c	3.39 E-07 c	2.86 4.49 c	0.3419 c	0.19 c	0.81 c	69.5 c	0.0 c	25.7 c	4.8 c
23	368	67989-24-6	9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (Monoester)	157 c	431 c	1.01 E-09 c	8.40 c	0.0010 c	0.07 c	6.5 c	28.8 c	0.1 c	7.3 c	63.9 c
24	431	68583-52-8	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	96 c	441 c	1.74 E-07 c	6.73 c	0.0035 c	0.22 c	1.1 c	42 c	0.0 c	7.3 c	50.7 c
24	447	18268-70-7	Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	89 c	439 c	2.28 E-07 c	5.33 c	0.0441 c	0.18 c	30.8 c	59.7 c	0.0 c	19.1 c	21.2 c
27	441	22788-19-8	Propylene glycol dilaurate	75 c	444 c	2.31 E-07 c	10.64 c	1.38 E-06 c	0.34 c	5.9 c	30.1 c	0.5 c	7.0 c	62.4 c
38	595	627-83-8	Stearic acid, ethylene ester (Diester)	79 212 c	241 (20 mm Hg) 579 c	8.01 E-11 c	16.12 c	2.97 E-12 c	0.23 c	1.8 c	30.6 c	0.3 c	7.0 c	62.1 c
39	605	105-62-4	Oleic acid, propylene ester	197 c	591 c	2.0 E-12 c	16.11 c	2.61 E-12 c	0.04 c	0.73 c	27.6 c	0.0 c	3.5 c	68.9 c
39	609	68958-54-3	Propylene glycol diisostearate	175 c	569 c	1.29 E-11 c	16.39 c	1.41 E-12 c	0.22 c	5.9 c	30.4 c	0.1 c	2.3 c	67.2 c
41	633	42222-50-4	9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediol ester (Diester)	234 c	609 c	2.38 E-13 c	17.05 c	2.67 E-13 c	0.03 c	3.3 c	27.6 c	0.0 c	3.5 c	68.9 c

Highlighted row denotes substance that was not on the HPV list for the Glycol Esters category but that was included in table to facilitate group evaluation or to bridge data due to their chemical/structural similarities as glycol esters.

c = calculated data using EPWIN; all other values in table are derived from measurements or data obtained from company reports, documents, MSDS, reference handbooks, secondary literature sources.

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data may not accurately reflect melting points for these substances.

** = Some boiling points may have been determined under reduced pressure and some values may have been extrapolated to one atmosphere

Table 3. Summary Table of Mammalian Health Effects, Ecotoxicity and Biodegradation Data for the Glycol Esters

Total Carbon Number in Ester	CAS Number	Chemical Name	Mammalian Health Effects							Ecotoxicity and Biodegradation			
			Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aberr.)	Reproductive Toxicity	Developmental Toxicity/Teratogenicity	Acute Fish LC50 or LL50	Daphnia EC50 or EL50	Algae EC50 or EL50	Biodegradation %	
15	71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol	>2 g/kg	28-Day Oral Gavage (rat) Doses up to 1000 mg/kg were well-tolerated. NOAEL was 180 mg/kg.	Negative (Ames)	Negative for chromosomal aberration (human peripheral lymphocytes)	Repeated-dose oral toxicity study has not been shown to adversely affect reproductive organs.	> 1000 mg/L Aquatic tox not expected at WSL*	> 2000 mg/L Aquatic tox not expected at WSL*	> 2000 mg/L Aquatic tox not expected at WSL*	87.3% in 28 days OECD 301B		
20	111-60-4	Stearic acid, 2-hydroxyethyl ester	> 5 g/kg >10 g/kg >21.3 g/kg		Negative (Ames)								
20	7434-40-4	Triethylene glycol, diheptanoate (a)			Negative (Ames)								
21	1323-39-3	Propylene glycol, monoacetate (b)	25.8 g/kg	6-Month Oral Study at 1.7% in diet. No signs of toxicity in rats and dogs. 13-Week Oral Study at 1.5, 3.6 and 7.52% in diet. No signs of systemic toxicity in rats.	Negative (Ames)		Repeated-dose oral toxicity study has not been shown to adversely affect reproductive organs.	> WSL* (ca. 30 mg/L) >1000 mg/L with emulsifier Aquatic tox not expected at WSL*	9.1 mg/L	559-712 mg/L Aquatic tox not expected at WSL*	65% in 28 days OECD 301B		
22	94-28-0	Hexanoic acid, 2-ethyl-, diester with triethylene glycol	12.5 g/kg 31.37 g/kg	12-Day Oral Study at 0.1% or 1% in diet. No adverse effects.	Negative (Ames, CHO - HGPRT focus)			> 100 µL/L (~97 mg/L) Aquatic tox not expected at WSL*					
22	70729-68-9	Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyloxy) ester	> 2 g/kg > 25 g/kg 24-25 g/kg	28-Day Oral NOAEL 1000 mg/kg				720 mg/L 4800 mg/L Aquatic tox not expected at WSL*	3800 mg/L Aquatic tox not expected at WSL*	25 mg/L Aquatic tox not expected at WSL*	98% in 28 days OECD 301E		
23	67989-24-6	9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (Monoester)	> 10 ml/kg										
24	68583-52-8	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol											
24	18268-70-7	Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol											
27	22788-19-8	Propylene glycol diheptanoate (b)	> 34.6 g/kg (c)										
38	627-83-8	Stearic acid, ethylene ester (Diester)	> 5 g/kg, > 10 g/kg > 16 g/kg										
39	105-62-4	Oleic acid, propylene ester (Diester)											
39	68958-54-3	Propylene glycol diacetate (b)	25.8 g/kg (c)										
41	42222-50-4	9-Octadecenoic acid (Z)-, 2,2-dimethyl 1,3-propanediyl ester (Diester)											

Highlighted row denotes read-across data from surrogate glycol esters that were included in the table in order to help facilitate category evaluation or A2 to help bridge data for HPV glycol esters due to their chemical/structural similarities.

a) Data for triethylene glycol diheptanoate based on European Chemical Bureau IUCLID toxicity data set for CAS No. 7434-40-4.
 b) Data for various ethylene or propylene glycol esters and their diesters were obtained from several references including: Andersen FA, Internat. J. Toxicol. 18 (Suppl. 2): 35-52 (1999).
 RL Elder, J. Amer. Coll. Toxicol. 1(2): 1-11 (1982); RL Elder, J. Amer. Coll. Toxicol. 2(5): 101-123 (1983).
 c) Read across for the oral LD50 for the propylene glycol diacetate was based on the LD50 for propylene glycol monoacetate; the diester was considered to be similar or less toxic than the corresponding monoester. Similarly, the oral LD50 for propylene glycol diacetate was estimated based on the oral toxicity data for the corresponding monoacetate.

* WSL = Water solubility limit or water saturation level. Actual experimental LC50 or EC50 value (nominal loading rate) was many times greater than water solubility limit (WSL) of the chemical. Therefore, aquatic toxicity would not be expected at the maximum water solubility limit or water saturated levels (WSL) of test material based on findings at nominal loading rate or water accommodated fractions (WAF).