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HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

FOR THE MONOESTERS CATEGORY OF THE

ALIPHATIC ESTERS CHEMICALS

Prepared by:

American Chemistry Council's
Aliphatic Esters Panel

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EXECUTIVE SUMMARY

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) hereby submits a revised test plan for the "monoesters" category of the "aliphatic esters" chemicals, under the High Production Volume (HPV) Chemical Challenge Program. The Panel 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 monoesters category.

This test plan addresses three HPV monoesters chemicals listed in Table 1A. The distinguishing feature of this category of chemicals is that they are simple monoesters comprised of natural fatty acids (i.e., palmitic, stearic, oleic and linoleic acid) and monoalcohols. The three monoesters are produced from reaction of palmitic, stearic or tall oil fatty acids with either 2-ethylhexyl (C8) or tridecyl (C13) alcohol. They fall within the carbon range of C24-C31 and have similar properties and structural characteristics. The monoesters in this category are used commercially as lubricants, emollients, cosmetic ingredients or solvents.

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

There was published information for six structurally analogous surrogate monoesters, which provided useful supplementary data to help toxicity data bridging for the HPV monoesters. The six structurally analogous surrogate monoesters are: [1] stearic acid, butyl ester (CAS 123-95-5); [2] fatty acids, C16-18 saturated and C18-unsaturated, 2-ethylhexyl ester (CAS 85049-37-2); [3] stearic acid, octyl ester (CAS 109-36-4); [4] oleic acid, decyl ester (CAS 3687-46-5); [5] stearic acid, myristyl ester (CAS 17661-50-6); and [6] stearic acid, isocetyl ester (CAS 25339-09-7). These surrogate monoesters are alkyl fatty acid esters that are commonly used in the cosmetic industry.

Measured physicochemical property data were available for the surrogate monoesters. Computer estimation models were used to calculate physicochemical property and environmental fate data for the monoesters in the category. The calculated data were obtained using the EPIWIN and EQC (Level III) models that EPA has cited for use in the HPV Chemical Challenge Program. Use of the calculated and experimental values for HPV and for the surrogate monoesters provided the information on the physicochemical and environmental fate properties of the chemicals in the monoesters category to satisfy HPV program requirements. No additional testing for physicochemical and environmental fate properties is proposed.

Aquatic toxicity and biodegradation data exist for a structurally analogous surrogate monoester to sufficiently allow for read-across assessments for the HPV monoesters. No further aquatic toxicity or biodegradation testing is proposed for the monoesters category of the aliphatic esters.

There were existing toxicity data for structurally related surrogate monoesters (i.e., alkyl fatty acid esters) to sufficiently make hazard assessments for mammalian health effects (SIDS data endpoints) for the HPV monoesters substances. Given the similar chemical and structural features and similar carbon-number range between the three HPV monoesters and structurally related surrogate monoesters, it was justifiable to utilize the available data to read-across and for toxicity data bridging for the HPV substances. No additional mammalian toxicity testing is proposed for substances in the monoesters category. This resourceful use of existing data will help minimize the use of animals for testing while assessing the potential hazards in the monoesters category of the aliphatic esters. A technical discussion was provided to address the genotoxicity potential of the HPV monoesters.

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

Arizona Chemical Company

The CP Hall Company

Crompton Corporation

ExxonMobil Chemical Company

Inolex Chemical Company

Stepan Company

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TEST PLAN FOR THE MONOESTERS CATEGORY OF THE ALIPHATIC ESTERS

1.0 INTRODUCTION

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) has committed to develop a Screening Information Data Set (SIDS) (i.e., physicochemical data, environmental fate and effects, and human health effects) for the monoesters 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 information needs for the three monoesters listed in Table 1A (organized by CAS Numbers in ascending order). The chemical structures of the monoesters are given in Figure 1. The chemicals in this test plan were originally part of a larger test plan submitted on December 20, 2001. As a result of comments on that test plan, the Panel has revised its original test plan for these chemicals, and the revised approach follows below.

The test plan identifies the CAS Numbers used to characterize the SIDS endpoints for the monoesters in this category, describes the chemical and structural features/similarities of the monoesters, identifies existing data of adequate quality for substances in the monoesters 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 monoesters category of the aliphatic esters consistent with the EPA HPV Program.

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 resourceful use of existing data will help minimize the use of animals for testing while assessing the potential hazards in the monoesters category of the aliphatic esters.

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

Chemical Name (designated TSCA HPV chemical name)	**CAS Number**
Palmitic acid, 2-ethylhexyl ester	29806-73-3
Stearic acid, tridecyl ester	31556-45-3
Fatty acids, tall oil, 2-ethylhexyl esters	68334-13-4

2.0 DESCRIPTION OF THE MONOESTERS CATEGORY

Three CAS Numbers are used to describe the monoesters in this HPV category of the aliphatic esters (Table 1A). The monoesters category of the HPV aliphatic esters is comprised of simple monoesters derived from naturally occurring fatty acids and monofunctional alcohols.

This test plan addresses three HPV monoesters chemicals listed in Table 1A. The distinguishing feature of this category of chemicals is that they are simple monoesters comprised of natural fatty acids and monoalcohols. The three monoesters are produced from reaction of palmitic, stearic or tall oil fatty acids (oleic and linoleic acids mainly) with either C8 or C13 alcohol. They fall within the carbon number range of C24-C31 and have similar properties and structural characteristics. The monoesters in this category find use as lubricants, emollients, cosmetic ingredients or solvents [Elder (1982 a,b; 1985); Randles (1999)]. Monoesters derivatives of natural fatty acids, as a general chemical class, have been extensively reviewed by the Cosmetic Ingredient Review (CIR) expert panel [Elder (1982 a,b; 1985); CIR (1982 a,b: 1997)] and in Patty's Toxicology (2001). Elder (1982 a,b; 1985) has reviewed and summarized other toxicity endpoints besides the SIDS toxicity endpoints for a number of alkyl fatty acid ester derivatives.

Metabolism of the HPV monoesters in animals would be expected to occur initially via enzymatic hydrolysis leading to the corresponding fatty acids and alcohols (Savary *et al.* 1970). These fatty acids and alcohols can be further metabolized or conjugated (e.g., glucuronides, sulfates, etc.) to polar products that are excreted in the urine [Bisesi (2001); Cragg (2001a,b); Bevan (2001b); Thurman (1992)]. The fatty acids are naturally occurring and have a low order of toxicity [Cragg (2001a,b); Chow (1999)]. The biological effects for 2-ethylhexyl alcohol (BIBRA, 1990; Bevan 2001b) and tridecyl alcohol (Bevan 2001b; HPV Challenge Program 2001) have been reviewed and both have been reported to have a low order of toxicity.

Metabolic hydrolytic reactions of esters have been extensively reviewed in the literature [Testa and Mayer (2003); Bisesi (2001); Buchwald (2001); Parkinson (2001); Satoh *et al.* (1998); Heyman (1982)]. 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 Monoesters and Surrogate Monoesters

It is useful to organize the three HPV monoesters on the basis of total carbon number 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 Three HPV Monoesters According to Total Carbon Number/Molecular Weight (MW)

Individual Monoester (according to total carbon number) Chemical Name (designated TSCA HPV names)	CAS Number	Carbon Number in Acid	Carbon Number in alcohol	Total carbons in Monoester	MW
Palmitic acid, 2-ethylhexyl ester	29806-73-3	C16	C8	C24	369
Fatty acids, tall oil, 2-ethylhexyl esters (major fatty acids are oleic and linoleic acids)	68334-13-4	C18	C8	C26	393-395
Stearic acid, tridecyl ester	31556-45-3	C18	C13	C31	467

There are relevant published or unpublished toxicity data that also exist for six structurally homologous or analogous monoesters (denoted as surrogate monoesters) that provide very useful and adequate read-across information to help complete the bridging of toxicity data.

The six surrogate monoesters are: (see Figure 2 for chemical structures)

- Stearic acid, butyl ester (CAS 123-95-5)
- Fatty acids, C16-18 saturated and C18-unsaturated, 2-ethylhexyl ester (CAS 85049-37-2)
- Stearic acid, octyl ester (CAS 109-36-4)
- Oleic acid, decyl ester (CAS 3687-46-5)
- Stearic acid, myristyl ester (CAS 17661-50-6)
- Stearic acid, isocetyl ester (CAS 25339-09-7)

Incorporation of these six surrogate monoesters into Table 1B leads to Table 1C below, which should be useful in the overall HPV data review and test plan evaluation and which should provide reasonable justification (based on total carbon number, structural or MW similarities, etc.) to support read-across assessments.

Table 1C. Organization of 3 HPV Monoesters and 6 Surrogate Monoesters According to Total Carbon Number/MW for use in HPV Data Assessment and Testing Rationale**

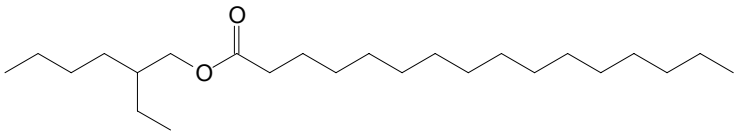
Individual Monoester (according to total carbon number) Chemical Name (designated TSCA HPV names)	CAS Number	Carbon Number in Acid	Carbon Number in alcohol	Total carbons in Mono-ester	MW
Stearic Acid, butyl ester **	123-95-5	C18	C4	C22	341
Palmitic acid, 2-ethylhexyl ester	29806-73-3	C16	C8	C24	369
Fatty acids, tall oil, 2-ethylhexyl esters (major fatty acids are oleic and linoleic acids)	68334-13-4	C18	C8	C26	393-395
Fatty Acid, C16-18 satd, C18 unsatd, 2-EH esters**	85049-37-2	C18	C8	C26	397
Stearic Acid, octyl ester **	109-36-4	C18	C8	C26	397
Oleic Acid, decyl ester **	3687-46-5	C18	C10	C28	428
Stearic Acid, tridecyl ester	31556-45-3	C18	C13	C31	467
Stearic Acid, myristyl ester **	17661-50-6	C18	C14	C32	481
Stearic Acid, isocetyl ester **	25339-09-7	C18	C16	C34	494

** These six surrogate monoesters (highlighted or shaded) are not part of the present HPV monoesters 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 toxicity data bridging to the HPV monoesters category members based on their chemical /structural similarities.

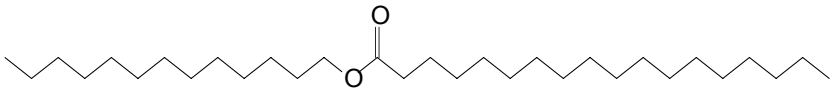
Figure 1. Chemical Structure of the Monoesters Listed in Table 1A

The structures of the HPV monoesters 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.

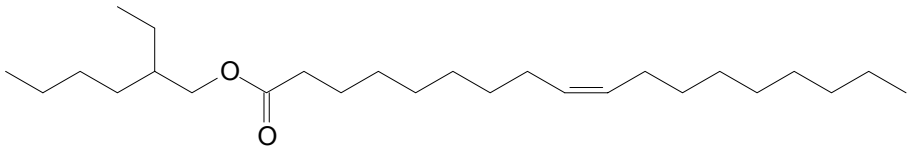
Palmitic acid, 2-ethylhexyl ester (CAS 29806-73-3)



Stearic acid, tridecyl ester (CAS 31556-45-3)



Fatty acids, tall oil, 2-ethylhexyl esters (CAS 68334-13-4)
(shown are the oleic acid and linoleic acid 2-hexylhexyl ester derivatives)



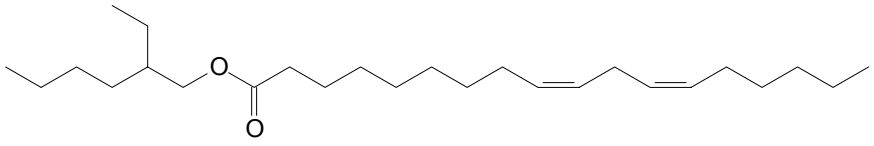
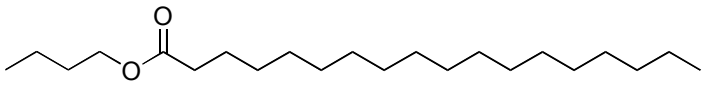
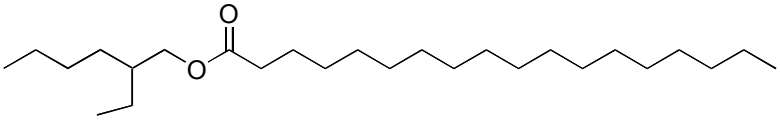


Figure 2. Chemical Structure of Surrogate Monoesters

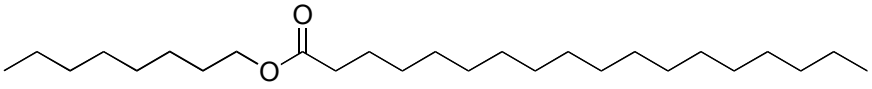
Stearic acid, butyl ester (CAS 123-95-5).



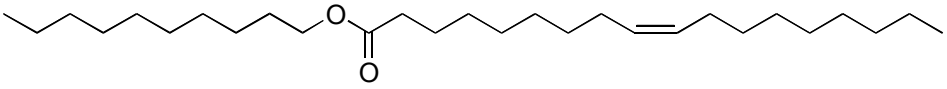
Fatty acids, C16-18 saturated and C18-unsaturated, 2-ethylhexyl ester (CAS 85049-37-2)
(structure shown is the 2-ethylhexyl ester of C18-saturated fatty acid)



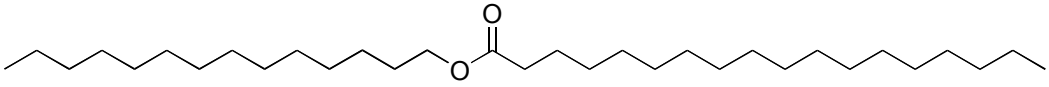
Stearic acid, octyl ester (CAS 109-36-4)



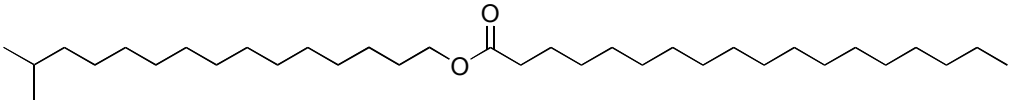
Oleic acid, decyl ester (CAS 3687-46-5)



Stearic acid, myristyl ester (CAS 17661-50-6)



Stearic acid, isocetyl ester (CAS 25339-09-7)



3.0 DESCRIPTION OF AVAILABLE PUBLIC AND COMPANY DATA

A review of the literature and confidential company data was conducted on the physicochemcial properties, mammalian toxicity endpoints, and environmental fate and effects for the three monoesters 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 [e.g., Patty's Toxicology (2001), Bisesi (2001)]. Safety assessment reviews for various alkyl 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 a,b); Elder (1985)]. Six surrogate monoesters (i.e., alkyl fatty acids esters) that were chemically or structurally-related (i.e., homologs, similar carbon number or molecular weight range or bracket) to the HPV monoesters were also reviewed to determine and to provide relevant data for bridging purposes 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 (kow)] for the HPV monoesters and surrogate monoesters 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 prerequsite to calculate fugacity or the chemical distribution in the environment (see below)
- Physicochemical properties data had yet to be developed for some of the monoesters.

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 monoesters 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 monoesters were reviewed using the literature searches to identify the most relevant studies for the substances in the monoesters category. For the HPV monoesters 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 LD_{50} 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 three HPV substances in Table 1A were grouped together under the monoesters category of aliphatic esters because they represented simple monoesters comprised of natural fatty acids and a monoalcohol (i.e., 2-ethylhexyl and tridecyl alcohol). In addition to existing data for the HPV substances, there were read-across data for six surrogate monoesters, not on the HPV list in this category. Because of their structural similarities, these six surrogate monoesters provided useful data for bridging toxicity information for structurally analogous HPV monoesters in regards to mammalian toxicity, aquatic toxicity and biodegradability endpoints.

The six surrogate monoesters were:

- Stearic acid, butyl ester (CAS 123-95-5)
- Fatty acids, C16-18 saturated and C18-unsaturated, 2-ethylhexyl ester (CAS 85049-37-2)
- Stearic acid, octyl ester (CAS 109-36-4)
- Oleic acid, decyl ester (CAS 3687-46-5)
- Stearic acid, myristyl ester (CAS 17661-50-6)
- Stearic acid, isocetyl ester (CAS 25339-09-7)

The existing data for the HPV monoesters and for the surrogate monoesters 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 monoesters and surrogate monoesters are summarized in Table 2. EPIWIN was used to calculate the physicochemical properties for the three HPV monoesters as well as for the six surrogate monoesters. The six surrogate alkyl fatty acid esters were selected to help bridge potential data gaps; their experimental and calculated (EPIWIN) data were included in Table 2 for comparison. Experimental data for the physicochemical properties of the surrogate monoesters are summarized in Table 2.

Data Assessment and Test Plan for Physicochemical Properties

The six surrogate monoesters were selected because they were structurally similar to the three HPV monoesters. The three HPV monoesters were palmitic, stearic or oleic acid ester derivatives (in the C24-C31 carbon number range) that were similar structurally to the six surrogate monoesters (also stearate, palmitate, oleate derivatives in the C22-C34 carbon number range). The six surrogate alkyl fatty acid monoesters were examined and their experimental and calculated (EPIWIN) data were used to help assess the physicochemical properties expected for the three HPV monoesters. Since the three HPV monoesters are higher fatty acid esters that fell within the same carbon number range of the surrogate monoesters (C22 to C34 range), they would be expected to be highly lipophilic in character [log P >10, due to the large number of carbon numbers in the ester molecule (e.g., 24, 26, 31 carbons)] and they would be ex-

pected to have relatively high boiling points (b.p. >350 C). Owing to the non-volatile nature of these esters, their vapor pressures would be expected to be very low and difficult to determine experimentally. Water solubility of the three HPV monoesters was calculated to be very low (less than 10^{-5} mg/L) (Table 2).

Based on the summarized data in Table 2, there are sufficient physicochemical data to characterize the substances in the monoesters 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 monoesters category are summarized in Table 2 and Table 3, respectively. While biodegradation testing has not been carried out specifically for the three HPV monoesters, relevant data have been reported for the surrogate monoester [i.e., fatty acids, C16-18 saturated and C18, unsaturated, 2-ethylhexyl ester (CAS 85049-37-2)] that basically is structurally homologous or analogous to the HPV monoesters (Table 3). The results for this surrogate monoester (CAS 85049-37-2) allow for read-across assessments of biodegradability for the HPV monoesters.

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 monoesters using the EPIWIN and EQC (Level III) models. Calculated hydrolysis half-lives and atmospheric photodegradation rates for the monoesters using EPIWIN are summarized in Table 2.

Chemical distribution of the monoesters in the environment has been calculated using EQC (Level III), a 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. The distribution between the environmental compartments for monoesters in this category appears to be influenced by water solubility and lipophilicity.

Data Assessment and Test Plan for Environmental Fate and Biodegradability

Biodegradation of HPV monoesters or alkyl fatty acid esters would be expected to occur extensively based on the reported 28-day test results (85% biodegradation, OECD 301D) for the structurally analogous surrogate monoester material, fatty acids, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester, (CAS 85049-37-2). Due to the striking similarities in the 2-ethylhexyl esters of the fatty acids [i.e., palmitic (C16 saturated), stearic (C18 saturated), oleic and linoleic (C18-unsaturated)] common between the tested surrogate monoester material and two of the HPV monoesters [i.e., palmitic acid, 2-ethylhexyl ester (CAS 29806-73-3) and fatty acids, tall oil, 2-ethylhexyl ester (CAS 68334-13-4)], read-across assessment for biodegradability would be justifiable. Hence, these two HPV 2-ethylhexyl monoesters would be expected to be extensively biodegraded in a similar manner as the surrogate.

The other HPV monoester, stearic acid, tridecyl ester (CAS 31556-45-3), would also be expected to undergo extensive biodegradation given its structural similarity to the surrogate. In addition, the fatty acids (i.e., palmitic, stearic, oleic, linoleic acid) in the HPV and surrogate monoesters are known to undergo rapid biodegradation (Verschueren, 1996), which would support extensive biodegradability expected for the HPV monoesters. Based on the above findings and the chemical similarity of the tested surrogate with the three HPV monoesters, no

further biodegradability testing is being proposed. By bridging these data, members of the monoesters category have been adequately assessed for biodegradability.

In addition, hydrolysis half-lives and atmospheric photodegradation rates were calculated by EPIWIN. The monoester hydrolysis rates were determined to be quite low and not a significant environmental fate route. Environmental distribution was determined using the EQC (Level III) model (Mackay *et al.* 1996). Fugacity modeling indicates that the fatty acid esters have similar distribution patterns in the environmental compartments (e.g., air, water, soil, sediment). Owing to their similar low volatility, poor water solubility and high lipophilicity, the HPV monoesters and the surrogate monoesters are mainly distributed into the sediment and soil environment compartments (Table 2).

Other environmental fate parameters (i.e., photodegradation, hydrolysis and chemical distribution in environment) have been calculated using the EPIWIN and EQC (Level III) modeling programs. Based on the calculated data for these environmental fate endpoints in Table 2, adequate data exist and that no additional testing is proposed.

4.3 Aquatic Toxicity Data

Summary of Aquatic Toxicity Data

Three acute aquatic toxicity studies (e.g., fish, invertebrates, algae) relevant to the monoesters category are summarized in Table 3. While aquatic toxicity testing has not been carried out specifically for the three HPV monoesters, relevant data have been reported for one surrogate monoester [i.e., fatty acids, C16-18 saturated and C18, unsaturated, 2-ethylhexyl ester (CAS 85049-37-2)], which basically is structurally homologous or analogous to the HPV monoesters. The supporting data for the surrogate monoester (CAS 85049-37-2) should allow for read-across aquatic toxicity assessments for the HPV monoesters.

Data Assessment and Test Plan for Aquatic Toxicity

Although the three HPV monoesters have not been specifically evaluated, information on their aquatic toxicity potential can be assessed from results reported for structurally similar surrogate monoester material [i.e., fatty acids, C16-18 saturated and C18, unsaturated, 2-ethylhexyl ester (CAS 85049-37-2)]. This tested surrogate monoester showed a low degree of toxicity to fish (LL_{50} 3200 mg/L). In daphnids, the acute LL50 value was reported to be 17 mg/L and in algae, the LL50 was reported to be 40-42 mg/L.

Due to the apparent similarities in the 2-ethylhexyl esters of the fatty acids [i.e., palmitic (C16 saturated), stearic (C18 saturated), oleic and linoleic (C18-unsaturated)] common between the tested surrogate monoester material and two of the HPV monoesters [i.e., palmitic acid, 2-ethylhexyl ester (CAS 29806-73-3) and fatty acids, tall oil, 2-ethylhexyl ester (CAS 68334-13-4)], read-across assessment for aquatic toxicity appears reasonably justifiable. Hence, the above two HPV monoesters would be expected to have similar effects to aquatic organisms as the surrogate monoester (CAS 85049-37-2). The third HPV monoester, stearic acid, tridecyl ester (CAS 31556-45-3), would be expected to show similar aquatic toxicity effects as those expected for the other two HPV monoesters given its structural similarity.

Based on the above findings and on close structural similarities between the tested surrogates and the HPV substances, the existing aquatic toxicity data should be adequate to address the

potential aquatic toxicity of members of the monoesters category and, therefore, no additional testing is proposed.

The acute aquatic studies followed generally accepted test guidelines in which water solutions or water accommodated fractions (WAFs) were often generated for poorly water-soluble lubricant or petroleum 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 WAFs) clearly exceed the water solubility of the monoester and appears exceeding improbable (e.g., >3200 mg/L), it would be more appropriate to note 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 monoesters (Table 2), the existing data suggest that aquatic toxicity would not be expected at the maximum water solubility limit (WSL) or at water saturated levels, typical of WAF solutions generated from high nominal loading rate concentrations.

4.4 Mammalian Toxicity Data

A) Acute Mammalian Toxicity

Summary of Available Acute Oral Toxicity Data

Acute oral toxicity data relevant to the monoesters category are summarized in Table 3 and have been reported for two of the three HPV monoesters and for all six of the surrogate monoesters. Overall, the acute oral LD_{50} for these substances was greater than the 2000 mg/kg, indicating a very low order of toxicity for the monoesters. It should be mentioned that acute dermal toxicity studies have also been carried out for the various monoesters, particularly the alkyl fatty acid esters used in cosmetic applications and have been reported to have very low degrees of acute dermal toxicity [see reviews by Elder (1982a,b); Elder (1985)].

Data Assessment and Test Plan for Acute Mammalian Toxicity

Adequate acute oral toxicity studies have been conducted for two of the three HPV monoesters and all six structurally analogous surrogate monoesters. There were no deaths when the HPV monoesters and the surrogate monoesters were administered at oral doses of >2000 mg/kg in rats or mice. The HPV monoesters, palmitic acid, 2-ethylhexyl ester (CAS 29806-73-3) and fatty acids, tall oil, 2-ethylhexyl ester (CAS 68334-13-4), have reported oral LD_{50} values of >5 g/kg and >64 g/kg, respectively. As summarized in Table 3, the surrogate monoesters were found to have acute oral LD_{50} values ranging from >5 g/kg to >64 g/kg. Hence, the data consistently demonstrate a very low order of acute oral toxicity for the monoesters over the C22-C34 carbon number range. No additional acute toxicity testing is proposed for HPV substances in the monoesters category.

B) Mutagenicity and Genotoxicity

Summary of Mutagenicity and Genotoxicity Data

A summary of the mutagenicity and genotoxicity data for the HPV substances in the monoesters category and structurally analogous surrogate substances are presented in Table 3. Bacterial gene mutation assays have not been conducted with the HPV monoesters. However, three surrogate monoesters have been evaluated in the bacterial mutation test. No mutagenicity was exhibited by any of the surrogate monoesters in the cited *in vitro* tests.

Bacterial Gene Mutation Assay

Although the HPV monoesters have not been tested, three of the surrogate monoesters [fatty acid, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester (CAS 85049-37-2); stearic acid, octyl ester (CAS 109-36-4); and oleic acid, decyl ester (CAS 3687-46-5)] have been evaluated in the bacterial reverse mutation tests. All three surrogate monoesters were shown to be negative for mutagenic activity, with and without activation.

Chromosomal Aberration Assay

Genotoxicity data (e.g., chromosomal aberration) have not been reported for the HPV monoesters or the surrogate monoesters.

Data Assessment and Test Plan for Mutagenicity and Genotoxicity

The HPV monoesters have not been tested but three structurally analogous and relevant surrogate monoesters materials [fatty acid, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester (CAS 85049-37-2); stearic acid, octyl ester (CAS 109-36-4); and oleic acid, decyl ester (CAS 3687-46-5)] have been adequately evaluated and have been shown to be negative in the Ames assay. Due to the very close structural and chemical similarities and carbon-number range between the three surrogate monoesters and the HPV monoesters, read-across assessment for mutagenic toxicity is reasonably justifiable. Based on the existing data for the surrogates, the HPV monoesters would be expected to be not mutagenic, with or without metabolic activation. By bridging these data, the potential mutagenicity of the members of the monoesters category has been addressed and, therefore, no testing is proposed.

A technical discussion to comment on the genotoxicity potential of the HPV monoesters is given below. The existing mutagenicity data for the surrogate monoesters indicate that based on read-across assessment, the HPV monoesters are not expected to be mutagenic, with or without metabolic activation. In addition, the chemistry of the long-chain fatty acid esters does not suggest the likelihood that these substances or their constituent components (i.e., natural fatty acids and alcohols) are inherently reactive or electrophilic in nature. Therefore, the likelihood that the HPV monoesters would cause chromosomal mutation is expected to be very low. The Cosmetic Ingredient Review (CIR) expert panel has extensively reviewed a number of alkyl fatty acid esters, many of which are used in food and cosmetic applications, and has not reported any clastogenic activity for such materials [Elder (1982 a,b; Elder (1985); CIR (1982a,b; 1997)]. There is no indication that the alkyl fatty acid esters are carcinogenic based on the reviews carried out to date by the CIR expert panel.

While no chromosomal aberration studies have been reported for the HPV monoesters or related surrogate monoesters, it should be noted there is a recent report that a long-chain alkyl carboxylic acid ester, namely, secondary dodecyl propanoate is not clastogenic in a chromosomal aberration assay and not genotoxic in an in vivo mouse micronuclei study (NICNAS, 2000). Secondary dodecyl propanoate was also evaluated in a bacterial reverse mutation test and was demonstrated to be negative for mutagenic activity, with and without metablic activation. Although secondary dodecyl propanoate is a long chain alkyl ester derivative of a carboxylic acid (propanoate), this compound, nevertheless, represents a lipophilic alkyl carboxylic acid ester with 15 carbon atoms that clearly has been demonstrated shown not to be a mutagen, not to be genotoxic and not be a clastogen (NICNAS, 2000).

Consideration of the above data suggests that the HPV monoesters would not be expected to be genotoxic. No further testing (e.g., chromosomal aberration assay) is being proposed at this time for the substances in the monoesters category.

C) Repeated-Dose Toxicity

Summary of Repeated-Dose Toxicity Data

Repeated-dose oral toxicity studies have been reported for three surrogate monoesters and the results are summarized in Table 3. No repeated-dose toxicity studies have been conducted for members of the HPV monoesters category.

Repeated-Dose Oral Toxicity

Oral gavage studies in rats with the surrogate monoester, oleic acid, decyl ester (CAS 3687-46-5), at doses of 100, 500 and 1000 mg/kg over 28 days showed no toxicity with respect to clinical symptoms, biochemistry, hematology, gross lesions or tissue/organ histopathology (IUCLID, 1996). The NOAEL was reported to be 1000 mg/kg. Similarly, the surrogate monoester, stearic acid, octyl ester (CAS 109-36-4) was found to have a NOAEL of 1000 mg/kg in 28-day oral gavage studies in rats. In chronic two-year feeding studies with butyl stearate (CAS 123-95-5) at concentrations of 1.25% and 6.25% in the diet, exposed rats showed no significant difference from control animals with respect to growth, survival, blood counts or other hematological parameters (Smith, 1953). The daily doses of butyl stearate corresponded approximately to 2500 and 6000 mg/kg/, respectively. Hence, the collective results from these studies showed a low order of repeated dose toxicity for the alkyl fatty acid monoesters.

Various other long-chain fatty acid esters have also been evaluated for repeated dose toxicity test and the findings support a very low order of toxicity for the monoesters or alkyl fatty acid esters in general [see reviews by Elder (1982a,b; 1985) and CIR (1982a,b; 1997)].

Data Assessment and Test Plan for Repeated-Dose Toxicity

Sufficient read-cross data (subchronic and chronic) from the surrogates suggest that members of the monoesters category exhibit a low order of toxicity following repeated applications. Since the three surrogate monoesters (CAS 123-95-5, CAS 109-36-4 and CAS 3687-46-5) are structurally similar to members of the HPV monoesters category, the available repeated-dose oral toxicity data are considered adequate for read-across assessment and for bridging toxicity data. Therefore, no further testing for repeated dose toxicity is proposed.

D) Reproductive/Developmental Toxicity

Summary of Reproductive/Developmental Toxicity Data

Reproductive and developmental toxicity studies of monoesters have been reported in the scientific literature but the Panel has not located any valid, relevant reproductive toxicity studies for members of the HPV monoesters category. However, reproductive toxicity data are available for one surrogate monoester [i.e., stearic acid, butyl esters (CAS 123-95-5)]. In addition, the Panel has not located any valid, relevant developmental toxicity studies on members of the HPV monoesters category. However, one structural analogous surrogate monoester [i.e., stearic acid, octyl ester (CAS 109-36-4)] has been tested for developmental toxicity. Results from these studies with

structural analogous surrogate monoesters showed a low order of reproductive/developmental toxicity and are summarized in Table 3.

Reproductive Toxicity

Assessment of reproductive effects of HPV monoesters is based primarily on studies with stearic acid, butyl ester (or butyl stearate) (CAS 123-95-5). Smith (1953) reported that fertility, litter size and survival of offspring were normal in rats fed diets containing 6.25% butyl stearate for 10 weeks prior to mating. However, growth was reduced in offspring during the pre-weaning and post-weaning periods. No gross lesions were noted among the offspring examined at the end of the 21-day post-weaning periods. These results indicate that long-chain fatty acid esters do not cause reproductive toxicity in rats. Given the relative low order of toxicity for long-chain fatty acid esters and their relative non-electrophilic and non-reactive nature, it seems unlikely that the alkyl fatty acid esters such as the three HPV monoesters would present serious reproductive concerns. Therefore, no further reproductive toxicity testing is proposed for members in this category.

Developmental Toxicity/Teratogenicity

One developmental toxicity study has been carried out with a structural analogous surrogate monoester. 2-Ethylhexyl stearate was tested for developmental toxicity in rats according to the OECD Test Guidelines No. 414 (Aulmann *et al.*, 2000). Dose levels of 0 (arachidis oil), 100, 300, and 1000 mg/kg body weight/day were administered by gavage. All developmental toxicological parameters revealed no treatment-related affects. The NOAEL for embryo-/fetotoxicity, teratogenicity and maternal toxicity was 1000 mg/kg. These results indicate that long-chain fatty acid esters do not cause developmental toxicity in rats. Given the relative low order of toxicity for long-chain fatty acid esters and their relative non-electrophilic and non-reactive nature, it seems unlikely that the alkyl fatty acid esters such as the three HPV monoesters would present serious developmental concerns. Therefore, no further developmental toxicity testing is proposed for members in this category.

Data Assessment and Test Plan for Reproductive/Developmental Toxicity

Since these two surrogate monoesters (i.e., CAS 123-95-5 and CAS 109-36-4) are structurally analogous or similar to members of the HPV monoesters category, the available reproductive/developmental toxicity data are considered adequate for read-across assessment. Therefore, no further testing for reproductive/developmental toxicity is proposed.

5.0 TEST PLAN SUMMARY

The American Chemistry Council's Aliphatic Esters Panel believes that sufficient health effects and toxicity data exist for the monoesters category of the aliphatic esters (taking into account data available for structurally related and analogous surrogate monoesters) 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 monoesters category of the aliphatic esters. This resourceful use of existing data will help minimize the use of animals for testing while assessing the potential hazards in the monoesters category of the aliphatic esters

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

Monoester	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
Stearic acid, butyl ester *	C22 341	√	√	--	--	√	--	--	--	--	--
Palmitic Acid, 2-EH ester	C24 369	√	R	R	TD	R	R	R	R	R	R
Fatty Acids, tall oil, 2-EH esters	C26 393-395	√	R	R	TD	R	R	R	R	R	R
Fatty Acid, C16-18 satd, C18 unsatd, 2-EH esters*	C26 397	√	R	√	--	--	--	√	√	√	√
Stearic Acid, octyl ester*	C26 397	√	√	√	--	--	√	--	--	--	--
Oleic Acid, decyl ester *	C28 423	√	√	√	--	--	--	--	--	--	--
Stearic Acid, tridecyl ester	C31 467	R	R	R	TD	R	R	R	R	R	R
Stearic Acid, myristyl ester*	C32 481	√	--	--	--	--	--	--	--	--	--
Stearic Acid, isocetyl ester*	C34 494	√	--	--	--	--	--	--	--	--	--

* Shaded (highlighted) areas denote surrogate monoester substances - their data are included in table for bridging purposes for structurally analogous HPV monoesters.

Abbreviations in table:
√ = adequate existing data available,
R = read-across data from structurally analogous monoesters
-- denotes that no valid, relevant studies were located for this specific toxicity endpoint for this surrogate monoester
TD = Technical discussion on genotoxicity potential for monoesters [see Section 4.4 (C)]

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

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

Aquatic toxicity and biodegradation data have been reported for a surrogate C26 monoester [i.e., CAS 85049-37-2] that should provide relevant results that can enable read-across assessment for the structurally analogous and homologous HPV monoesters (C24-C31). No further aquatic and biodegradation testing are proposed for the monoesters category of the aliphatic esters.

There were existing toxicity data for structurally related surrogate monoesters (i.e., alkyl fatty acid esters) to sufficiently make hazard assessments for mammalian health effects (SIDS data endpoints) for the HPV monoesters substances. Given the similar chemical and structural features and similar carbon-number range between the three HPV monoesters and structurally related surrogate monoesters, it was justifiable to utilize the available data to read-across and to bridge the toxicity data gaps for the HPV substances. No additional mammalian toxicity testing is proposed for substances in the monoesters category. A technical discussion was provided to address the genotoxicity potential of the HPV monoesters.

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

6.0 REFERENCES *

Aulmann W, Pittermann W, Bartnik F, Sterzel W, Kastner W, Potokar (2000). Developmental toxicity of 2-ethylhexyl stearate. Food Chem. Toxicol., 38: 57-63.

Bevan C (2001a). Monohydric Alcohols - C1 to C6 *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 77, pp. 365-460. J. Wiley & Sons, New York.

Bevan C (2001b). Monohydric Alcohols - C7 to C18, Aromatic and other alcohols. *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 78, pp. 461-541. J. Wiley & Sons, New York.

BIBRA (1990). Toxicity profile for 2-ethyl-1-hexanol. British Industrial Biological Research Associaton (BIBRA).

Bisesi MS (2001). Esters of mono- and alkenyl carboxylic acids and mono- and polyalcohols *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 80, pp. 635-932, J. Wiley & Sons, New York

Buchwald P (2001). Structure-metabolism relationship: steric effects and the enzymatic hydrolysis of carboxylic esters. Mini. Rev. Med. Chem. **1:** 101-111.

Chow CK (1999). Biological and toxicological properties of fatty acids and derivatives *in* Fatty Acids in Industry: Process, Properties, Derivatives, Applications. Johnson RW, Fritz E (eds.), Marcel Dekker, New York, pp. 617-658.

CIR (1982a). Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of myristyl myristate and isopropyl myristate. J. Am. Coll. Toxicol., 1 (4): 55-80.

CIR (1982b). Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of cetearyl octanoate. J. Am. Coll. Toxicol., 1 (4): 81-90.

CIR (1997). Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of cetyl esters. Int. J. Toxicol., 16 (Suppl. 1): 123-130.

Cragg ST (2001a). Aliphatic carboxylic acids, saturated *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 5, Chapter 70, pp. 689-787. J. Wiley & Sons, New York.

Cragg ST (2001b). Aliphatic carboxylic acids, unsaturated *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 5, Chapter 71, pp. 789-861. J. Wiley & Sons, New York.

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* The list of references is not a comprehensive bibliography of the literature for the HPV monoesters substances. Pertinent papers cited in the text are those that are important in health hazard assessments or for toxicity data bridging for structurally analogous surrogate monoesters. The information and data in the papers and reviews supplement the robust summaries developed for the toxicology studies of the HPV substances, which are ultimately used to address the SIDS toxicity endpoints for the monoesters in this HPV test plan.

David RM, *et al.* (2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri-, or polyalcohols *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 6, Chapter 80, pp. 635-932. J. Wiley & Sons, New York. The monoesters of dicarboxylic acids were specifically covered in pages 737-810.

Eisenhard WC (1999). Esterification *in* Fatty Acids in Industry: Process, Properties, Derivatives, Applications. Johnson RW, Fritz E (eds.), Marcel Dekker, New York, pp. 139-152.

Elder RL (1982a). Final report on the safety assessment of octyl palmitate, cetyl palmitate and isopropyl palmitate, J. Amer. Coll. Toxicol. 1(2): 13-35.

Elder RL (1982b). Final report on the safety assessment of decyl and isodecyl oleates, J. Amer. Coll. Toxicol. 1(2): 85-95.

Elder RL (1985). Final report on the safety assessment of butyl stearate, cetyl stearate, isobutyl stearate, isopropyl stearate, myristyl stearate and octyl stearate , J. Amer. Coll. Toxicol. 4(5): 107-146.

EPIWIN (1999). Estimation Program Interface for Windows. Version 3.02. Syracuse Research Corp., Syracuse, New York, USA.

Heyman E (1982). Hydrolysis of carboxylic esters and amides in Metabolic Basis of Detoxification (Jakoby WB, Bend JR, Caldwell J (eds.), Academic Press, New York, pp.229-245

High Production Volume (HPV) (2001). See HPV chemical categories (e.g., dicarboxylic acids, alkyl alcohols C6-C13 categories) submitted to U.S. EPA.

IUCLID (1996). International Union Chemical Information Database, European Chemicals Bureau Existing Chemicals. Data sheet for each chemical found by CAS number or chemical name. See IUCLID for Fatty acid, C16-18 satd and C18 unsatd, 2-ethylhexyl ester (CAS No. 85040-37-6); Fatty acids, C16-18, 2-ethylhexyl ester (CAS No. 91031-48-0); decyl oleate or oleic acid, decyl ester (CAS No. 3687-46-5).

Klimisch H, Andreae M, Tillman U (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. **15:** 1-5.

Leinweber FJ (1987). Possible physiological roles of carboxylic ester hydrolases. Drug Metab. Rev. **18:** 379-439.

Longland RC, Schilling WH, Gangolli (1977). The hydrolysis of flavouring esters by artificial gastrointestinal juices and rat tissue preparations. Toxicology. **8:** 197-204.

Mackay D, DiGuardo A, Paterson S, Cowan CE (1996). Evaluating the environmental fate of a variety of types of chemicals using the EQC model. Environ. Toxicol. Chem. **15:** 1627-1637.

Monick JA (1968). Alcohols: Their Chemistry, Properties and Manufacture. Reinhold Book Corp., New York.

NICNAS (2000). National Industrial Chemicals Notification and Assessment Scheme. Full Public Report. File No: NA/728. Assessment of a Proprietary Ester Product. 41 pp. Report is available at http://www.nicnas.gov.au/publications/car/new/na/nasummr/na0700sr/na728.htm

Parkinson A (2001). Biotransformation of xenobiotics: (hydrolysis) in Casarett & Doull's Toxicology: The Basic Science of Poisons (Klassen CD, ed.), McGraw-Hill, New York, pp. 137-142.

Patty's Toxicology, 5th edition. Bingham E, Cohrssen B, Powell C (editors). 8-Volumes. J. Wiley & Sons, New York (2001).

Randles SJ (1999). Esters *in* Synthetic Lubricants and High Performance Functional Fluids (2nd ed.), Rudnick LR and Shubkin RL (eds.), Marcel Dekker, New York, pp. 63-101.

RTECS (Registry of Toxic Effects of Chemical Substances (2001). National Institute for Occupational Safety and Health of the U.S. Department of Health and Human Services. Health hazard and toxicity data for individual chemical was found by CAS number or chemical name.

Savary P, Constantin MJ (1970). Intestinal hydrolysis and lymphatic absorption in isopropyl esters of long-chain fatty acids in the rat. Biochim. Biophys. Acta. 218 (2): 195-200.

Satoh T, Hosokawa M. (1998). The mammalian carboxylesterases: from molecules to functions. Ann. Rev. Toxicol. Pharmacol. **38:** 257-288.

Smith CC (1953). Toxicity of butyl stearate, dibutyl sebacate, dibutyl phthalate and methoxyethyl oleate. AMA Arch. Ind. Hyg. Occup. Med. **7:** 310-318

Testa B, Mayer J.(2003). Hydrolysis in Drug and Prodrug Metabolism: chemistry, biochemistry and enzymology, J. Wiley, New York, 800 pp.

Thurman RG, Kauffman FC (eds.)(1992). Alcohols and Esters. Volume 3 in Ethel Browning's Toxicity and Metabolism of Industrial Solvents (2nd Ed.), Snyder R (Series Editor), Elsevier, Amsterdam.

U.S. EPA (1999a). Determining the adequacy of existing data. OPPT, EPA.

U.S. EPA (1999b). The use of structure-activity relationships (SAR) in the High Production Volume (HPV) Chemical Challenge Program. OPPT. EPA.

Verschueren K (1996). Handbook of Environmental Data on Organic Chemicals (3 rd ed.), Wiley, New York.

von Oettingen WF (1960). The aliphatic acids and their esters: toxicity and potential dangers, AMA Arch. Ind Health, **21:** 24-37; 100-113

7.0 List of Tables and Figures

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

Total Carbon Number	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 %
22	341	123-95-5	Stearic acid, butyl ester	27.5 109 c	343 384 c	11 mm Hg (150C) 8.1 E-04 c	9.7 c	3.6 E-05 c	0.411 c	9.09 c	27.8 c	0.07 c	7.25 c	64.3 c
24	369	29806-73-3	Palmitic acid, 2-ethylhexyl ester	117 c	400 c	1.02 E-06 c	10.6 c	4.13 E-06 c	0.36 c	14.1 c	28.3 c	0.57 c	7.2 c	63.9 c
26	393-395	68334-13-4	Fatty acids, tall oil, 2-ethylhexyl ester	114 c	427 c	1.98 E-05 c	11.4 c	6.3 E-07 c	0.056 c	0.056 l/mol s c	28 c	0.5-0.9 c	7.3 c	64 c
26	397	85049-37-2	Fatty Acids, C16-18 satd and C18 unsatd, 2-ethylhexyl ester	135 c	423 c	1.76 E-07 c	11.6 c	4.02 E-07 c	0.331 c	14.1 c	29.1 c	0.1 c	7.1 c	63.3 c
26	397	109-36-4	Stearic acid, octyl ester	145 c	430 c	9.28 E-08c	11.67 c	3.48 E-07c	0.34 c	20.4 c	29.5 c	0.48 c	7.09 c	62.9 c
28	423	3687-46-5	Oleic acid, decyl ester	161 c	457 c	1.31 E-08c	12.44 c	5.3 E-08 c	0.12 c	20.4 c	28.5 c	0.09 c	7.23 c	64.2 c
31	467	31556-45-3	Stearic acid, tridecyl ester	190 c	488 c	1.40 E-07 c	14.1 c	1.0 E-09 c	0.28 c	20.4 c	30.9 c	0.35 c	7.0 c	61.8 c
32	481	17661-50-6	Stearic acid, myristyl ester	54 192 c	500 c	1.5 E-08 c	14.6 c	3.13 E-10 c	0.27 c	20.4 c	29.8 c	0.38 c	7.07 c	62.8 c
34	494	25339-09-7	Stearic acid, isocetyl ester	207 c	516 c	1.25 E-10 c	15.52 c	3.47 E-11 c	0.25 c	20.4 c	30 c	0.13 c	3.4 c	66.6 c

Highlighted rows denote surrogate monoesters not in the HPV category but which were included in Table to facilitate read-across assessments or for bridging purposes owing to their chemical/structural similarities.

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

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

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

				Mammalian Health Effects						Ecotoxicity and Biodegradation			
Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Reproductive Toxicity	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia EC50 or EL50	Algal EC50 or EL50	Biodegradation %
22	341	123-95-5	Stearic acid, butyl ester	>32 g/kg	2-Year Feeding Study (rat) 1.25% and 6.25% in diet showed no significant difference between treated animals and controls. NOAEL 6.25% diet (~6000 mg/kg/day)			6.25% in diet for 10 weeks in rats showed no effect on fertility, litter size, survival of offspring	6.25% in diet for 10 weeks in rats showed no effect on fertility, litter size, survival of offspring				
24	369	29806-73-3	Palmitic acid, 2-ethylhexyl ester	>5 g/kg									
26	393-395	68334-13-4	Fatty acids, tall oil, 2-ethylhexyl ester	> 64 ml/kg									
26	397	85049-37-2	Fatty Acids, C16-18 satd and C18 unsatd, 2-ethylhexyl ester	>17.2 g/kg		Negative (Ames)				3200 mg/L Aq. toxicity not expected at WSL*	17 mg/L Aq. toxicity not expected at WSL*	40-42 mg/L Aq. toxicity not expected at WSL*	85% in 28 days OECD 301D Closed Bottle
26	397	109-36-4	Stearic acid, octyl ester	> 8 ml/kg	28-day Oral Gavage (rat) NOAEL 1000 mg/kg	Negative (Ames)			Developmental study at 0, 100, 300 and 1000 mg/kg (rats) NOAEL 1000 mg/kg for embryotox fetotox, teratogenicity and maternal tox.				
28	423	3687-46-5	Oleic acid, decyl ester	> 40 ml/kg	28-day Oral Gavage (rat) NOAEL 1000 mg/kg	Negative (Ames)		28 days oral toxicity study in rats reported no adverse effects to male and female reprod organs (gross observation or histopathology).					
31	467	31556-45-3	Stearic acid, tridecyl ester										
32	481	17661-50-6	Stearic acid, myristyl ester	> 10 g/kg (mice)									
34	494	25339-09-7	Stearic acid, isocetyl ester	> 10 g/kg									

Highlighted rows denote surrogate monoesters not on the HPV monoesters category list but which were included in Table to facilitate read-across assessments or for bridging purposes owing to their chemical/structural similarities.

* 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).