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HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

FINAL SUBMISSION

for

FATTY ACID DIMERS AND TRIMER

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CAS No. 61788-89-4
CAS No. 68937-90-6
CAS No. 68783-41-5
CAS No. 71808-39-4

Submitted to the US EPA
December 2004

By

The Pine Chemicals Association, Inc.
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HPV Task Force
Consortium Registration

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Final Submission for Fatty Acid Dimers and Trimer

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Summary

As part of the High Production Volume (HPV) Program, the Pine Chemicals Association, Inc. (PCA) sponsored four substances in the fatty acid family referred to as fatty acid dimers and trimer. This final submission addresses the following four chemicals, known collectively as Fatty Acid Dimers and Trimer:

CAS Number	IUR Name	Common Name
61788-89-4	Fatty acids, C18-unsaturated, dimers	Dimer
68937-90-6	Fatty acids, C18-unsaturated, trimers	Trimer
68783-41-5	Fatty acids, C18-unsaturated, dimers, hydrogenated	Hydrogenated dimer
71808-39-4	Fatty acids, C16 and C18-unsaturated, dimerized	Crude dimer

All of the members of this category of substances (hereafter referred to by their common names) are derived from unsaturated fatty acids, primarily tall oil fatty acids. As with other fatty acid-based products, these substances are complex mixtures and considered to be Class 2 substances.

Crude dimer is manufactured from tall oil fatty acids through heat treatment with or without an appropriate catalyst. The other members of this category are then obtained from crude dimer either by distillation and/or hydrogenation.

The physical properties of all the members of this group are similar. They are all slightly viscous to viscous liquids and range in color from clear to dark brown. The largest end use for dimer is in the manufacture of polyamide resins for use in adhesives, inks and coatings.

There were existing data on dimer for many SIDS endpoints. These compounds are non-toxic in acute toxicity tests and repeat-dose studies show no toxicity or potential for reproductive/developmental effects. Bacterial and mammalian mutagenicity data are negative.

Where applicable, PCA conducted physical/chemical property and environmental fate testing on all of the substances in the category for which data were not already available. PCA elected to treat these four substances as a category for purposes of the HPV Program. Dimer (CAS # 61788-89-4) was selected as the representative substance in this category for testing as it has the largest production volume and, in particular the distilled form to be used for testing, has the highest dimer content of the members of this category.

The totality of the SIDS data for the substances in this category is briefly summarized below and in Tables 1-3. As shown in these summaries, because dimer is non-toxic in both mammalian and aquatic test systems, it is reasonable to conclude that all substances in this category are similarly non-toxic. These data are described and discussed in the main document. Detailed Robust Summaries of all relevant data are appended to this document.

Physical/Chemical Properties

Physical and chemical properties were determined where appropriate; however, many of these endpoints are either inappropriate or cannot be measured for these compounds:

- Melting or boiling points were not determined because these substances will either will not give a sharp melting point when heated or will decompose before they melt or boil.
- Under ambient conditions, the vapor pressure of these substances is essentially zero and experimental measurement is not possible.
- Water solubility and partition coefficients are summarized in Table 1. It should be noted that considerable effort was undertaken to accurately determine water solubility.
- With respect to the partition coefficient (K_{ow}), the approved method (OECD 117) yields a range of values rather than a single value representative of the mixture as summarized in Table 1. The range of values reflects the partition coefficients of the individual constituents of these complex mixtures.

—The details on these test results are provided in the Robust Summaries.
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Table 1. Summary of Physical/Chemical and Environmental Fate Data*

Chemical	Required SIDS Endpoints		
	Partition Coefficient	**Water Solubility (mg/l)**	**Percent Biodegradation At 28 Days**
Dimer	1 – 2.5	< 0.12	6.0
Trimer	2.2 – 8.9	< 0.37	11.1
Hydrogenated dimer	0.7 – 6.2	< 0.52	9.46
Crude dimer	2.4 – 7.5	< 0.41	29.29

*No testing was conducted for melting point, boiling point, vapor pressure, hydrolysis, photodegradation, and transport and distribution between environmental compartments as explained in main document.

Environmental Fate

The SIDS environmental fate endpoints were determined where appropriate; however, many of these endpoints are either inapplicable or cannot be measured for these compounds.

- Photodegradation was not relevant, since the vapor pressure of these compounds is essentially zero and they could not enter the atmosphere.
- Hydrolysis in water was not determined for any of the compounds in this category because all have low water solubility and also lack a functional group that would be susceptible to hydrolysis.
- Transport and distribution between environmental compartments (i.e., fugacity) was not determined due to the inability to provide usable inputs to the required model.
- Biodegradation data are summarized in Table 1 and show that none of these substances are substantially biodegradable in the environment.

The details on these test results are provided in the Robust Summaries.

Ecotoxicity

Dimer was tested for acute toxicity to fish, daphnia and algae at the maximum measured water solubility. These data are summarized in Table 2 and show that dimer is non-toxic to fish, daphnia and algae with the $NOEL_r$ for all endpoints at 1000 mg/l. The details of these test results are provided in the Robust Summaries.

Table 2. Summary of Ecotoxicity Data

Chemical Name	**Required SIDS Endpoint**		
	Acute Fish 96 hr $NOEL_r$	**Acute Daphnia 48 hr $NOEL_r$**	**Acute Algae 72 hr $NOEL_r$**
Dimer	1000 mg/l	1000 mg/l	1000 mg/l
Trimer	C	C	C
Hydrogenated dimer	C	C	C
Crude dimer	C	C	C

C = Indicates category read-down from available data
$NOEL_r$ = no observed effect loading rate

Mammalian Toxicity

For the SIDS human health endpoints, there were sufficient data on acute toxicity, repeat dose and reproductive toxicity and genotoxicity for dimer demonstrating that this compound is non-toxic. Dimer was tested for reproductive/developmental toxicity using OECD 422. The mammalian toxicity data are summarized in Table 3 and demonstrate that dimer is non-toxic. Based on the category approach, results for the test substance also represent other members of the category. The details of these test results are provided in the Robust Summaries.

Table 3. Summary of Mammalian Toxicity Data

Substance	Required SIDS Endpoints					
	Acute Oral	**Repeat Dose**	**Genetox (*Salmonella*)**	**Genetox (Mouse lymphoma)**	**Genetox (Human lymphocytes)**	**Repro/ Develop**
Dimer	LD_{50} > 2000 mg/kg	NOEL 180 mg/kg/d	+S9 Neg. -S9 Neg.	+S9 Neg. -S9 Neg.	+S9 Neg. -S9 Neg.	No effects; NOEL 1858 mg/kg/d
Trimer	C	C	C	C	C	C
Hydrogenated dimer	LD_{50} > 5000 mg/kg	C	C	C	C	C
Crude dimer	C	C	C	C	C	C

C = Indicates category read-down from available data.

Overall Hazard Evaluation and Potential Exposure

For potential human health effects, the totality of the SIDS data demonstrates that dimer is non-toxic. Accordingly, based on the category approach, it can be inferred that all of the substances in this group are also non-toxic.

Dimer has no acute oral toxicity (i.e., LD_{50} > 5,000 mg/kg), and repeat dose toxicity data demonstrate a no observed effect level (NOEL) of approximately 180 mg/kg/day and a NOEL of approximately 1858 mg/kg/day for reproductive/developmental effects. *In vitro* genotoxicity test results show no evidence of mutagenicity in *Salmonella* (i.e., Ames test), and no effects on mouse lymphoma cells or human lymphocytes for dimer.

Consequently, no adverse health consequences would be associated with any exposures to dimer or related substances. For potential ecotoxicological effects, the data on dimer demonstrate that all of the substances in this category are non-toxic to aquatic organisms including fish, daphnia and algae with the $NOEL_r$ for each test at 1000 mg/l.

With respect to potential exposure to the substances in this category, all are consumed almost entirely as industrial intermediates where they are reacted or further distilled to produce other chemicals. Tall oil fatty acids (TOFA) are the

starting point for all of the substances in this category where it is reacted or further distilled to produce other chemicals. Of the various TOFA distillation and reaction products, it is estimated that greater than 75% are marketed and consumed in non-dispersive commercial applications in the production of dimer acids (as well as the other three substances in this category), polyamide adhesive resins, alkyd resins for paint, polyester lubricants, plasticizers, and metal working fluids. As such, inhalation exposure or volatization to air would be minimal. Exposure in all of these industrial applications is generally limited to dermal contact during manufacture of the various products derived from TOFA.

The Pine Chemicals Association, Inc. HPV Task Force includes the following companies:

Akzo Nobel Resins
Akzo Nobel - Eka Chemicals Incorporated
Arizona Chemical Company
Asphalt Emulsion Manufacturers Association
Boise Cascade Corporation
Cognis Corporation
Crompton Corporation
Eastman Chemical Co. (including the former Hercules Inc. Resins Division)
Georgia-Pacific Resins Inc.
Hercules Incorporated
ICI Americas (including the former Uniqema)
Inland Paperboard & Packaging, Inc.
International Paper Co. (including the former Champion International Corporation)
Koch Materials Co.
McConnaughay Technologies, Inc.
MeadWestvaco (including the former Mead Corp. and the former Westvaco)
Packaging Corporation of America
Plasmine Technology, Inc.
Raisio Chemicals
Rayonier
Riverwood International
Smurfit – Stone Container Corporation
Weyerhaeuser Co.

The Task Force has filed multiple test plans covering various chemicals. Not all members of the Task Force produce the substances covered by this test plan.

I. Description of Fatty Acid Dimers and Trimer

The Pine Chemicals Association, Inc. (PCA) sponsored four HPV chemicals known collectively as Fatty Acid Dimers and Trimer. The Test Plan for this group of substances was posted on EPA's HPV website on April 4, 2002, with comments from Environmental Defense, the EPA, and Animal Protection Organizations posted on July 23, 2002, August 2, 2002, and August 15, 2002, respectively. After reviewing these comments, PCA prepared a response which was subsequently posted on EPA's HPV website on November 10, 2002. This final submission addresses the following four substances:

CAS Number	IUR Name	Common Name
61788-89-4	Fatty acids, C18-unsaturated, dimers	Dimer
68937-90-6	Fatty acids, C18-unsaturated, trimers	Trimer
68783-41-5	Fatty acids, C18-unsaturated, dimers, hydrogenated	Hydrogenated dimer
71808-39-4	Fatty acids, C16 and C18-unsaturated, dimerized	Crude dimer

For convenience, the common names of these substances are used in this final submission.

All the members of this category are produced by the dimerization of C18 unsaturated fatty acids, primarily tall oil fatty acids. As with other fatty acid-based products, these substances are complex mixtures and therefore are considered Class 2 substances.[1]

The classical production process begins by heating unsaturated fatty acid in the presence of an acid-treated clay catalyst to a temperature greater than 200^0 C. Under these conditions, some of the fatty acids dimerize, a lesser amount trimerizes, and some isomerizes to monomer (Zinkel and Russell 1989). This reaction mixture is called crude dimer.

Based on EPA guidance (letter of May 4,1995), the reaction mixture can have two different CAS Registry Numbers depending on its intended use:

- If it is used as the feedstock for the production of dimer, it has CAS # 71808-39-4.

[1] As defined in the TSCA Inventory, *"In terms of composition, some chemical substances are single compounds composed of molecules with particular atoms arranged in a definite known structure. For purposes of this discussion, such substances will be denoted Class 1 substances. Many commercial chemical substances are not in this class. They may have variable compositions or be composed of a complex combination of different molecules. These substances will be denoted Class 2 substances."*

- If it is sold as a commercial raw material for the production of products other than dimer, then it has CAS # 61788-89-4.

The typical fatty acid dimerization process is shown in Figure 1.

Figure 1. Typical Fatty Acid Dimerization Process

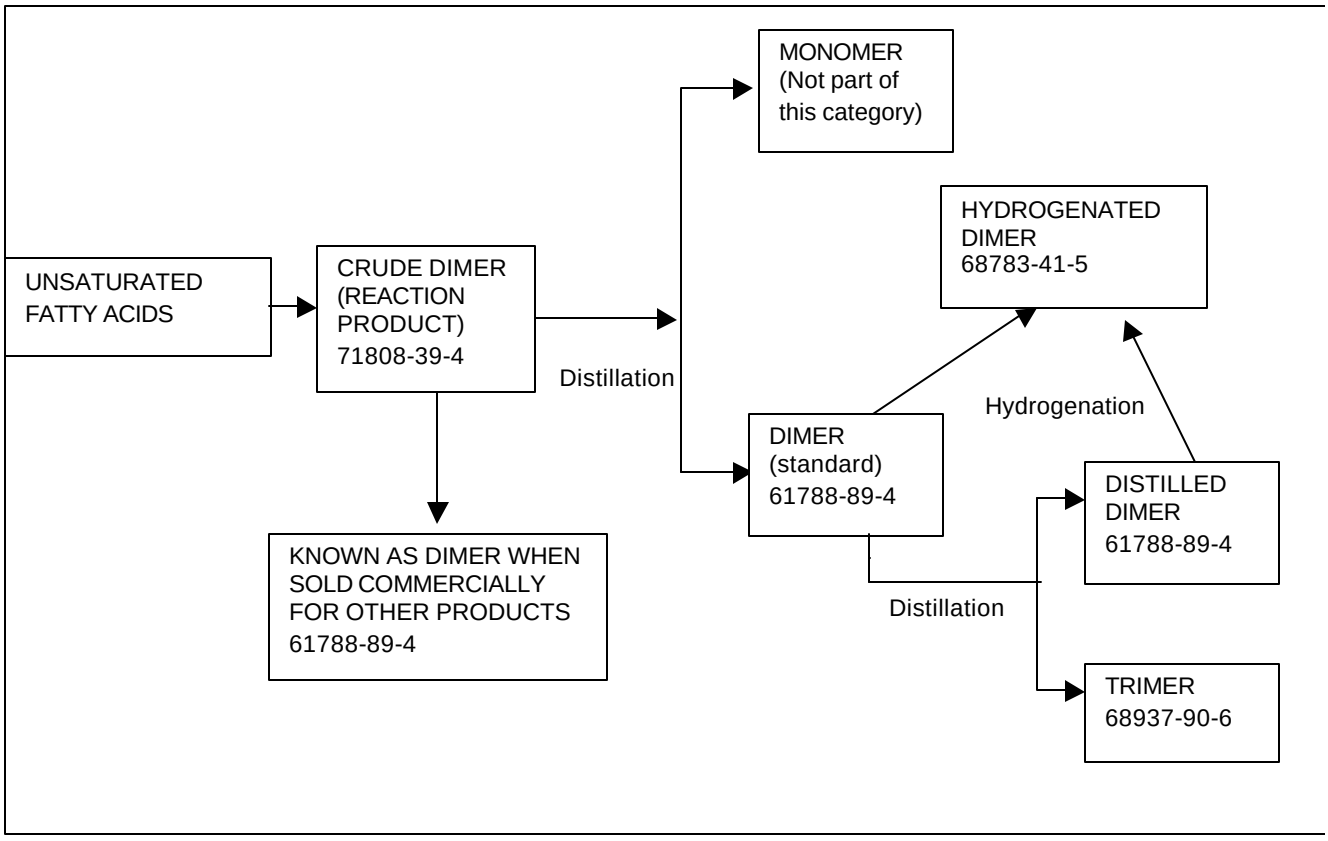


Figure 1 shows schematically how the other members of this category of substances are produced from crude dimer, e.g.,

- To produce the other members of the category, crude dimer is distilled, which removes most of the monomer, leaving dimer (known in the industry as standard dimer). The monomer acid is not a member of this category, but is included in the *Final Submission for Tall Oil Fatty Acids*.

- Standard dimer can be further distilled to give distilled dimer and trimer.

- Standard dimer and distilled dimer can also be hydrogenated to yield hydrogenated dimer, which has improved stability to heat and oxygen.

Composition

All the members of this category are liquids, ranging in color from clear to dark brown. The viscosity of the members depends on the dimer and trimer content, with crude dimer being a low viscosity liquid and at the other extreme, trimer being a very viscous liquid. The typical composition of the substances in this category is shown in Table 4 (below).

Table 4

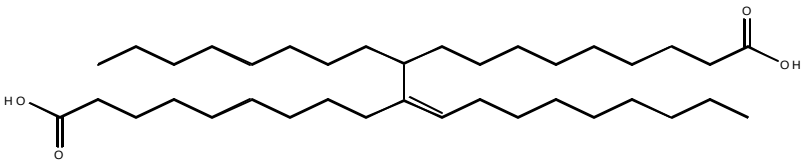
Representative Compositions of Dimer Acids

Substance	C18 Acids (Monomeric) %	C36 Acids (Dimeric) %	C54 Acids (Trimeric) %
Dimer			
Crude dimer	30	60	10
Dimer	2	80	18
Distilled dimer	1	94	5
Trimer	<1	40	60
Hydrogenated dimer	2	80	18

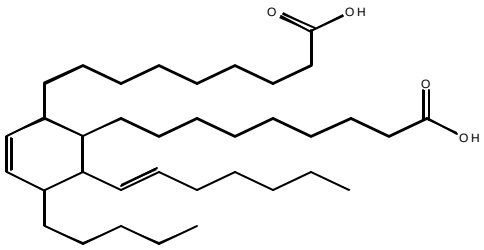
The composition of dimer and trimer is complex. Several representative dimer structures are shown schematically in Figure 2. Dimers and trimers are predominantly cyclic addition compounds of unsaturated fatty acids, although bicyclic, non cyclic and other structures are present.

Figure 2. Representative Structures of Fatty Acid Dimers. (Many geometric isomers of the structures below are present in fatty acid dimers.)

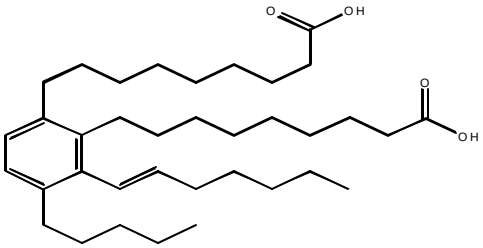
Acyclic Dimer



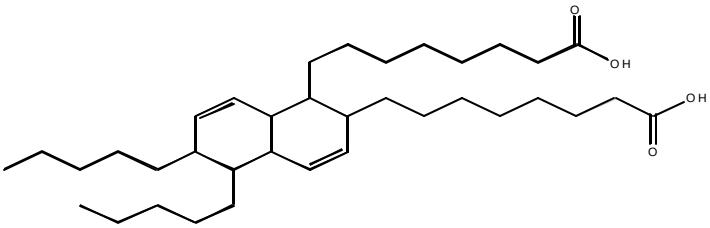
Cyclic Dimer



Aromatic



Polycyclic



A. Commercial Uses of Dimer Acids

Dimer produced from tall oil fatty acid is used primarily in the production of non-nylon polyamide resins. Polyamide resins are used in various formulations for high performance adhesives and printing inks for flexible packaging, and as a cross linking agent for epoxy resins. Dimer is also used as a raw material for the production of surface coatings, primarily coatings for metal coils. Derivatives of dimer (imidazolines) are used as corrosion inhibitors in petroleum production and refining. Trimers find application as a component in oil well drilling fluids.

B. Complexity of Analytical Methodology

All the substances in this category are Class 2 substances. This, combined with the fact that they are essentially insoluble in water and decompose rather than vaporize on heating at ambient pressure, created a variety of analytical challenges. The large size of the dimer and trimer molecules and their non-volatility makes gas chromatography impractical. The technique adopted for analyzing members of this category was gel permeation chromatography (GPC). However, this technique is not normally used for detecting low levels of dimer; rather, it was used for determining the monomer, dimer and trimer content of dimer products at percentage levels.

Method validation undertaken as a predicate to solubility testing indicated that under the correct conditions it was possible to use GPC to determine levels of dimer <10 ppm, which was the determined solubility of these substances in water. While the level of dimer to be detected was considerably higher in the animal feeding study, the analysis was complicated by the presence of materials in animal feed that are similar to dimer with respect to molecular weight and solubility. However, this complication was overcome and the GPC methodology proved to be satisfactory for the developmental study.

II. Rationale for Selection of Representative Compound for Testing

Dimer (CAS # 61788-89-4) was selected as the representative substance in this category for testing for several reasons. Chemically, the members of this category are very similar as they are all essentially mixtures of monomer, dimer and trimer. Dimer is also the most commercially important substance in this category, with the largest production volume. Furthermore, the distilled dimer that was used for testing has the highest dimer content of any of the members of this category so that the results are the most representative of the category.

In addition, since all of the substances in this category are either dimers or trimers of fatty acids, they are in the same family of compounds. Thus, these substances meet EPA's criterion of using the "family approach" to group chemicals into a category to examine related chemicals. Consequently, the four four substances in this group -- all from the same family -- fit the requirements of the EPA's HPV Challenge Program for a category, and dimer is the most appropriate representative test material from this category. It should be noted that EPA as well as other commenters agreed that the proposed category was correct and that dimer was representative of other category members.

III. Summary of Data

Where applicable, physical/chemical property and environmental fate testing was conducted on all of the substances in the category. With respect to toxicological testing, dimer was selected as a representative of the category and used for the necessary ecotoxicity and mammalian toxicity testing. Table 5 summarizes the results from all of the testing conducted on the substances in this category.

A. Physicochemical Data

The basic physicochemical data required in the SIDS battery includes melting point, boiling point, vapor pressure, partition coefficient (K_{ow}), and water solubility.

Some of these measures are inapplicable given the nature of the materials in this category. Moreover, Class 2 substances are composed of a complex mixture of substances and are often difficult to characterize. Dimers and trimer are not only Class 2 substances, but also are derived from natural sources. Therefore, their composition is variable and cannot be represented by a single chemical structural diagram. Due to this "complex mixture" characteristic of dimers some physical property measurements, such as partition coefficient, do not give single definitive results because the methodology used to determine these properties will actually fractionate or partition the substance into various components. Consequently, some results are likely to be erroneous, difficult to interpret, or meaningless.

1. Melting Point

Melting points were not determined because all of the substances in this category are liquids under ambient conditions.

2. Boiling Point

All of the substances in this category are produced at high temperatures, and generally by high vacuum distillation, and are non-volatile liquids at ambient temperatures. A boiling point at ambient temperature has no significance because these materials will thermally decompose before they boil. Accordingly, measurement of this property was inappropriate for all the substances in this category.

Table 5
Summary of Data
Fatty Acid Dimers and Trimers*

Chemical and CAS #	Required SIDS Endpoints											
	Partition Coef.	**Water Sol. Mg/l**	**Biodeg. % @ 28 days**	**Acute Fish NOELr**	**Acute Daph. NOELr**	**Acute Algae NOELr**	**Acute oral**	**Repeat Dose**	**Genetox (*Salmonella*))**	**Genotox (Mouse lymphoma)**	**Genetox (Human lymph-ocytes)**	**Repro/ Develop**
Dimer 61788-89-4	1 -2.5	<0.12	6.0	1000 mg/l	1000 mg/l	1000 mg/l	> 2000 mg/kg	NOEL 180 mg/kg/d	+S9 Neg. -S9 Neg.	+S9 Neg. -S9 Neg.	+S9 Neg. -S9 Neg.	No effects NOEL 1858 mg/kg/d
Trimer 68937-90-6	2.2 – 8.9	<0.37	11.1	C	C	C	C	C	C	C	C	C
Hydrogenated dimer 68783-41-5	0.7 – 6.2	<0.52	9.46	C	C	C	> 5000 mg/kg/d	C	C	C	C	C
Crude dimer 71808-39-4	2.4 – 7.5	<0.41	29.29	C	C	C	C	C	C	C	C	C

C Indicates category read-down from existing or proposed test data on dimer.

***** No testing was conducted for melting point, boiling point, vapor pressure, hydrolysis, photodegradation and transport and distribution between environmental compartments as explained in the text.

3. Vapor Pressure

Vapor pressures for the substances in this category are effectively zero at ambient temperatures, and their experimental measurement is inappropriate.

In commenting on the *Dimers and Trimers Test Plan* and the decision not to determine melting point, boiling point, and vapor pressure due to the physical characteristics of the substances, EPA noted that *"…the submitter can get measured/estimated values for these endpoints for representative substances."* The recommendation that these parameters be measured or estimated for "representative substances" is not relevant for the four substances in this category since all are composed of several types of large molecules and none of the individual constituents of these complex mixtures can be reasonably considered as representative of the mixture (i.e., the specific substance) itself.

4. Water Solubility

The water solubility of the four substances in this category was determined using OECD (105). The solubility data are shown in Table 6.

Table 6

Chemical	Water Solubility (mg/l)
Dimer	<0.12
Trimer	<0.37
Hydrogenated dimer	<0.52
Crude dimer	<0.41

All of these data are presented in detail in the Robust Summaries.

5. Partition Coefficient

The partition coefficients (i.e., K_{ow}) for all of the compounds in this category were determined. Because all of these substances are Class 2 mixtures, the procedure (OECD 117) to determine the K_{ow} typically yields a range of K_{ow} values rather than a single value representative of the mixture. Thus, the results reflect the partition coefficients of the components rather than the mixture. The partition coefficient data are shown below in Table 7.

Table 7

Chemical	Partition Coefficient (K_{ow})
Dimer	1.0 – 2.5
Trimer	2.2 – 8.9
Hydrogenated dimer	0.7 – 6.2
Crude dimer	2.4 – 7.5

All of these data are presented in detail in the Robust Summaries.

B. Environmental Fate Data

The fate or behavior of a chemical in the environment is determined by the reaction rates for the most important transformation (degradation) processes. The basic environmental fate data covered by the HPV Program include biodegradation, stability in water (hydrolysis as a function of pH), photodegradation and transport and distribution between environmental compartments (fugacity).

1. Biodegradation

Biodegradability provides a measure for the potential of compounds to be degraded by microorganisms. Depending on the nature of the test material, several standard test methods are available to assess potential biodegradability. One of the chemicals in this category (dimer) had existing data on the biodegradation endpoint. Biodegradation for the other three substances in this category was determined using OECD method 301B. The biodegradation data are shown in Table 8 and demonstrate that none of the substances in this category are substantially biodegradable.

Table 8

Chemical	Percent Biodegradation At 28 Days
Dimer	6.0
Trimer	11.1
Hydrogenated dimer	9.46
Crude dimer	29.29

All of these data are presented in greater detail in the Robust Summaries.

2. Hydrolysis

Hydrolysis as a function of pH is used to assess the stability of a substance in water. Hydrolysis is a reaction in which a water molecule (or hydroxide ion) substitutes for another atom or group of atoms present in an organic molecule. None of the substances in this category contain a functional group that would be susceptible to hydrolysis. Therefore, hydrolysis need not be measured. In addition, low water solubility often limits the ability to determine hydrolysis as a function of pH. All of the substances in this category have very low solubility in water. Therefore, these materials are expected to be stable in water and it was unnecessary to attempt to measure the products of hydrolysis.

3. Photodegradation

Due to their lack of any vapor pressure under ambient conditions, there is essentially no opportunity for any of the fatty acid dimers or trimer to enter the atmosphere. Thus, photodegradation is irrelevant. In addition, based on the constituents in these complex mixtures, there is no reason to suspect that they would be subject to breakdown by a photodegradative mechanism. Consequently, this endpoint was not determined for any of the substances in this category.

4. Transport and Distribution between Environmental Compartments

The transport and distribution between environmental compartments (fugacity) is intended to estimate the ability of a chemical to move or partition in the environment. The determination of this property requires the use of various models. One of the most frequently referenced models is the level III model from the Canadian Environment Modeling Centre at Trent University. Even the simplest of these models requires estimates of solubility, vapor pressure and octanol/water partition coefficient to estimate fugacity for a single component. For complex class 2 substances such as dimers and trimer, estimates of any one of these physical parameters for the various known components could span a range of more that a order of magnitude. When combining three or more parameters of equally variable ranges to derive estimates for different environmental media, the variability in the estimate for any given medium could grow geometrically to three or more orders of magnitude. This suggests that any estimates based on arbitrarily selected individual components would be essentially useless for any practical purpose. Add to this the additional fact that there is variability in the chemical composition of these substances and the possible permutations become unmanageable. Consequently, for complex mixtures such as dimers, the mathematical models which rely upon estimates for individual components are of no practical use in predicting environmental fate. Therefore, due to the inability to provide usable inputs to the required model, no

determination of transportation and distribution between environmental compartments was undertaken for any of the substances in the dimer category.

In commenting on the *Test Plan for Dimers and Trimer*, EPA suggested that photodegradation and the other required inputs can be "measured/estimated" for representative substances so that a fugacity model could be run. As noted above, there is no basis or rationale for assuming that the vapor pressure, photodegradation or partition coefficient of one randomly selected substance in a multi-substance complex mixture would be representative of the entire mixture.

C. Ecotoxicity Data

The basic ecotoxicity data that are part of the HPV Program include acute toxicity to fish, daphnia and algae. Dimer was tested for these endpoints under conditions that maximize the solubility under the specific test exposure conditions, but reduce exposure to insoluble fractions, which may cause nonspecific toxicological effects. In addition, the effect of both filtering, to further minimize nonspecific physical effects, and of reducing the pH to the lower end of the acceptable range for test organism survival, was also investigated for changes in toxicological effects. The results of preliminary tests were used to select the most appropriate test conditions for the definitive test for each species. The ecotoxicity data are summarized in Table 9.

Table 9

Chemical	**Fish 96 hr *NOELr**	**Daphnia 48 hr NOELr**	**Algae 72 hr NOELr**
Dimer	1000 mg/l	1000 mg/l	1000 mg/l

*$NOEL_r$ = No Observed Effect Loading Rate

These data are presented in greater detail in the Robust Summaries.

In commenting on the *Test Plan for Dimers and Trimer*, EPA incorrectly assumed that dimer salts were included in this category when, in fact, they are not. EPA was concerned that these substances have an inherent tendency to form an aqueous milky dispersion, emulsion, or critical micelles and noted that the soluble salts of these chemicals should be dispersible in water just as surfactants and detergents are dispersible in water. Similarly, EPA commented that *"when testing, the overall test substance concentrations should not exceed the dispersibility limit or the critical micelle concentration. The test substance solubility should not be viewed as a water solubility limit."* Although salts of the category substances may form micelles, the dimers and trimer in this category,

as non-salts, will not form micelles. With respect to the comment that *"the test substance solubility should not be viewed as a water solubility limit,"* while this may be true in some instances, it is not accurate with respect to dimer. Since the method used to maximize the solubility of dimer for the determination of water solubility was essentially identical to the method used for ecotoxicity testing, this process does, in fact, determine the limit of water solubility. This procedure was adopted in order to ensure that ecotoxicity testing was conducted at the limit of actual water solubility. As described above, all of the substances in this category are essentially non-soluble in water.

EPA also recommended that the tests be done at pH 7 and disagreed with using filters, centrifugation, or water-accommodated fractions of the test substance. However, OECD protocols for ecotoxicity testing (as well as OECD's guidance for difficult to test substances) do not require a specific pH of 7 and all testing conducted was consistent with applicable protocols and guidance. The Agency also stated that it disagreed with using filters, centrifugation, or water-accommodated fractions (WAF) of the test substance. While some of these techniques (other than centrifugation which was never mentioned in the Test Plan) were explored in preliminary range finding tests, none were used in the definitive testing. It should be noted that the use of WAF as well as filtration are both methods that are recommended for difficult to test substances (OECD 2000).

Finally, EPA suggested that the chemical should be tested as manufactured. Because the protocol that was used to prepare water samples for ecotoxicity testing was identical to the protocol used to measure water solubility, this is precisely the manner in which ecotoxicity testing on dimer was conducted, i.e., as manufactured.

D. Human Health Effects Data

1. Acute Oral Toxicity

Acute oral toxicity studies investigate the effect(s) of a single exposure to a relatively high dose of a substance. This test is conducted by administering the test material to animals (typically rats or mice) in a single gavage dose. Harmonized EPA testing guidelines (August 1998) set the limit dose for acute oral toxicity studies at 2000 mg/kg body weight. If less than 50 percent mortality is observed at the limit dose, no further testing is needed. A test substance that shows no effects at the limit dose is considered essentially nontoxic. If compound-related mortality is observed, then further testing may be necessary.

Summary of Acute Oral Toxicity Data

Dimer is non-toxic following acute oral exposure, with LD_{50} values > 2,000 mg/kg in several studies. Hydrogenated dimer is also non-toxic following acute oral exposure with an LD_{50} value > 5,000 mg/kg. These data are presented in greater detail in the Robust Summaries.

2. Repeat Dose Toxicity

Subchronic repeat dose toxicity studies are designed to evaluate the effect of repeated exposure to a chemical over a significant period of the life span of an animal. Typically, the exposure regimen in a subchronic study involves daily exposure (at least 5 consecutive days per week) for a period of not less than 28 days or up to 90 days (i.e., 4 to 13 weeks). The HPV program calls for a repeat dose test of at least 28 days. The dose levels evaluated are lower than the relatively high doses used in acute toxicity (i.e., LD_{50}) studies. In general, repeat dose studies are designed to assess systemic toxicity, but the study protocol can be modified to incorporate evaluation of potential adverse reproductive and/or developmental effects.

Summary of Repeat Dose Toxicity Data

Dimer was administered to Sprague-Dawley rats at dietary concentrations of 0, 0.1, 1, or 5% for 13 weeks. The approximate doses were 0, 100, 1,000, or 5,000 mg/kg/day. Parameters evaluated included clinical signs, body weight, food and water consumption, hematology, clinical chemistry, and gross pathology, organ weights and microscopic pathology.

No deaths occurred and no treatment-related effects on clinical signs, body weight, body weight gain, or water intake were noted. A transient, statistically significantly decrease in food consumption occurred in the 5% males and females during the first four weeks of study. Slight changes in hemoglobin (increased in 5% males) and prothrombin time (increased in 1% females and 5% males and females) were considered not to be toxicologically significant. Treatment-related clinical chemistry changes included increased alkaline phosphatase (1 and 5% males and females) and ALT (5% males and females), and decreases in total cholesterol and triglycerides (1 and 5% males and females), total serum protein and albumin (5% males and females), and beta-globulin fraction (1 and 5% males). While some decreased organ weights were noted, they did not correlate to any microscopic changes. Although a no-effect-level was not identified in this study, 0.1% (approximately 100 mg/kg/day) can be considered a no-observed-adverse-effect-level (NOAEL) based on minimal increases in clinical chemistry parameters and histopathological findings at the

higher doses. These data are presented in greater detail in the Robust Summaries.

3. Genotoxicity – In vitro

Genetic testing is conducted to determine the effects of substances on genetic material (i.e., DNA and chromosomes). The gene, which is composed of DNA, is the simplest functional genetic unit. Mutations of genes can occur spontaneously or as a consequence of exposure to chemicals or radiation. Genetic mutations are commonly measured in bacterial and mammalian cells, and the HPV program calls for completing both types of tests.

Summary of Genotoxicity Data

Dimer has been tested for potential genotoxicity in several test systems including the Ames *Salmonella* assay, mouse lymphoma cell assay and a metaphase chromosome analysis of human lymphocytes. As summarized below in Table 10, none of these test systems showed any indication of genotoxicity.

Table 10

Chemical	**Ames *Salmonella***		**Mouse lymphoma**		**Human lymphocytes**	
	+S9	**-S9**	**+S9**	**-S9**	**+S9**	**-S9**
Dimer	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

These data are presented in greater detail in the Robust Summaries.

4. Reproductive and Developmental Toxicity

Reproductive toxicity includes any adverse effect on fertility and reproduction, including effects on gonadal function, mating behavior, conception, and parturition. Developmental toxicity is any adverse effect induced during the period of fetal development, including structural abnormalities, altered growth and post-partum development of the offspring.

The “toxicity to reproduction” aspect of the HPV Challenge Program can be met by conducting a reproductive/developmental toxicity screening test or adding a reproductive/developmental toxicity screening test to the repeat dose study (OECD 421 or OECD 422, respectively).

Summary of Reproductive/Developmental Toxicity Data

As noted in the SIDS guidelines for the reproduction toxicity endpoint, *"when a 90-day repeated dose study is available and demonstrates no effects on the reproductive organs, in particular the testes, then a developmental study can be considered as an adequate test to complete information on reproduction/developmental effect."* Dimer was tested in a 13-week repeat dose study. This study included histopathology of reproductive organs (*i.e*., testes, ovaries, uterus) and showed no evidence of reproductive organ toxicity at any dose level. Therefore, this study satisfies the SIDS reproductive toxicity endpoint.

Dimer was also tested for the developmental toxicity endpoint using OECD 421. Four groups of 10 male and 10 female Sprague-Dawley rats were exposed to dimer in the diet at concentrations of 0, 200, 2000 and 20000 ppm. The males were treated for 2 weeks prior to mating, through until necropsy after 4 weeks of treatment. The females were treated for 2 weeks prior to mating, then through mating, gestation and until termination on at least Day 4 of lactation.

The animals were monitored for clinical signs, body weight, food consumption, mating and litter performance. At termination, the adults received a gross necropsy, with weights of testes and epididymides recorded; histological examination was restricted to the testes, epididymides and ovaries from control and high dose animals.

Paternal toxicity was exhibited at 20000 ppm as a slight decrease in weight gain and an increase in piloerection. There were no obvious maternal effects at this level. There were no obvious parental effects at 200 or 2000 ppm, nor any effects of treatment on the reproductive parameters at any dose level.

Under the conditions of this study, the parental No Observed Effect Level (NOEL) was considered to be 2000 ppm (approximately 180 mg/kg/day) and for reproductive parameters the NOEL was considered to be 20000 ppm (approximately 1858 mg/kg/day). These data are presented in greater detail in the Robust Summaries.

IV. Category Justification: Validation of Dimer as Representative of Other Category Members for SIDS Endpoints

All four members of this category are produced by the dimerization of C18 unsaturated fatty acids, primarily tall oil fatty acids. Dimer was selected as the representative substance in this category for testing for the applicable SIDS endpoints. Chemically, the members of this category are very similar as they are all essentially mixtures of monomer, dimer and trimer. Dimer, particularly the distilled form that was used for testing, has the highest dimer content of any of the members of this category so that the results are most representative of the

category. Hydrogenated dimer is similar in composition to distilled dimer with the exception of fewer unsaturated sites which improves stability to heat and oxygen.

Because of their similar compositions, it is reasonable to assume that dimer is toxicologically representative of the other three substances. Dimer is non-toxic following acute oral exposure, with LD_{50} values > 2,000 mg/kg in several studies. Hydrogenated dimer is also non-toxic following acute oral exposure with an LD_{50} value > 5,000 mg/kg. With respect to repeat dose and reproductive/developmental toxicity, the parental NOEL for dimer is approximately 200 mg/kg/day while the NOEL for reproductive/developmental parameters was approximately 1800 mg/kg/day. Dimer has been tested for potential genotoxicity in several test systems including the Ames *Salmonella* assay, mouse lymphoma cell assay and a metaphase chromosome analysis of human lymphocytes. None of these test systems showed any indication of genotoxicity. In summary, based on a detailed understanding of the composition of the four substances in this category, the toxicological data on dimer can be reliably extrapolated to the entire category thereby validating the composition of the category.

V. Hazard Characterization of Dimer and Related Substances

For potential human health effects, the totality of the SIDS data demonstrates that dimer is non-toxic. Because all of the chemicals in this group are closely related to dimer, as well as the fact that all members of this group are similar in chemical composition, being predominantly cyclic addition compounds of C18 unsaturated and saturated fatty acids, based on the category approach, it can be inferred that all of the substances in this group are also non-toxic.

Dimer has no acute oral toxicity (i.e., LD_{50} > 2,000 mg/kg), and repeat dose toxicity data demonstrate a no observed effect level (NOEL) of approximately 180 mg/kg/day. There was no evidence of reproductive or developmental toxicity with a NOEL of approximately 1858 mg/kg/day for these endpoints. The lack of acute oral toxicity (i.e., LD_{50} > 5000 mg/kg) for the hydrogenated dimer is confirmatory of the lack of acute toxicity of the substances in this category. Genotoxicity test results show no evidence of mutagenicity in *Salmonella* (i.e., Ames test), mouse lymphoma cells or a human lymphocyte assay for dimer. Consequently, no adverse health consequences would be associated with any anticipated exposures to dimer or related substances.

With respect to potential ecotoxicological effects, the totality of SIDS data on dimer, the representative substance in this category, demonstrate that the substances in this category are non-toxic to aquatic organisms including fish, daphnia and algae. The No Observed Effect Loading Rate ($NOEL_r$) for dimer to fish, daphnia and algae was 1000 mg/l.

VI. Potential Exposure to Fatty Acid Dimers and Trimer

This brief summary provides an overview of market end uses and potential exposure to products derived from Tall Oil, a major feed stock to the pine chemicals industry with emphasis on fatty acid dimers and trimer. This information along with hazard data developed as part of the High Production Volume Chemical Testing Program should be useful in evaluating the potential risks (if any) that might be associated with various uses of tall oil derived chemicals.

During the process of pulping coniferous trees to make paper, sodium salts of chemicals occurring naturally in the trees are produced as a co-product. When acidulated, this soap becomes Tall Oil. Typically, Tall Oil is a mixture of 25–35% rosin acids and 45–55% fatty acids with the balance being neutral compounds. Tall oil can be further processed or separated into its major components by a process of high temperature low pressure distillation. The recovery and distillation of tall oil began on a commercial scale in the mid twentieth century. As the pulp and paper industry has expanded globally so has the processing of tall oil, and the production of tall oil derivatives. At the present time there are 10 companies operating a total of 19 tall oil distillation plants in 10 countries. The total production of tall oil is approximately two billion pounds per year.

Human exposure is limited by the fact that most tall oil chemicals are industrial intermediates consumed in the production of other chemicals As such there is little, if any, potential for exposure of the general consumer population. Environmental exposure is limited by the fact that the chemical processes used in the tall oil industry are essentially closed system processes where temperature and pressure are carefully controlled.

Environmental releases from tall oil processing plants are limited to (1) treated waste water discharge, and (2) ambient emissions following treatment with scrubbers or thermal oxidizers. Waste water can be generated from operation of the plant pressure control system or from minor spills and leaks associated with the process and/or handling of chemical products and routine housekeeping activities. In all cases the waste water is collected, the stream is treated to remove any free oil, and is then discharged into a lager biological waste treatment facility (either municipal treatment system or the treatment system of the parent company's paper mill). Air emissions generated from the pressure control system or from the storage and transfer of various streams, are generally collected and treated in chemical scrubbers or thermal oxidizers.

The entire array of tall oil based chemicals and their related processing steps are best depicted by a "family tree" or flow diagram rather than a listing of discrete independent chemicals. Such a diagram demonstrates how various "parent" chemicals are consumed in the production of down stream chemicals. Figure 3 is a representation of the "family tree" for tall oil products and the relationship

between these products. Based on industry data approximately 95% of tall oil is consumed during the production of other downstream products.

Two primary fractions (rosin, fatty acids) are derived form the initial processing of tall oil. As can be seen from Figure 3 these primary fractions are further processed to a wide variety of intermediates including dimers and trimer. Tall oil "Heads," tall oil "Pitch" and distilled tall oil (DTO) are the remaining fractions derived from the processing of tall oil. Each of these fractions or intermediates and their end uses are described in the appropriate Final Summary documents for each category of substances.

Fatty Acid Dimers and Trimer

Tall oil fatty acids (TOFA) are consumed almost entirely as an industrial intermediate where they are reacted or further distilled to produce other chemicals including fatty acid dimers and trimer. Table 11 illustrates general use categories and potential exposures to TOFA and related substances. Of the various TOFA distillation and reaction products, it is estimated that greater than 75% are marketed and consumed in non-dispersive commercial applications in the production of dimers and trimer, polyamide adhesive resins, alkyd resins for paint, polyester lubricants, plasticizers, and metal working fluids. Volatization to air and hence inhalation exposure would be minimal due to the essential lack of a vapor pressure for any of these substances. Exposure in all of these industrial applications is generally limited to dermal contact during manufacture of the numerous products derived from TOFA and related substances including fatty acid dimers and trimer. The only other potential exposure to any of the substances in this category occurs during their production from activities such as changing reaction vessels, sampling for quality control, transferring material from one work area to another, loading and unloading bulk containers, changing filters, and cleaning equipment.

Figure 3

U.S. TALL OIL INDUSTRY

PRODUCTION & MARKET DISTRIBUTION
POUNDS/YEAR (000)

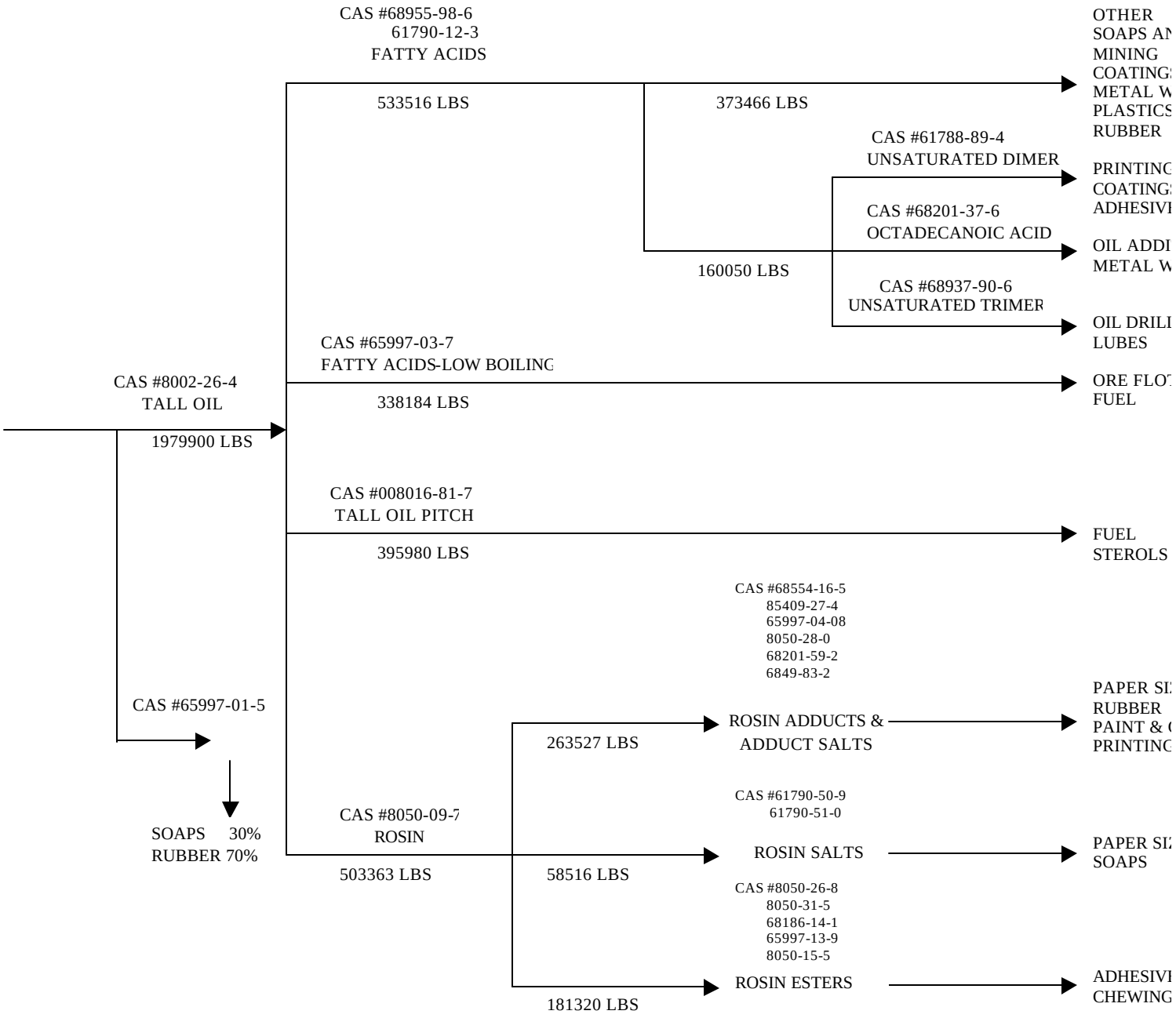


Table 11

Distribution, Application and Potential Occupational Exposure to Fatty Acid Dimers and Trimer

Substance	CAS #	Primary Function	Use Category	Major End Use Application	%
Dimer	61788-89-4	Chemical intermediate (feed for polyamide resins)	Industrial	Printing inks Coatings Adhesives	30 40 30
Trimer	68937-90-6	Chemical intermediate	Industrial	Oil drilling Lubes	85 15
Hydrogenated dimer	68783-41-5	Chemical intermediate (feed for polyamide resins)	Industrial	Adhesives Coatings	80 20
Crude dimer	71803-39-4	Chemical intermediate	Industrial	Monomer, dimer & trimer Oil drilling	90 10

References

Zinkel, D.F. and Russell, J., Eds. 1989. Naval Stores. Production, Chemistry, Utilization. Pulp Chemicals Association, New York.

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