**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

July 31, 2002

MEMORANDUM

FROM: Kathryn Boyle, CoChair IIFG

and

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TO: Robert Forrest, Chief
Minor Use, Inerts, and Emergency Response Branch

SUBJECT: IIFG Decision Documents on Reassessment of Exemptions from the Requirement of a Tolerance for Fatty Acids

The Inert Ingredient Focus Group reassessment is based on various conclusions of the FAO/WHO Joint Expert Committee on Food Additives, conclusions of various FDA GRAS (Generally Recognized As Safe) Assessments, Cosmetic Ingredient Reviews , and other information available on various websites.

Six exemptions from the requirement of a tolerance in 40 CFR 180.1001 are reassessed.

INERT INGREDIENT FOCUS GROUP

DECISION DOCUMENT for

Free Fatty Acids

**Petition No.:** No

**Tolerance Reassessments?:** Yes

**Chemical Category/Group:** Free Fatty Acids

**HPV Chemical?** Yes **Data Posted?** No

## 1. General Information

**Table 1. General Information and Inert Ingredient Uses**

| Inert Ingredient [Number of Carbons] | CAS No. | Inert List | OPP Chem Code: Inert | Uses Listed in 40 CFR 180.1001 |
|---|---|---|---|---|
| Caprylic acid [C8]* (1-octanoic acid) | 124-07-2 | 4B | 900180 | (c) |
| Capric acid [C10]* (1-decanoic acid) | 334-48-5 | 3 | 828955 | (c) |
| Lauric acid [C12]* (1-dodecanoic acid) | 143-07-7 | 3 | 828918 | (c) |
| Myristic acid [C14]* (1-tetradecanoic acid) | 544-63-8 | 3 | 879021 | (c) |
| Palmitic acid [C16] (1-hexadecanoic acid) | 57-10-3 | 3 | 900110 | (c) Diluent |
| Stearic acid [C18, saturated] (1-octadecanoic acid) | 57-11-4 | 3 | 800195 | (c) Diluent |
| | | | | (e) Lubricant, component ear tag |
| Oleic acid [C18, unsaturated] (cis-9-octadecanoic acid) | 112-80-1 | 4B | 831702 | (c) Diluent |
| Oleic acid, conforming to 21 CFR 172.862 | 112-80-1 | 4B | 831702 | (e) Defoaming Agent |

* These chemicals are not listed as discrete chemicals in 40 CFR 180.1001, but are included in the definition of the tolerance exemption "Fatty acids, conforming to 21 CFR 172.860" in 40 CFR 180.1001(c), where the uses are listed as binder, defoaming agent and lubricant.

Caprylic acid is registered as an active pesticide ingredient for use as a sterilizer, disinfectant, sanitizer, virucide, and fungicide/fungistat. Capric acid is registered for use as a sanitizer.

**Table 2 . Non-Pesticidal Uses**

| Inert Ingredient | Non-Pesticidal Uses* |
|---|---|
| Caprylic Acid | Synthesis of dyes, drugs, perfumes, anti-septics and fungicides, ore separations, synthetic flavors; soaps; used in hydraulic fluids, machining oils, and as a wood preservative |
| Capric Acid | Esters for perfumes and fruit flavor, base for wetting agents, intermediates, plasticizer, resins, intermediate for food-grade additives |
| Lauric Acid | Alkylated resins, wetting agents, soaps, detergents, cosmetics, insecticides, food additives |
| Myristic Acid | Soaps and perfumes, in synthesis of esters for flavorings and perfumes, and a component of food-grade additives |
| Palmitic Acid | Soaps; lube oils; water-proofing agent; cosmetics; food additive |
| Stearic Acid | Food additive; soaps; greases & lubricants; cosmetics; lotions; food packaging |
| Oleic Acid | Waterproofing textiles; soaps & detergents; food additive; cosmetics |

* Includes information provided in the Hazardous Substance Data Bank (TOXNET).

## 2. Physical/Chemical Properties

As a group the solubilities, vapor pressures, and Henry's Law Constants decrease with increasing chain length, but the *n*-octanol-water partition coefficients and strength of binding to soils increase with increasing chain length.

## 3. Introduction

Fatty acids are a group of compounds which are monocarboxylic acids attached to aliphatic carbon chains. The most common are palmitic, stearic, and oleic acids. They are naturally occurring, typically contain an even number of carbon atoms and usually range in chain length from 12 to 24 (long-chain), although fatty acids containing 2 to 4 carbons (short-chain) and 6 to 10 carbons (medium-chain) are not uncommon. This document addresses C8-C18, linear fatty acids as free acids, rather than as esters, salts or non-ester derivatives. The free fatty acids addressed in this document are caprylic, capric, lauric, myristic, palmitic, stearic and oleic acids, of which only oleic is unsaturated. Fatty acids are present in common fats and oils (such

as corn oil, peanut oil, and butter) as triglycerides. A triglyceride is composed of three fatty acid molecules and a single molecule of glycerol. Refer to the following table for more information regarding the composition of commonly consumed fats and oils:

**Table 3 . Fatty Acid Composition of Selected Fats and Oils (%)**

| Fatty acid | Soy-bean | Corn | Cotton-seed | Sun-flower | Peanut | Olive | Rape-seed (canola) | Palm Kernel | Coconut | Butter | Lard (pork) | Beef Tallow |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Caprylic | | | | | | | | 2.4-6.2 | 3.4-15 | 1.2 | | |
| Capric | | | | | | | | 2.6-7.0 | 3.2-15 | 2.8 | | |
| Lauric | | | | | | | | 41-55 | 41-56 | 2.8 | | |
| Myristic | 0.4 | <0.1 | 0.4-2.0 | <0.5 | <0.4 | 0.05 | <1.0 | 14-20 | 13-23 | 10.1 | 2.0 | 2.5 |
| Palmitic | 7-14 | 8-19 | 17-31 | 3-10 | 6.0-16 | 7.5-20 | 1.5-6.4 | 6.5-11 | 4.2-12 | 25.0 | 27.1 | 27.0 |
| Stearic | 1.4-5.5 | 0.5-4.0 | 1.0-4.0 | 1.0-10 | 1.3-6.5 | 0.5-3.5 | 0.5-3.1 | 10-23 | 3.4-12 | 12.1 | 11.0 | 7.4 |
| Oleic | 19-30 | 19-50 | 13-44 | 14-65 | 35-72 | 56-83 | 8-45 | 0.7-54 | 0.9-3.7 | 27.1 | 44.4 | 47.5 |

Upon consumption of fats and oils, the triglycerides (which typically comprise greater than 98% of fats and refined oils) are rapidly hydrolyzed in the human body forming glycerol and free fatty acids. Free fatty acids are then degraded to produce acetyl CoA (one acetyl CoA for each 2 carbons in the chain) which is used in the Citric Acid Cycle or for ketone body synthesis. Fats and oils account for 30-40% (average) of dietary intake in the U.S. During the 1990s, average per capita fat consumption in the U.S. ranged from 60 to about 100 grams/day.

## 4. Information Sources

Information from the following sources was used in performing this assessment:

- FirstGov (www.firstgov.gov),
- TOXNET ( www.toxnet.nlm.nih.gov.),
- FDA GRAS assessments
- Cosmetic Ingredient Review (CIR) evaluations
- Structure-Activity Relationship (SAR) assessments
- Food and Agriculture Organization of the World Health Organization (FAO/WHO) evaluations

## 5. Toxicological Profile

The Agency has not reviewed any of the toxicological studies for these fatty acids. The following toxicological data were obtained from ToxNet, as well as other government websites, and most of these studies are also included in the Cosmetic Ingredient Review (CIR) safety assessments.

Caprylic Acid

- Acute oral: Rat: $LD_{50}$ = 10.8 g/kg
- Acute Dermal: Rabbit: $LD_{50}$ > 5 g/kg
- Skin Irritation: Rabbit (500 mg, 24 hr): Moderate irritation
- Eye Irritation: Rabbit: Rated a 9 on a scale of 1 to 10 with 10 being the most severe injuries
- Mutagenicity: Ames test (*Salmonella typhimurium*), with strains TA 100, TA 1535, TA 1537, TA 97, and TA 98, with and without activation with both hamster and rat liver cells: Negative

*Saccharomyces cerevisiae* tested with or without liver preparations from mouse, rat, or monkey: Not mutagenic

Sex chromosome loss and nondisjunction occurred in *S. cerevisiae* exposed to 5 ppm.

Capric Acid

- Acute Oral: Rat: $LD_{50}$ > 10 g/kg
- Acute Inhalation: Rat: no deaths when exposed for 8 hrs to "concentrated vapors"
- Skin Irritation: Rabbit (500 mg, 24 hr): Moderate to severe irritation
- Eye Irritation: Rabbit: Irritating; in addition, mixed isomers of capric acid produced severe corneal burns
- Eye Irritation: Rabbit: Rated a 9 on a scale of 1 to 10 with 10 being the most severe injuries
- Mutagenicity: Ames test (*Salmonella typhimurium*), with strains TA 100, TA 1535, TA 1537, TA 97, and TA 98, with and without activation with both hamster and rat liver cells: Negative

Lauric Acid

- Acute Oral: Rat: $LD_{50}$ = 12 g/kg
- Skin Irritation: Rabbit (500 mg): Mild irritation
- Eye Irritation: Rabbit (100 mg): Mild irritation
- Subchronic/chronic: Rat: oral ingestion from a diet containing 35% lauric acid for 2 yrs: no effects
- Mutagenicity/Genotoxicity: Ames test (*Salmonella typhimurium*), with strains TA 100, TA 1535, TA 1537, TA 97, and TA 98, with and without activation with both hamster and rat liver cells: Negative;

In *S. cerevisiae* at 50 mg/L (µg/mL) of lauric acid, no mitotic crossing-over, but increased aneuploidy at 10 mg/L.

Myristic Acid

- Acute Oral: Rat: $LD_{50}$ > 10 g/kg

• Skin Irritation: Human (75 mg, 3 days, intermittent): Moderate
• Eye Irritation: Rabbit (100 mg): Mild irritation
• Subchronic/chronic: Rat: oral ingestion of a diet containing 10% myristic acid for 33 days: no effects on body weight, but evidence of increased erythrocyte (red blood cell) fragility; not carcinogenic
• Mutagenicity: Ames test (*Salmonella typhimurium*), with strains TA 100, TA 1535, TA 1537, TA 97, and TA 98, with and without activation with both hamster and rat liver cells: Negative;
• Genotoxicity: *Saccharomyces cerevisiae* cells exposed to 2.5 ppm: sex chromosome loss and nondisjunction.

Palmitic Acid

• Acute Oral: Rat: $LD_{50} > 10$ g/kg
• Skin Irritation: Human (75 mg, 3 days, intermittent): Mild irritant
• Eye Irritation: Rabbit: Mild irritation, primarily conjunctival
• Subchronic/chronic: Rats, weanlings fed a diet containing 50% palmitic acid developed lipogranulomas in adipose tissue within 8 weeks of treatment. Adults developed artherosclerotic lesions when fed at 6% for 16 weeks; however, no stomach lesions were seen when fed 10% for 150 days.

Stearic Acid

• Acute Oral: Rat: LDLo (Lowest published lethal dose): 4640 mg/kg
• Acute Dermal: Rabbit: $LD_{50} > 5$ g/kg
• Skin Irritation: Human (75 mg, 3 days, intermittent): Mild irritant;
Rabbit (500 mg/24hr): Moderate irritation
• Eye Irritation: Rabbit (100 mg): Mild irritation, conjunctival erythema
• Subchronic/chronic: Rats: weanlings fed diets containing 5 to 50% stearic acid (as the monoglyceride) for 3 weeks, depression of weight gain at doses above 10% dietary level, but mortality only occurred at 50% in diet; rats fed 50% stearic acid in the diet, death after 8 to 10 days; rats fed at 3000 ppm for about 30 weeks, erratic weight gain, anorexia, increased mortality, incidences of pulmonary infection, but no pathologic lesions; rats fed 50 g/kg/day for 24 weeks developed lipogranulomas in adipose tissue; rats fed a diet containing 5% stearic acid (as part of high-fat diet) for 6 weeks, or 6% for 9 weeks showed decreased blood clotting time and hyperlipemia; rats fed a diet containing 15% stearic acid showed increased plasma cholesterol.
• Mutagenicity/Genotoxicity: Ames test (*Salmonella typhimurium*), strains TA 98, TA100, TA 1535, TA 1537, and TA 1538, both with and without activation with rat liver cells (S-9): Negative;
In *S. cerevisiae* at 500 mg/L (μg/mL) of stearic acid: Negative, no mitotic crossing-over and no increased aneuploidy.
*Escherichia coli* with strain polA to assay for bacterial DNA repair: Negative;
*E. coli* with strain WP2 UVRA, with and without activation with rat liver cells: Negative.

Oleic Acid

• Acute Oral: Rat: $LD_{50}$ = 74 g/kg
• Acute Dermal: Guinea Pig: > 3000 mg/kg (no deaths)
• Skin Irritation: Human (15 mg, 3 days, intermittent): Mild irritant;
Rabbit (500 mg): Mild irritation
• Eye Irritation: Rabbit (100 mg): Mild irritation, conjunctivitis
• Subchronic/chronic: Rabbits: receiving 10 mL by gavage every other day for 4 days showed hair loss, scaling lesions on the ears, and death: NOAEL of 600 mg/kg.
• Reproductive/developmental: Rats: fed a diet containing 15% oleic acid for 5 months showed reduction in spermatogenesis and prolonged estrous cycles.
• Mutagenicity: Ames test (*Salmonella typhimurium*), with strains TA 100, TA 1535, TA 1537, TA 98, and TA 1538, with and without activation with both hamster and rat liver cells: Negative;
• Genotoxicity: Mouse cells: Unscheduled DNA synthesis at 35 mg/kg of oleic acid; Chinese Hamster lung fibroblasts: Cytogenetic analysis was positive at 2.5 mg/L of oleic acid, with higher incidences of both tetraploidy and for aneuploidy, but not for sister chromatid exchanges per metaphase.
In *S. cerevisiae* at 100 mg/L (µg/mL) of oleic acid, increased aneuploidy, but no increased crossing-over at concentrations up to 50 mg/L.

## 6. FDA GRAS (Generally Recognized As Safe) Assessments

Fatty Acids (21 CFR 172.860)

As a group, caprylic, capric, lauric, myristic, palmitic, stearic and oleic acids are classified by FDA as food additives permitted for direct addition to food for human consumption when used as lubricants, binders or defoaming agents.

Caprylic Acid (21 CFR 184.1025)

Caprylic acid is classified as a direct food substance affirmed as GRAS when used as a flavoring agent and adjuvant under good manufacturing practices.

Oleic Acid (21 CFR 182.90)

Oleic acid is specified as GRAS substance when migrating to food from paper and paperboard products used in food packaging. The FDA assessment resulting in this classification is entitled "Evaluation of the Health Aspects of Coconut oil, Peanut Oil, and Oleic Acid as they may Migrate to Food From Packaging Materials, and Linoleic Acid as a Food Ingredient." This assessment states that "(N)one of the available biological information indicates that these substances are hazardous to man or animals even when consumed at levels that are orders of

magnitude greater than could result from their use for the purposes covered in this report."

Stearic Acid (21 CFR 184.1090)

Stearic acid is classified as a direct food substance affirmed as GRAS when used as a flavoring agent and adjuvant under good manufacturing practices.

## 7. FAO/WHO Expert Committee on Food Additives

In 1999 the FAO/WHO published the "Evaluation of Certain Food Additives and Contaminants, WHO/FAS 49/TRS 884" which addresses a group of flavoring agents including caprylic, capric, lauric, myristic, palmitic and stearic acids. This evaluation considered acute toxicity, reproductive/developmental, and mutagenicity/genotoxicity studies for some of these fatty acids, and estimated that exposure to these fatty acids (as flavoring agents) ranged from 0.05 mg (stearic) to 3.8 mg (caprylic) per person per day. The committee concluded that "the substances in this group would not present safety concerns at the current level of intake." While considering the possibility of combined (or simultaneous) intake of these flavoring agents, the committee stated that "all of the substances in this group and their metabolites are innocuous and endogenous, and their combined intake was judged by the committee not to give rise to perturbations outside the physiological range."

## 8. Cosmetic Ingredient Review Evaluation

A 1987 safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid and stearic acid (Journal of the American College of Toxicology, 6[3]) was performed by an expert panel of the Cosmetic Ingredient Review (CIR). This assessment considered numerous toxicological studies, including various acute, subchronic, and chronic/carcinogenicity toxicity studies, and mutagenicity studies. This report also details extensive use of these fatty acids in numerous cosmetic products at concentrations ranging from 1-25 percent. Based on the available information, the panel concluded that "oleic, lauric, palmitic, myristic, and stearic acids are safe in present practices of use and concentration in cosmetics."

## 9. Structural Activity Relationship (SAR) Assessment

There are Structure-Activity-Relationship (SAR) assessments on mixed fatty acids, fatty acids (C8-18 and C18 unsaturated), lauric acid, and capric acid. With the exception of lauric acid, these evaluations indicated low concern for human health hazard and asserted that poor absorption by the skin is expected. The SAR assessment of lauric acid indicated low to moderate concern for human health effects due to concern for lung effects (through surfactant activity) if inhaled.

## 10. Hazard Characterization

As discussed above, fatty acids are present as triglycerides in fats and oils. Since

triglycerides typically make up greater than 98% of fats and refined oils, the fatty acids addressed in this document are present at significant concentrations in many common fats and oils, as indicated in Table 3. Fats and oils are a major source of calories in the human diet, comprising on average between 30% and 40% of dietary intake in the United States. Once a fat or oil is consumed, the triglycerides are rapidly hydrolyzed in the human body into glycerol and the free fatty acids. Free fatty acids are then degraded to produce acetyl CoA (one acetyl CoA for each 2 carbons in the chain) which is used in the Citric Acid Cycle or for ketone body synthesis.

Consumption of saturated fatty acids contributes to cardiovascular disease; in fact the American Heart Association recommends that daily saturated fat consumption not exceed 10% of dietary intake. However, dietary consumption of fatty acids is considered an individual choice and not necessarily the only risk factor associated with such disease. Because of these considerations, this document does not address the role of saturated fatty acids in cardiovascular disease as a "toxic" effect.

Caprylic, capric, lauric, myristic, palmitic, stearic and oleic acids have a history of safe use as natural components of many foods, as direct food additives and as cosmetic ingredients. Furthermore, fatty acids are processed by known metabolic pathways within the body and contribute to normal function. Considering this information as well as the FDA, WHO, CIR and SAR evaluation findings, adequate data are available to determine that the use of these materials in pesticide products is unlikely to pose a significant hazard to the general public or any population subgroup from consumption of residues of fatty acids. No additional information is needed to assess their safety.

## 11. Type of risk assessment

Qualitative for all pathways of human exposure (food, drinking water, and residential) because of the low toxicity of these compounds as well as the body's ability to metabolize these chemicals.

## 12. Sensitivity of Infants and Children

At this time, there is no concern for potential sensitivity to infants and children. A safety factor analysis has not been used to assess the risk. For the same reasons the additional tenfold safety factor is unnecessary.

## 13. Environmental Fate Characterization

Microbial degradation is the major route of transformation in the environment. Adsorption onto soil and sediment particulates is strong and, therefore, there is limited potential to reach surface water by dissolved runoff and/or leach to ground water. Volatilization from soils and water is not likely to be a transport process in the environment. Although the potential to bioaccumulate is high, bioavailability is offset by the tendency to adsorb strongly to soil and sediment particulates. However, concentration at the water-air interface is likely to be higher

than in the water column, which results in lowering the surface tension of the aqueous system. The lowering of the surface tension and the hydrophobic layer at the water-air interface has the potential to alter the physical and chemical characteristics of the aquatic environment.

As a group these compounds show the following trends with increasing chain length: decreasing water solubility, decreasing potential for volatilization, greater likelihood to partition and bind to soil and or sediment. Volatility from soil and water (Henry's Law Constant) and microbial mediated degradation are expected to limit transport to surface and ground water from applications or releases to land, with biodegradation being the major route of environmental dissipation.

## 14. Ecotoxicity and Ecological Risk Characterization

Fatty Acids (Free Acids), C8- C14 (Saturated)

The only ecotoxicity data for this group of fatty acids are limited to estimated 14-day $LC_{50}$ data on fish. The toxicity ranges from moderately toxic (4.02 ppm) for the C10 to highly toxic (0.1 ppm) for the C14. Although the 96-hour $LC_{50}$ values will be higher, that is appears to be less toxic then the 14-day values, without more information, it is not possible to categorize the acute toxicity based on a 96-hour exposure period. In conclusion, these compounds, notably the C12 and C14, are not likely to be found in water at concentrations that would cause acute risk to fish.

Fatty Acids (Free Acids), C16- C18 (saturated) and C18 (unsaturated)

The only ecotoxicity data for this group of fatty acids are limited to estimated 14-day $LC_{50}$ data on fish and the rat acute oral. Based on this limited data set (toxicity ranges from 0.02 to 0.004 ppm), these compounds appear to be very highly toxic to fish. The 96-hour $LC_{50}$ values will be higher, that is appears to be less toxic then the 14-day values, but without more information, it is not possible to categorize the acute toxicity based on a 96-hour exposure period. Although this group of fatty acids is more toxic to fish then the C8 to C14 free acids, they are far less mobile, are bound more tightly to sediment and their water solubility and toxicity values are much closer to one another (i.e. Palmitic acid has a water solubility of 0.04 ppm and a 14-day $LC_{50}$ value of 0.02 ppm) such that the potential risk to fish should be less then the C8 to C14. Terrestrial animal toxicity based on available rat data would indicate the C16 through C18 free acids are practically non-toxic on an acute basis.

## 15. Cumulative Exposure

Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The free fatty acids are structurally related; however, all are low toxicity chemicals. Therefore, the resultant risks separately and/or combined should also be low. EPA does not

have, at this time, available data to determine whether these chemicals have a common mechanism of toxicity with other substances or how to include these pesticide chemicals in a cumulative risk assessment.

## 16. Determination of Safety

Based on its review and evaluation of the available information, EPA concludes that there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to residues of the C8 to C18 fatty acids. Therefore, the following exemptions from the requirement of a tolerance are reassessed: In 40 CFR 180.1001 (c), fatty acids, conforming to 21CFR 172.860, palmitic acid, stearic acid, and oleic acid. In 40CFR 180.1001 (e), stearic acid, and oleic acid conforming to 21CFR 172.862.

## 17. List Reclassification

Due to low toxicity of these compounds, the body's ability to metabolize these fatty acids, and their natural occurrence in the food supply, reclassification to List 4A is appropriate with the exception of caprylic and capric acid.

List Classification:
Caprylic acid - 4B due to severe eye irritation
Capric acid - 4B due to severe eye irritation
Lauric acid - 4A
Myristic acid - 4A
Palmitic acid - 4A
Stearic acid - 4A
Oleic acid - 4A

Attachment:

EFED Review of Fatty Acids (S. Termes, 5/15/02)