UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

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Memorandum

Subject: Oleic Acid Sulfonates and Related Compounds: Antimicrobials Division Risk Assessment for the Reregistration Eligibility Decision (RED) Document and for Tolerance Reassessment
Barcode:323799

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To: Lower Risk Pesticide Chemical Focus Group
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Background:

This document represents the Antimicrobials Division's risk assessment to support the Reregistration Eligibility Decision (RED) on oleic acid, sulfonated, sodium salt (CAS Reg. Nos. 68443-05-0 and 67998-94-1), which is used as an active ingredient in food-contact sanitizing solutions. In addition, this document evaluates sulfonated oleic acid, which is used as an inert

ingredient in food-contact sanitizing solutions (68988-76-1). This assessment summarizes the available information on the use, physical/chemical properties, toxicological effects, exposure profiles, and environmental fate and ecotoxicity for these chemicals. This assessment relies primarily on a Structure Activity Relationship (SAR) assessments conducted by the Agency, in addition to some limited information submitted by the registrant of the active ingredient oleic acid, sulfonated, sodium salt.

The purpose of this document is to reassess the oleic acid sulfonate, sodium salt and oleic acid, sulfonated tolerance exemptions when used as active and/or inert ingredients in food contact surface sanitizing pesticide formulations. In addition, the two tolerance exemptions need to be reassessed to meet the Food Quality Protection Act (FQPA) standard. The Agency has considered any new data generated after the tolerance exemption was issued, new Agency guidance or other federal regulations, as well as previously available information in this assessment.

1.0 EXECUTIVE SUMMARY

This document addresses the exposures and risks from use of oleic acid, sulfonated, sodium salt, an active ingredient (food-contact sanitizer), and oleic acid sulfonate, which is an inert ingredient in food-contact sanitizing solutions. Potential residential exposures and risks are also addressed pursuant to the language and intent of the Food Quality Protection Act (FQPA).

The Agency believes these compounds are generally of low toxicity for human health concerns, based primarily on the SAR assessments conducted by the Agency. In this process, the chemical's structural similarity to other chemicals (for which data are available) is used to determine toxicity. For human health, this process can be used to assess absorption and metabolism, mutagenicity, carcinogenicity, developmental and reproductive effects, neurotoxicity, systemic effects, immunotoxicity, and sensitization and irritation. This is a qualitative assessment using terms such as good, not likely, poor, moderate, or high. SAR assessments have been performed by OPPT for over 25 years. It is an expert judgment by a group of Agency scientists who evaluate the toxicity of the chemical in a systematic, efficient, and effective hazard/ toxicity review process that is predicative in nature. Based on the SAR for these compounds, there are concerns for surfactant effects on the lung and concern for irritation effects. However, the use pattern as food-contact sanitizers are unlikely to result in significant inhalation exposures, based on their low vapor pressure ($<1x10^{-6}$ mmHg), and because the application method to food processing equipment and utensils is unlikely to generate aerosol particles that will be respirable. In addition, there are limitations on the end-use concentrations of oleic acid, sulfonated, sodium salt, and oleic acid sulfonate (not to exceed 200 and 312 ppm, respectively), which will further limit the potential for exposure**.** Furthermore, these concerns would be handled at the time of product reregistration via the label review process.

Although the Agency believes it can make a safety finding at this time, the Agency still requests some confirmatory data for oleic acid, sulfonated, sodium salt, because the active

ingredient food-contact sanitizer use is considered to be an indirect food additive use. The Agency requests a 90-day oral toxicity study and a developmental study to confirm the conclusions of the SAR. It is noted that the registrant has proposed to bridge toxicity data from other anionic surfactants, such as alkylbenzene sulfonates and alcohol sulfates, to satisfy the data requirements for the sulfonated oleic acid, sodium salt. The Agency believes there may be some merit in this approach, but would still require a minimum toxicity data set to confirm that this bridging argument is appropriate.

Given the available toxicological information and emphasizing the predictive nature of the SARs' judgment of low to moderate toxicity, a qualitative assessment of the risk of these two chemicals is appropriate. Adequate review of labeling considering the results of the end-product acute toxicity testing should address all concerns.

Although these chemicals show moderate to strong tendency to bind with soils and sediments, and show a tendency to be immobile, the dissipation pathway, estimated by various degradation models, for these chemicals appear to be through biodegradation in soils and sediments within a couple of weeks maximum. Hence, the possibility of surface and ground water contamination is low.

The SAR predicted low to moderate toxicity concern for ecological effects for these three chemicals (68443-05-0, 67998-94-1 and 68988-76-1). However, these compounds are immobile, bind tightly to sediment and soils, and undergo fairly rapid microbial degradation, which is expected to mitigate any potential for risk. EPA believes that these compounds will not cause unreasonable adverse effects on the environment. However, the Agency is requesting confirmatory ecotoxicity data to support the registered use of oleic acid, sulfonated, sodium salt. These studies include an acute oral bird study, an acute fish study and an acute invertebrate study. These studies are necessary for product labeling in case of an accidental spill during transport.

Based on its review and evaluation of all available information, AD concludes that there is a reasonable certainty of no harm resulting from exposure to oleic acid, sulfonated sodium salt as an active (sanitizer) ingredient, or oleic acid, sulfonated as an inert ingredient (sanitizer) to the general population and to infants and children in particular. As a result, AD has determined that a qualitative approach to assessing human health risks from exposure to the oleic acid sulfonates is appropriate.

2.0 USE INFORMATION

Sulfonated oleic acid, sodium salt is registered as an active ingredient as a no-rinse sanitizer for food processing facilities. The active ingredient consists of two chemical constituents, one as the primary ingredient (9-octadecenoic acid, sulfonated, sodium salt, CAS Reg. No. 68443-05-0) and the other as a by-product (octadecanoic acid, sulfo, sodium salt, 67998-94-1). The registrant supports the following use sites: non-porous dairy, beverage, brewery and food processing equipment. There is currently one registered product containing

2.66% sulfonated oleic acid, sodium salt (approximately 200 ppm) as an active pesticide ingredient (PER-VAD® Low Foam Anionic Acid Sanitizer, EPA 875-90).

The tolerance exemptions being reassessed in this document, the 40 CFR location of the established tolerance exemption, and the use pattern as an inert or active ingredient are listed in Table 1.

	Table 1 Exemptions from the Requirement of a Tolerance Being Reassessed in this Document						
Nomenclature or Synonyms	**Tolerance Exemption Expression/ Chemical Name**	**CAS No.**	**PC Code**	**40 CFR ◊ 180.**	**Use Pattern (Pesticidal)**	**List Classification**	**Active Products**
oleic acid, sulfonated, sodium salt	9-octadecenoic acid (9Z-), sulfonated, sodium salt	68443-05-0	079064 (active) (inert)	940 (c)	food contact sanitizing solutions for food processing equipment and utensils; end use concentration not to exceed 200 ppm	3	1 Product (PC 079064)
	octadecanoic acid, sulfo, sodium salt	67998-94-1	079064 (active)	no tolerance exemption	---	---	---
sulfonated oleic acid	9-octadecenoic acid (9Z-), sulfonated	68988-76-1	(inert)	940 (c)	food contact sanitizing solutions for food processing equipment and utensils; end use concentration not to exceed 312 ppm	3	1 Product

— = Not relevant

Use in Food Contact Surface Sanitizing Solutions

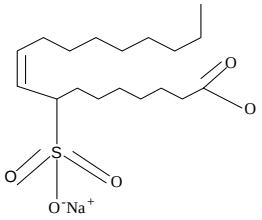
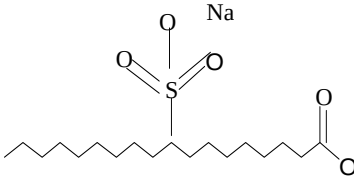
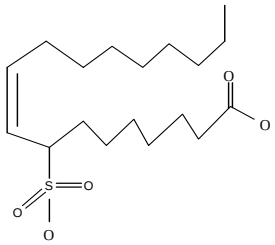
Oleic acid sulfonates have uses in food contact surface sanitizing solutions as specified under 40 CFR 180.940 (c). Residues for these compounds are exempt from the requirement of a tolerance when used in accordance with good manufacturing practice as ingredients in an antimicrobial pesticide formulation, provided that the substance is applied on a semi-permanent or permanent food-contact surface (other than being applied on food packaging) with adequate draining before contact with food. Both 9-octadecenoic acid (9Z-), sulfonated, sodium salt (CAS Reg. No. 68443-05-0) and 9-octadecenoic acid (9Z-), sulfonated (68988-76-1) have limitations for the ready-to-use end-use concentration not to exceed 200 ppm and 312 ppm, respectively

Other Uses

The Agency notes that 9-octadecanoic acid (9Z-), sulfonated, sodium salt (one of the active ingredients assessed in this document, CAS No. 67998-94-1) is included on the Agency's list of chemicals included in the High Production Volume (HPV) Challenge Program. HPV chemicals are those that are manufactured or imported into the United States in volumes greater than one million pounds per year. There are approximately 3,000 HPV chemicals that are produced or imported into the United States. The HPV Challenge Program is a voluntary partnership between industry, environmental groups, and the EPA which invites chemical manufacturers and importers to provide basic hazard data on the HPV chemicals they produce/import. The goal of this program is to facilitate the public's right-to-know about the potential hazards of chemicals found in their environment, their homes, their workplace, and in consumer products. This chemical is not sponsored by any industry groups for data development.

3.0 PHYSICAL/CHEMICAL PROPERTIES

The physical and chemical characteristics of the oleic acid sulfonates have been extracted from two major sources for this document: 1) EPISuite, developed by EPA's OPPT Program; 2) Structure Activity Relationship Assessments, also performed by the Agency's OPPT Program. Both compounds are fatty acid derivatives. Fatty acids are carboxylic acids containing long, aliphatic carbon chains. It is the structural features of fatty acids that define the physical and chemical behavior of these compounds. The long carbon chain provides a hydrophobic (lipophilic) end, generally referred as the "hydrophobic tail," whereas the carboxylic acid constitutes the polar, hydrophilic (lipophobic) headgroup. The hydrophobic end interacts with hydrophobic substances while the hydrophilic group interacts with hydrophilic substances, in a "like-dissolves-like" manner (USEPA 2002, EFED memo). Table 3 lists the physical and chemical characteristics of the three chemicals evaluated in this document. Some of these characteristics are estimated and some may be actual measured values.

Table 3. Physical and Chemical Properties of Oleic Acid Sulfonates			
Physical and Chemical Property	**9-Octadecenoic acid (9Z-), sulfonated, sodium salt 68443-05-0**	**Oleic acid, sulfonated, sodium salt (octadecanoic acid, sulfo, sodium salt) 67998-94-1**	**9-Octadecenoic acid (9Z-), sulfonated (sulfonated oleic acid) 68988-76-1**
Molecular Formula	$C_{18}H_{33}NaO_5S$	$C_{18}H_{35}NaO_5S$	$C_{18}H_{34}O_5S$
Molecular Weight	384.51	386.52	363
Water Solubility, mg/L	(dispersible)	608	2
Vapor Pressure, mmHg	$<1 \times 10^{-6}$	2.29×10^{-20}, estimated	$<1 \times 10^{-6}$
Henry's Law Constant, atm-m^3/mole	$<1 \times 10^{-8}$	8.75×10^{-12}	$<1 \times 10^{-8}$
Log K_{ow}	2.29	2.51, estimated	4.44
Log K_{oc}	2.92	2.92	2.92
Log BCF	1.85, estimated	1.85, estimated	1.85, estimated
Melting point, ^{0}C	312	311.7	219
Boiling point, ^{0}C	>400	712	>400
Structure	 Sulfonated Oleic acid, sodium salt		

4.0 HAZARD CHARACTERIZATION

4.1 Hazard Profile

Very limited toxicological data are available for the three compounds assessed in this document. A few acute toxicity studies are available for sulfonated oleic acid, sodium salt, which were submitted by the Registrant. In addition, the Agency conducted an extensive literature search including TOXNET databases (HSDB, IRIS, CCRIS, GENE-TOX, TOXLINE, and DART/ ETIC) and searched the internet (using the Google search engine). Given the limited toxicity data available in the literature, the Agency conducted Structure Activity Relationship (SAR) assessments for these compounds assessed in this document. In addition, the Agency has considered the toxicity data for other anionic surfactants (such as linear alkyl benzene sulfonate and alcohol sulfates), which the Registrant believes are toxicologically similar to sulfonated oleic acid, sodium salt.

The oleic acid sulfonates are considered to be fatty acid derivatives. Fatty acids are a group of compounds which are monocarboxylic acids attached to aliphatic carbon chains. Oleic acid (unsaturated C18) is one of the most common naturally occurring fatty acids. 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. For example, oleic acid is a natural constituent of common oils such as soybean oil (19-30%), corn oil (19-50%), cottonseed oil (13-44%), sunflower seed oil (14-65%), peanut oil (35-72%), olive oil (56-83%), rapeseed (canola) oil (8-45%), palm kernel oil (0.7-54%), coconut oil (0.9-3.7%), butter (27%), lard (pork) (44.4%) and beef tallow (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.

<u>SAR Assessments Performed by USEPA (2004)</u>

The Agency conducted Structure Activity Relationship (SAR) assessments for these three chemicals because limited toxicological information were found in the literature. In this process, the chemical's structural similarity to other chemicals (for which data are available) is used to determine toxicity. For human health, this process, can be used to assess absorption and metabolism, mutagenicity, carcinogenicity, developmental and reproductive effects, neurotoxicity, systemic effects, immunotoxicity, and sensitization and irritation. This is a qualitative assessment using terms such as good, not likely, poor, moderate, or high.

SAR assessments were performed in June 2004 by the Office of Pollution Prevention and

Toxics (OPPT) (USEPA 2004). For these chemicals, absorption is expected to be poor from the skin, moderate from the gastrointestinal tract and good from the lung. There is concern for surfactant effects on the lung; irritation to the eye, skin (chronic), mucous membranes and lung based on surfactant properties of the compounds. These three compounds were judged to be of low to moderate toxicity concern. There are no concerns for mutagenicity, carcinogenicity, developmental or reproductive effects.

A. Toxicological Data Available for Oleic Acid Sulfonates

The Agency has some limited information on acute toxicity of sulfonated oleic acid, sodium salt that indicate a low toxicity concern for the active ingredient (AI) pesticide and the one actively registered end-use pesticide product.

The acute toxicity of sulfonated oleic acid, sodium salt is low for oral and inhalation toxicity (Toxicity Category IV), and moderate for dermal toxicity (Toxicity Category III). It is a minimal primary skin irritant (Toxicity Category IV), but is a moderate to severe eye irritant (Toxicity Category II). It is noted that the acute inhalation toxicity value could be higher, but this study did not satisfy the guideline requirements because the exposure duration was only one hour (when a 4-hour exposure is required). Table 4 presents the acute toxicity data for sulfonated oleic acid, sodium salt.

Table 4. Summary of Acute Toxicity Data for Sulfonated Oleic Acid, Sodium Salt

Test	Species	Results	Reference
Oral LD_{50}	Rat	>5000 mg/kg (Toxicity Category IV)	MRID 41861503 Slover 1991
		>5000 mg/kg (a) (Toxicity Category IV)	MRID 43423804 Christopher 1994
Dermal LD_{50}	Rabbit	>2000 mg/kg (Toxicity Category III)	MRID 41861503 Slover 1991
Inhalation LC_{50}	Rat	>207 mg/L (1-Hour) (Toxicity Category IV)	MRID 41861503 Slover 1991
		>2.02 mg/L (4-Hour)(a) (Toxicity Category IV)	MRID 44008401 Douds, 1996
Dermal Irritation	Rabbit	Slight Erythema and Edema (Toxicity Category IV)	MRID 41861503 Slover 1991
Eye Irritation	Rabbit	24-Hr: 19.3; 48-Hr: 12.3; 72-Hr: 13.3; 7-Day: 1 (Toxicity Category II)	

(a) Contains 2.6% sodium sulfonated oleic acid

B. Consideration of Toxicity Data for Anionic Surfactants: Linear Alkylbenzene Sulfonates and Alcohol Sulfates

Recently, a submission was made by one of the registrants supporting sulfonated oleic acid (Johnson Diversey 2004), in which it was stated that "the acute and chronic toxicity of [sulfonated oleic acid] is expected to be similar to that of other anionic surfactants. As a class, these materials are irritants." Specifically, the registrant stated that the "acute toxicology data on [sulfonated oleic acid, sodium salt] are consistent with what is known about other anionic surfactants that contain fatty alkyl chains" (such as alcohol sulfates and linear alkylbenzene sulfonates). The Registrant believes that "on an acute basis, the data reported for sulfonated oleic acid, sodium salt are very similar to those available from HERA on the longer chain alcohol sulfates and linear alkylbenzene sulfonate."

"Both the alcohol sulfates and linear alkylbenzene sulfonate have been extensively studied; no evidence of any significant acute or chronic effects has been reported. These surfactant types are not considered to be mutagenic, carcinogenic or reproductive/ developmentally toxic. All have enjoyed a long history of safe use in conventional cleaning products in both the consumer and institutional markets. Some members of these categories are also approved for use in food contact applications." (JohnsonDiversey 2004).

In conclusion, the Registrant states that "We believe that the overall toxicity of [sulfonated oleic acid, sodium salt] will be similar to that of both the alcohol sulfates and linear alkyl benzene. [Sulfonated oleic acid, sodium salt] is structurally similar to both the alcohol sulfates and linear alkyl benzene and is likely metabolized and excreted by similar mechanisms. Additional testing to further characterize the toxicity of oleic acid sulfonate is not necessary."

The Agency has considered the Registrant's submission on this toxicity bridging argument in a memorandum from T. McMahon to D. Smegal, dated September 23, 2004 (D308387) (Attachment 1). The Agency believes the information provided on alcohol sulfates may be more closely similar to oleic acid sulfonates than the linear alkylbenzene sulfonates, which contain a benzene ring. The Agency was not able to obtain and independently review the primary literature summarized in the HERA documents, because these are unpublished studies, many of which were conducted in the early 1970s. The following information is a summary from the EPA memo.

<u>Alcohol Sulfates</u>

Based on toxicity data in the HERA (2002) assessment, a low order of acute toxicity is observed for the alcohol sulfates. Oral LD_{50} values are reported as ranging from 1.4 to > 8 g/kg. Acute dermal LD_{50} values were not available, but testing up to 500 mg/kg did not cause mortality in rabbits. Skin and eye irritation are observed with the alcohol sulfates at concentrations of 5-10% and above. No dermal sensitization is reported for this class of chemicals.

With regard to developmental and reproductive toxicity of alcohol sulfates, only one

reproductive toxicity study was available for what is claimed to be a structurally related compound, alpha olefin sulfonate. The summary of this study indicates no significant treatment-related effects up to 250 mg/kg/day in a 2-generation study. One published developmental toxicity study was available for an alcohol sulfate which was tested up to 600 mg/kg/day by oral gavage in rats, mice, and rabbits (Palmer et al., 1975, in http://www.heraproject.com/RiskAssessment.cfm) and which reported a maternal NOAEL of 2 mg/kg/day for all species and developmental NOAELs of 300 mg/kg/day in rabbits and mice and 600 mg/kg/day in rats.

With respect to mutagenicity, data on *in vitro* and *in vivo* mutagenicity tests were summarized in an Appendix to the HERA document. As the data are extensive, they are not reproduced here. However, in summary, it is noted that most of the studies show negative results. There are some data indicating a positive response, for example, in an *in vivo* chromosome aberration test in hamsters, a dose of 2.5 g/kg showed marginal but statistically significant increases in chromatid gaps in high dose females. In a rodent dominant lethal assay at doses of 210/300, 960/980, and 3050/3010 mg/kg/day, decreased pregnancy frequency and increased early embryonic deaths were observed at week four of an 8-week study, although the dose causing this effect was not noted in the summary. The nature of the positive response may be based upon a non-specific disruption of cell membranes by a high concentration of the surfactant and not a specific mechanism.

USEPA Conclusions:

The EPA memo concludes the following:

> The data cited by the Registrant in support of characterizing the toxicity of sulfonated oleic acid raises several issues with respect to the risk from exposure to sulfonated oleic acid:
>
> 1) The position by the Registrant that sulfonated oleic acid is biotransformed (metabolized and excreted) in a manner similar to the alcohol sulfates and/or linear alkylbenzene sulfonates is not supported by actual data but only by modeling results. An actual metabolism study would be helpful in addressing this issue.
>
> 2) The observation of liver and kidney toxicity from administration of the alcohol sulfates and the linear alkylbenzene sulfonates.....raises questions regarding the potential for sulfonated oleic acid to produce similar effects. In addition, the range of NOAEL values observed for both the results of testing of both classes of chemicals makes it difficult to compare results for a single chemical entity (i.e. sulfonated oleic acid) with chemical classes composed of more than one component. In order to determine whether there is any similarity, some side-by-side toxicity comparisons would need to be conducted with sulfonated oleic acid and the linear alkylbenzene sulfonates and alcohol sulfates to conclude with any certainty that data can be bridged from the alcohol sulfates and/or linear alkylbenzene sulfonates. A minimum data set of one oral 90 day rodent study and an oral

developmental study are required to determine if bridging is feasible.

3) As with the repeated dose toxicity data, the available data on developmental toxicity and reproductive toxicity show NOAELs over a range of doses but no actual data on sulfonated oleic acid for comparison. Thus, a determination of an FQPA safety assessment, as needed for the indirect food uses of sulfonated oleic acid, could only be addressed through generation of data relevant for bridging as noted above, or generation of data specific to sulfonated oleic acid to fulfill data requirements for the uses being supported in the Reregistration Eligibility Decision.

4.2 FQPA Considerations (Special Considerations for Infants and Children)

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

At this time, there is no concern for potential sensitivity to infants and children based on the SARs for these three compounds and the available data for other anionic surfactants (linear alkylbenzene sulfonates and alcohol sulfates) that show all developmental effects occurred at or above those dose levels associated with maternal effects. A safety factor analysis has not been used to assess the risk. For the same reasons the additional tenfold safety factor is unnecessary. However, the Agency is requesting a developmental study for sulfonated oleic acid, sodium salt to confirm the conclusions of the SAR.

4.3 Dose-Response Assessment

The Antimicrobials Division Toxicology Endpoint Selection Committee (ADTC) met in February 2003 to review the available toxicity data for sulfonated oleic acid and to discuss potential endpoint selection for use in risk assessment. The potential for increased susceptibility of infants and children from exposure to sulfonated oleic acid was also evaluated by the committee in order to meet the statutory requirements of the Food Quality Protection Act (FQPA) of 1996. The committee considered that the registered uses for sulfonated oleic acid may result in residues in food.

The ADTC committee concluded that no toxicity endpoints of concern are necessary for sulfonated oleic acid. These conclusions are based on the following information: the FDA has approved the indirect food use of sulfonated oleic acid up to 200 ppm for food processing equipment and glass bottles for milk. This level of clearance is orders of magnitude greater than the Agency's level of concern for indirect food uses of antimicrobial pesticides (ie., > 200 ppb), so the ADTC believes that sulfonated oleic acid is of a low order of toxicity. Further, the ADTC recognized that sulfonated oleic acid is a fatty acid derivative. Fatty acids are processed by known metabolic pathways within the body and are necessary for normal cellular functioning. As the exposures anticipated from the indirect food uses (as well as non-dietary dermal and/or inhalation exposure) are insignificant in comparison to levels encountered for fatty acids in the normal human diet, use of these chemicals in pesticide products is unlikely to pose any significant hazard to the general population or to any subgroup, including infants and children. Therefore, the Agency's ADTC did not select toxicity endpoints for sulfonated oleic acid.

4.4 Endocrine Disruption

FQPA requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the Endocrine Disruptor Screening Program (EDSP), the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the EDSP.

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, oleic acid sulfonates may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

5.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

The primary uses of sulfonated oleic acid and its sodium salt as antimicrobial pesticides are non-porous dairy, beverage, brewery and food processing equipment as indirect food-contact sanitizers. In addition, the Agency notes that sulfonated oleic acid, sodium salt (67998-94-1) is on EPA's HPV Challenge Program list, indicating that the manufacture of importation is greater than 1 million lbs/year, and thus there is significant use by industry that could lead to additional human exposures.

Residues from the pesticide uses of these three oleic acid sulfonates are expected to be

low because both 9-octadecenoic acid (9Z-), sulfonated, sodium salt (CAS Reg. No. 68443-05-0) and 9-octadecenoic acid (9Z-), sulfonated (68988-76-1) have limitations for ready to use end-use concentration not to exceed 200 ppm and 312 ppm, respectively. In addition, there is only one currently registered product for sulfonated oleic acid, sodium salt, that contains 2.66% AI. The SARs predict low to moderate toxicity to humans for both compounds, and there is no reason to expect that reasonable use will constitute any significant hazard. In addition, oleic acid sulfonates have no appreciable vapor pressure at ambient temperatures, and thus inhalation exposure is expected to be minimal. Therefore, a quantitative screening-level exposure assessment has not been conducted.

Drinking Water Considerations

The Agency believes the possibility of surface and ground water contamination is low. This is because these chemicals show moderate to strong tendency to bind with soils and sediments and show a tendency to be immobile. The dissipation pathway, estimated by various degradation models, for these chemicals appear to be through biodegradation in soils and sediments within a couple of weeks maximum. A more detailed discussion of environmental fate and potential for ground and surface water impacts is discussed below in Section 10.

6.0 RISK CHARACTERIZATION

The chemistry of fatty acids is important in understanding the human metabolism of these chemicals. Edible fatty acids are an important dietary source of calories and nutrition. The compounds evaluated are fatty acid derivatives that contain several of the same fatty acids that are derived from crops such as corn, peanut and sunflower oils.

SARs (Structure Activity Relationship assessments) are available for the oleic acid sulfonates. These SARs are almost identical for human health, as these three chemicals are judged to be low to moderate concern. Of note, these chemicals are considered to have poor absorption from the skin and moderate absorption from the gastrointestinal tract. SAR assessments have been performed by OPPT for over 25 years. It is an expert judgment by a group of Agency scientists who evaluate the toxicity of the chemical in a systematic, efficient, and effective hazard/ toxicity review process that is predicative in nature. Based on the SARs for these compounds, there are concerns for respiratory effects (because they are surfactants) and concerns for irritation effects. However, the use patterns of sulfonated oleic acid and its sodium salt as food-contact sanitizers are unlikely to result in significant inhalation exposures, based on their low vapor pressure ($<1x10^{-6}$ mmHg), and because the application method to food processing equipment and utensils is unlikely to generate aerosol particles that will be respirable. In addition, there are limitations on the end-use concentrations of oleic acid, sulfonated, sodium salt and oleic acid sulfonate (not to exceed 200 and 312 ppm, respectively), which will further limit the potential for exposure. Furthermore, these concerns would be handled at the time of product re-registration via the label review process.

Given the available toxicological information and emphasizing the predictive nature of the SARs' judgment of low to moderate toxicity, a qualitative assessment of the risk of these three chemicals is appropriate. Adequate review of labeling considering the results of the end-product acute toxicity testing should address all concerns.

7.0 AGGREGATE EXPOSURE AND RISK

In examining aggregate exposure, FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For the oleic acid sulfonates assessed in this document, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given their low toxicity, and the body's ability to metabolize these sulfonated/sulfated fatty acid compounds. The SAR assessments further support the low concern for human health hazard.

8.0 INCIDENT REPORTS (HUMAN EXPOSURE)

In the data sources available to the Agency, no reports of serious illness have been associated with human exposure to the oleic acid sulfonates. The Agency has reviewed the databases of the OPP Incidence Data System (IDS), the Poison Control Centers (from 1993-1998), California Department of Pesticide Regulation (from 1982-1996), and the National Pesticide Telecommunications Network (NPTN) for reported incident information of oleic acid sulfonates.

9.0. CUMULATIVE EXPOSURE AND RISK:

Section 408(b)(2)(D)(v) of the FFDCA 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 three oleic acid sulfonates 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 the oleic acid sulfonates assessed in this document have a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to the oleic acid sulfonates and any other substances and they do not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that the oleic acid sulfonates have a common mechanism of toxicity with

other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

10.0. ENVIRONMENTAL FATE CHARACTERIZATION/DRINKING WATER CONSIDERATIONS

The fate and transport processes for sulfonic acid and/or sodium salts of sulfonic acid of oleic acid are presented in Table 5. Although these chemicals show moderate to strong tendency to bind with soils and sediments and show a tendency to be immobile, the dissipation pathway, estimated by various degradation models, for these chemicals appear to be through biodegradation in soils and sediments within a couple of weeks maximum. Hence, the possibility of surface and ground water contamination is low.

These chemicals do not appear to persist in air for a long period of time as half-lives of these compounds is about six hours. No hydrolytic study on these ionic substances has been reported. Various fate models have indicated that the half lives of these substances in water will be similar to their half lives in soils and sediments. Hence aerobically or anaerobically, these chemicals will likely degrade in aquatic systems as readily as in soils and sediments.

These three chemicals have moderate (log K_{ow} = 2.29) to high (log K_{ow} = 4.44, CAS No. 68988-76-1) log K_{ow}s. These K_{ow}s are estimates based on modeling programs. Despite these moderate to high K_{ow}s, the compounds are not likely to bioaccumulate in aquatic organisms as they biodegrade readily in soils and sediments.

In general, these chemicals are not persistent in air, water or soils, and are not bioaccumulative in aquatic organisms and at this time the Agency has no concerns for fate and transport processes in air, soils or water.

Table 5
Environmental Fate Risk Assessment of Oleic Acid Sulfonates

Chemical Name	CAS No.	Fate Parameters	Fate/Risk Assessment
9-Octadecenoic acid (9Z-), sulfonated, sodium salt	68443-05-0	log K_{oc} = 2.92; log BCF = 1.85 (BCF = 70.8); POTW removal (%) = 90% via sorption and biodeg; complete ultimate aerobic biodeg: 1 week; sorption to soils and sediments = moderate to strong; migration to ground water = negligible	It can biodegradate within a week and hence is not likely to persist in soils; it has been shown to be over 90% removed in POTW. Probability of migration to ground water is negligible. It is not likely to bioaccumulate.
Octadecanoic acid, sulfo, sodium salt	67998-94-1	Prob. of rapid biodegradation: linear model: 0.6719; non-linear model: 0.9873; expert survey biodegradation: ultimate survey	The most probable route of degradation of this chemical is likely through biodegradation as predicted by

Table 5 Environmental Fate Risk Assessment of Oleic Acid Sulfonates			
Chemical Name	**CAS No.**	**Fate Parameters**	**Fate/Risk Assessment**
		model: 2.53 (weeks-months); primary survey model: 3.467 (days-weeks); readily biodeg prob (MITI model): linear model: 0.402; non-linear model: 0.208 atmospheric oxidation: half life= 5.62 hours; removal in wastewater treatment: total removal: 1.88%; total biodeg: 0.09%; total sludge adsorption: 1.79; total to air: 0.00 Level III fugacity model: air: 11.2 hours; water: 900 hours; soil: 900 hours; sediment: 900 hours	various fate models. It has a tendency to bind strongly with soils, and hence ground water contamination is not likely to occur. It is not stable in air as its half-life is about six hours, and it oxidizes through hydroxy radical route. It is not likely to bioaccumulate. It is not likely to contaminate surface water. It biodegrades readily.
9-Octadecenoic acid (9Z-), sulfonated	68988-76-1	POTW removal %: = 90% via sorption and biodeg; time for complete ultimate biodeg: = 1 week; sorption to soil/sediment: moderate to strong; migration to ground water = negligible	It has a low Koc and has a tendency to moderately to strongly bind with soils and sediments. It readily biodegrades through adsorption with in POTW (90% removal rate), and the half-life is about a week. Although it is likely to bioaccumulate (Kow = 4.44), since it dissipates through microbial degradation in soils and sediments, it is not bioaccumulative.

Source: EPI Suite/ OPPT Structure and Activity Team Report (USEPA 2004)

11.0 ECOTOXICITY AND ECOLOGICAL RISK CHARACTERIZATION

No ecotoxicity data were located for the sulfonated oleic acid and its sodium salt. Thus, the Agency conducted Structure Activity Relationship (SAR) assessments for these three compounds (USEPA 2004). The results of the assessments are presented on Table 6. All three chemicals (67998-94-1, 68443-05-0, 68988-76-1) were of moderate toxicity concern. The greater the length of the hydrophobe to the sulfonic acid, the greater the toxicity and surfactancy. All three chemicals had a low potential for persistence, bioaccumulation and toxicity. These compounds are immobile, bind tightly to sediment and soils, and undergo fairly rapid microbial degradation, which is expected to mitigate any potential for risk. EPA believes that these compounds will not cause unreasonable adverse effects on the environment. Adequate review of labeling considering the results of the end-product acute toxicity testing should address all concerns.

The Agency has developed the Endangered Species Protection Program to identify pesticides whose use may cause adverse impacts on endangered and threatened species and to implement mitigation measures that address these impacts. The Endangered Species Act requires federal agencies to ensure that their actions are not likely to jeopardize listed species or adversely modify designated critical habitat. To analyze the potential of registered pesticide uses to affect any particular species, EPA puts basic toxicity and exposure data developed for risk assessments into context for individual listed species and their locations by evaluating important ecological

parameters, pesticide use information, the geographic relationship between specific pesticide uses and species locations, and biological requirements and behavioral aspects of the particular species. A determination that there is a likelihood of potential impact to a listed species may result in limitations on use of the pesticide, other measures to mitigate any potential impact, or consultations with the Fish and Wildlife Service and/or the National Marine Fisheries Service as necessary.

The labeled use of oleic acid sulfonate and its sodium salt as food contact sanitizers is not expected to result in significant environmental exposure. Therefore, adverse effects on endangered/threatened terrestrial and aquatic animal species are not anticipated. Nevertheless, the Agency is requesting confirmatory ecotoxicity data to support the registered use as a pesticidal active ingredient, which is a data requirement for labeling in case there is an accidental spill during transport. These studies include an acute fish, acute invertebrate and an acute bird study.

Table 6. Summary of Ecotoxicity Data for Oleic Acid Sulfonates

Parameter	**Oleic acid, sulfonated, sodium salt (octadecanoic acid, sulfo, sodium salt) 67998-94-1**	**9-Octadecenoic acid (9Z-), sulfonated, sodium salt 68443-05-0**	**9-Octadecenoic acid (9Z-), sulfonated (sulfonated oleic acid) 68988-76-1**
Fish 96-Hour LC_{50} (mg/L)	≥100, predicted	≥50, predicted	
Daphnid 48-Hour LC_{50} (mg/L)	≥100, predicted	≥40, predicted	
Green Algae 96-Hour LC_{50} (mg/L)	≥100, predicted	≥50,predicted	
Chronic Fish Value (mg/L)	≥20, predicted	≥8, predicted	
Chronic Daphnid Value (mg/L)	≥20, predicted	≥6, predicted	
Chronic Algal Value (mg/L)	≥30, predicted	>10, predicted	
SAR Conclusions	Moderate concern for toxicity	Moderate concern for toxicity	

XI. Conclusions

Based on its review and evaluation of all available information, AD concludes that there is a reasonable certainty of no harm resulting from exposure to oleic acid, sulfonated, sodium salt as an active (sanitizer) or oleic acid, sulfonated as an inert ingredient (sanitizer solution), to the general population and to infants and children in particular. As a result, AD has determined that a qualitative approach to assessing human health risks from exposure to the oleic acid sulfonates is appropriate.

References:

Human and Environmental Risk Assessment (HERA). 2004. Linear Alkylbenzene Sulphonate (CAS No. 68411-30-3). May 2004. http://www.heraproject.com/RiskAssessment.cfm

Human and Environmental Risk Assessment (HERA). 2002. Human and Environmental Risk Assessment on the ingredients of European household cleaning products. Alcohol Sulphates Human Health Risk Assessment. Draft. December 2002.
http://www.heraproject.com/RiskAssessment.cfm

JohnsonDiversey 2004. Memorandum from F. Heitfeld to L. Amadio. Toxicity Review of Sulfonated Oleic Acid, Sodium Salt. September 2, 2004.

U.S. Environmental Protection Agency (USEPA). 2004 Structure Activity Relationship (SAR) for octadecanoic acid, sulfo, sodium salt (67998-94-1), 9-octadecen-1-ol, hydrogen sulfate, sodium salt, (Z)- (1847-55-8), 9-Octadecenoic acid, 12-(sulfooxy)-,disodium salt, [R-(Z)] (61702-68-9), 9-Octadecenoic acid, 12-(sulfooxy)-, monosodium salt, (9Z,12R)- (29704-46-9), 9-Octadecenoic acid, 12-(sulfooxy)-,sodium salt , (9Z,12R) (8043-44-5), octadecanoic acid, 9(or 10)-sulfooxy)-monosodium salt (68964-56-7), Octadecanoic acid, 9(or 10)-(sulfooxy)-, sodium salt (68331-91-9), octadecanoic acid, 9-(sulfooxy)-,sodium salt (68413-72-9), Octadecanoic acid, 9-(sulfooxy)-, disodium salt (65151-76-0), 9-Octadecenoic acid (9Z)-sulfonated, sodium salt (68443-05-0), 9-Octadecenoic acid (9Z)-sulfonated (68988-76-1), Structure Activity Team Report. OPPT. June 8, 2004.

U.S. Environmental Protection Agency (EPA) 2002. IIFG Decision Documents on Reassessment of Exemptions from the Requirement of a Tolerance for Fatty Acids. Memorandum from K. Boyle and K.Leifer to F. Forrest. July 21, 2002.

U.S. Environmental Protection Agency (EPA). 2002. "Tolerance Review of Compounds Known as Fatty Acids, Fatty Acid Salts, and Fatty Acid Esters, and Fatty Acid Derivatives Classified as Inert Ingredients in Terrestrial and/or Aquatic Agricultural and Non-Agricultural Uses". Memorandum from S. C. Termes/H. Craven, Environmental Fate and Effects Division (EFED) to M. Perry, Special Review and Reregistration Division (SRRD). May 15, 2002.

U.S. Environmental Protection Agency (EPA) 2003. Salts of Fatty Acids: Antimicrobials Division Science Assessment Document for Tolerance Reassessment. Memorandum from D. Smegal to K. Boyle, Chair of the Lower Toxicity Pesticide Chemical Focus Group. September 25, 2003.

ATTACHMENT 1

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Date: September 23, 2004

Subject: Similarity of Linear Alkylbenzene Sulfonates and Alcohol Sulfates to Sulfonated Oleic Acid with Respect to Toxicity
Barcode: D308387

FROM: Timothy F. McMahon, Ph.D.
Chair, Antimicrobials Division Toxicity Endpoint Selection Committee
Antimicrobials Division, OPP

TO: Deborah Smegal, Risk Assessor
Antimicrobials Division, OPP

This memorandum addresses data cited by the Registrant Johnson Diversey in support of the RED for sulfonated oleic acid and issues raised with respect to the bridging of toxicity data from linear alkylbenzene sulfonates and alcohol sulfates to sulfonated oleic acid.

In conclusion, the Agency believes that there are insufficient information at this time to bridge the toxicity data for linear alkylbenzene sulfonates and alcohol sulfates to the oleic acid sulfonates and its sodium salt. At a minimum, a mutagenicity battery (bacterial reverse mutation assay, in vitro mammalian gene mutation, and in vivo cytogenetics study), a 90-day oral rat study, and an oral developmental toxicity study would be required for oleic acid, sulfonated, sodium salt to demonstrate that these chemicals are toxicologically similar.

Background:

Oleic acid, sulfonated, sodium salt, is a pesticidal active ingredient currently being reassessed as part of reregistration. There are very few toxicity data available for this chemical, which are limited to acute toxicity data (acute oral, dermal, and inhalation studies and dermal irritation, and eye irritation studies). These data indicate low acute toxicity and that sulfonated oleic acid, sodium salt is a dermal and eye irritant.

On February 25, 2003, the Antimicrobials Division's Toxicity Endpoint Selection Committee (ADTC) met to discuss toxicology data for sulfonated oleic acid and discussed endpoint selection for use as appropriate in occupational/residential exposure risk assessments. This meeting was held as part of the development of the risk assessment for the Reregistration Eligibility Decision for sulfonated oleic acid.

At the ADTC meeting, the committee concluded that sulfonated oleic acid was related to oleic acid itself, a fatty acid that has been determined to be of low toxicity by OPP's Low Risk Focus Group and that has received food additive clearances by the Food and Drug Administration (FDA) without limitation, supporting the low toxicity of this chemical. Therefore, there is no risk of concern from the uses of sulfonated oleic acid as an antimicrobial pesticidal active ingredient (as an indirect food-contact sanitizer in milking equipment, food processing, handling, and storage areas, breweries, milk processing plants, meat processing plants, and beverage processing plants), and no toxicity endpoints are needed.

Registrant Submission:

Recently, a submission was made by one of the registrants supporting sulfonated oleic acid (Johnson Diversey 2004), in which it was stated that "the acute and chronic toxicity of [sulfonated oleic acid] is expected to be similar to that of other anionic surfactants." Specifically, the registrant states that "We believe that the overall toxicity of [sulfonated oleic acid] will be similar to that of both the alcohol sulfates and linear alkyl benzene. [Sulfonated oleic acid] is structurally similar to both the alcohol sulfates and linear alkyl benzene and is likely metabolized and excreted by similar mechanisms. Additional testing to further characterize the toxicity of oleic acid sulfonate is not necessary."

The OPP has no formal toxicology studies for sulfonated oleic acid (except the acute toxicity studies) but initially relied on the similarity of this chemical to oleic acid itself, which has shown a low order of toxicity from available data, analysis by the Low Risk Focus Group in OPP, and existing food additive clearances by the FDA. However, data are presented in the Human and Environmental Risk Assessment (HERA) documents that the registrant claims can be used to support the hazard of sulfonated oleic acid (available at www.heraproject.com). A summary is presented for both, taken from the HERA assessments.

Linear Alkylbenzene Sulfonates

Acute toxicity data for the linear alkylbenzene sulfonates (LAS) show a low order of toxicity for acute oral toxicity (LD_{50} values from 1086-1980 mg/kg) and dermal toxicity (LD_{50} of > 2000 mg/kg), some skin irritation potential (moderately irritating at 5%) and significant eye irritation using a 47% solution, non-irritating at 1%, and no dermal sensitization potential. Acute inhalation data are inconclusive but showed no effect up to 260 mg/m^3 (HERA 2004).

Non-acute testing shows effects on the liver and kidney, as summarized from the report below:

Summary of Repeated Dose Toxicity Studies for Linear Alkylbenzene Sulfonate

Table 23: Summary of the repeated dose toxicity tests

Animal	Route	Duration	NOAEL mg/kg bw/day	LOAEL mg/kg bw/day	Doses mg/kg bw/day	Reference
Monkey	Gavage+ subcutaneo us injection	28 days	150 (po) + 0.5 (sc)		30,150,300 (po) + 0.1, 0.5, 1.0 (sc)	Heywood et al.,1978
Rat	Gavage	1 month	125	250	125, 250, 500	Ito et al.,1978
Rat	Oral feed	2 months	225		22.5, 112.5, 225	Nolen et al.,1975
Rat	Oral feed	90 days	50	250	50, 250	Oser et al.,1965
Rat	Oral feed	90 days	750 (*)		750	Ikawa et al.,1978
Rat	Oral feed	90 days	220		8.8, 44, 220	Kay et al.,1965
Rat	Oral feed	6 months	40	115	40,115,340, 1030	Yoneyama et al.,1972
Mouse	Drinking water	6 months		20 (**)	20	Watari et al.,1977
Rat	Oral feed	9 months	260	780	260, 780	Yoneyama et al.,1976
Rat	Drinking water	9 months	85	145	85, 145, 430	Yoneyama et al.,1976
Mouse	Oral feed	9 months	< 500	500	500, 1000	Yoneyama et al.,1976
Mouse	Drinking water	9 months	100	250	100, 250, 750	Yoneyama et al.,1976
Rat	Dermal	15 days	< 286	286	286, 427	Sadai et al.,1972

(*) the only dose tested
(**) effects disappeared during the course of the study

Data reproduced from http://www.heraproject.com/RiskAssessment.cfm

This table, reproduced from the risk assessment for the linear alkyl benzene sulfonates, shows the effect levels from the various oral toxicity studies cited in the risk assessment. Although not indicated in this table, the text of the risk assessment indicated effects in the liver and kidney from oral administration, including liver weight increase at 250 mg/kg/day (Oser et al., 1965), degeneration of renal tubules at 115 mg/kg/day (Yoneyama et al., 1972), enzyme changes of the liver and kidneys at 780 mg/kg/day (Yoneyama et al., 1976), increases in alkaline phosphatase, decreased glucose-6-phosphatase and glucose-6-phosphate dehydrogenase, increased isocitrate dehydrogeanse at 750 mg/kg/day (Ikawa et al., 1978), and hepatic damage at 20 mg/kg/day in

mice (Watari et al., 1977) (HERA 2004).

It should be noted also from these data that the NOAEL values vary widely, without an obvious explanation. It could be based upon the use of compounds of this class of varying chain lengths (as noted in the HERA assessment, "commercial LAS consists of more than 20 individual components") .

In vitro mutagenicity tests conducted with LAS (Ames Salmonella, recombination assay with *bacillus subtilis*, reverse mutation with *E. coli*) were negative, as were *in vivo* mutagenicity assays (chromosomal aberration test, dominant lethal assay, micronucleus assay).

A summary of developmental and reproductive toxicity studies for LAS was also presented in the HERA document and is shown below. These data show Maternal NOAEL values from oral studies ranging from 10 mg/kg/day in mice to 780 mg/kg/day in rat oral studies, with LOAELs ranging from 100 to 3330 mg/kg/day. There are no apparent developmental NOAELs that are below the maternal NOAELs, but only summary data are provided in the HERA assessment (2004). Oral NOAELs for teratogenicity ranged from 135 to 600 mg/kg/day, with a LOAEL of 600 mg/kg/day identified in one study. Dermal developmental maternal NOAELs range from 0.9 to 150 mg/kg/day, while maternal LOAELs range from 9 to 1500 mg/kg/day, possibly suggesting the LAS may be more toxic via the dermal route of exposure in some studies.

Table 24: Summary of the developmental and teratogenicity tests

Animal	**Route**	**Exposure in pregnancy**	**NOAEL maternal** mg/kg bw/day	**NOAEL Teratogenicity** mg/kg bw/day	**Dose** mg/kg bw/day	**Reference**
Rat	Drinking water	Day 6-15	383	383	383	Endo et al.,1980
Rat	Oral feed	Day 0-20	780	780	80, 780	Tiba et al.,1976
Rat	Oral feed	Day 6-15 + 60 days prior mating	225	225	22.5, 112.5, 225	Nolen et al.,1975
Rat	Gavage	Day 6-15	300	600	0.2, 2, 300, 600	Palmer-a et al.,1975
Mouse	Gavage	Day 7-13	40	400	4, 40, 400	Takahashi et al.,1975
Mouse	Gavage	Day 6-15	10	300	10, 100, 300	Shiobara et al.,1976
Mouse	Gavage	Day 6-15	(2)	300	0.2, 2, 300, 600	Palmer-a et al.,1975
Rabbit	Gavage	Day 2-16	135	135	22.5, 45 ,135	Nolen et al.,1975
Rabbit	Drinking water	Day 6-18	3330 (**LOAEL**)	3330 (**LOAEL**)	3030	Endo et al.,1980
Rat	Dermal	Day 2-15	6	60	0.6, 6, 60	Palmer-b et al.,1975
Rat	Dermal	Day 0-21	20	400	20, 100, 400	Daly et al.,1980
Mouse	Dermal	Day 0-13	110	110	110	Sato et al.,1972
Mouse	Dermal	Day 6-15	150	1500	15, 150, 1500	Imahori et al.,1976
Rabbit	Dermal	Day 1-16	0.9	90	0.9, 9, 90	Palmer-b e4t al.,1975
Mouse	SC	Day 0-3 or Day 8-11	20	200	20, 200	Takahashi et al., 1975

Alcohol Sulfates

With respect to the alcohol sulfates, from the summary of toxicity data in the HERA (2002) assessment, a similar low order of acute toxicity is observed as with the linear alkylbenzene sulfonates. Oral LD_{50} values are reported as ranging from 1.4 to > 8 g/kg. Acute dermal LD_{50} values were not available but testing up to 500 mg/kg did not cause mortality in rabbits. As with the linear alkylbenzene sulfonates, skin and eye irritation are observed with the alcohol sulfates at concentrations of 5-10% and above. No dermal sensitization is reported for this class of chemicals.

Toxic effects are observed from repeated dose administration of alcohol sulfates. These data are again reproduced from the HERA risk assessment below:

Table 4
Repeated dose toxicity profile following oral administration of AS (selected studies)

Surfactant	Species	Route	Exposure duration	Dose/ Concentration	NOEL/LOEL	Dose-dependent Target Organ Effects (males: m; females f)	References (App. III)
C_{12} AS Na	Rat	Oral (gavage)	28-days (29-day post exposure observation period)	0, 30, 100, 300, 600 mg/kg/day	NOEL= 100 mg/kg/day LOEL = 300 mg/kg/day	Forestomach (irritation, ulceration, partially reversible (both sexes). Organ weight/body weight increases: liver (f); kidneys (m); testes.	Henkel, 1987 (unpublished, TRS 16)
C_{12-14} AS TEA	Rat	Oral (gavage)	28-days	0, 70, 250, 750 mg/kg/day	NOEL= 70 mg/kg/day LOEL = 250 mg/kg/day	Forestomach (inflammation, edema and ulceration); reversible.	Henkel 1988 (unpublished TRS 15,)
C_{16-18} AS Na	Rat	Oral (gavage)	90-days (33-day post exposure observation period)	0, 100, 300, 900 mg/kg/day	NOEL= 100 mg/kg/day LOEL = 300 mg/kg/day	Some deaths at high dose. Forestomach (inflammation, ulceration, both sexes, partially reversible). Organ weight/body weight increases: liver (m, f). Organ weight-body weight decreases: thymus, adrenals (f); (reversible).	Henkel 1987 (unpublished, HESA 1)
C_{12} AS Na	Rat	Oral (dietary)	21-days	0, 0.023%, 0.047%, 0.094%, 0.188%, 0.375%, 0.75%, 1.5% in diet (0, 25, 52, 108, 208, 423, 830, 1643 mg/kg/day)	NOEL= 109 mg/kg/day LOEL = 208 mg/kg/day	Liver: hypertrophy, reduced cytoplasmic fat and glycogenic vacuolation (especially in f). Liver enzyme changes. Organ weight/body weight increases: liver (especially in f); kidneys: (f); brain (f). Decreased weight gains (m). Depleted body fat.	Unilever, 1976 (unpublished study L35,)
C_{12} AS Na	Rat	Oral (dietary)	90-days	0, 0.07%, 0.14%, 0.28%, 0.56%, 1.13%, 2.25%, in diet (0, 59, 116, 230, 470, 950, 1900 mg/kg/day)	NOEL= 116 mg/kg/day LOEL = 230 mg/kg/day	Liver: hypertrophy, reduced cytoplasmic fat and glycogenic vacuolation (especially in f); liver enzyme changes. Organ weight/body weight increases: liver (m, f); kidneys (f); adrenals (f); brain (m, f); testes. Decreased weight gains (m, f). Depleted body fat.	Unilever, 1977 (unpublished study, L 36)

Page 22/104

Data reproduced from http://www.heraproject.com/RiskAssessment.cfm

As for the linear alkylbenzene sulfonates, the alcohol sulfates also show effects on the liver from repeated dose toxicity studies at doses which could be considered for setting toxicity endpoints of concern. There is less variation in NOAEL values compared to the linear alkylbenzene sulfonates but consistent effects on the liver are noted.

With regard to developmental and reproductive toxicity of alcohol sulfates, only one reproductive toxicity study was available for what is claimed to be a structurally-related compound, alpha olefin sulfonate. The summary of this study indicates no significant treatment-related effects up to 250 mg/kg/day in a 2-generation study. One published developmental toxicity study was available for alcohol sulfate which was tested up to 600 mg/kg/day by oral gavage in rats, mice, and rabbits (Palmer et al., 1975, in http://www.heraproject.com/RiskAssessment.cfm) and which reported a maternal NOAEL of 2 mg/kg/day for all species and developmental NOAELs of 300 mg/kg/day in rabbits and mice and 600 mg/kg/day in rats.

With respect to mutagenicity, data on *in vitro* and *in vivo* mutagenicity tests were summarized in an Appendix to the HERA document. As the data are extensive, they are not reproduced here. However, in summary, it is noted that most of the studies show negative results. There are some data indicating a positive response, for example, in an *in vivo* chromosome aberration test in hamsters, a dose of 2.5 g/kg showed marginal but statistically significant increases in chromatid gaps in high dose females. In a rodent dominant lethal assay at doses of 210/300, 960/980, and 3050/3010 mg/kg/day, decreased pregnancy frequency and increased early embryonic deaths were observed at week four of an 8-week study, although the dose causing this effect was not noted in the summary. The nature of the positive response may be based upon a non-specific disruption of cell membranes by a high concentration of the surfactant and not a specific mechanism.

Conclusions

The data cited by the Registrant in support of characterizing the toxicity of sulfonated oleic acid raises several issues with respect to the risk from exposure to sulfonated oleic acid:

1) The position by the Registrant that sulfonated oleic acid is biotransformed (metabolized and excreted) in a manner similar to the alcohol sulfates and/or linear alkylbenzene sulfonates is not supported by actual data but only by modeling results. An actual metabolism study would be helpful in addressing this issue.

2) The observation of liver and kidney toxicity from administration of the alcohol sulfates and the linear alkylbenzene sulfonates, as shown in the summary tables included in this memorandum, raises questions regarding the potential for sulfonated oleic acid to produce similar effects. In addition, the range of NOAEL values observed for both the results of testing of both classes of chemicals makes it difficult to compare results for a single chemical entity (i.e. sulfonated oleic acid) with chemical classes composed of more than one component. In order to determine whether there is any similarity, some side-by-side toxicity comparisons would need to be conducted with sulfonated oleic acid and the linear alkylbenzene sulfonates and alcohol sulfates to conclude with any certainty

that data can be bridged from the alcohol sulfates and/or linear alkylbenzene sulfonates. A minimum data set of one oral 90-day rodent study and an oral developmental study, in addition to the mutagenicity battery (bacterial reverse mutation assay, in vitro mammalian gene mutation assay and in vivo cytogenetics study) are required to determine if bridging is feasible.

Alternately, toxicology data on sulfonated oleic acid could be developed to meet the data requirements in support of the registered uses as a food-contact sanitizer. This would include (in addition to the acute toxicity data and standard mutagenicity battery) a developmental toxicity study in the rat, a 2-generation reproduction toxicity study in the rat, and subchronic toxicity studies in the rodent and non-rodent to support the indirect food uses for this active ingredient.

3) As with the repeated dose toxicity data, the available data on developmental toxicity and reproductive toxicity show NOAELs over a range of doses but no actual data on sulfonated oleic acid for comparison. Thus, a determination of an FQPA safety assessment, as needed for the indirect food uses of sulfonated oleic acid, could only be addressed through generation of data relevant for bridging as noted above or generation of data specific to sulfonated oleic acid to fulfill data requirements for the uses being supported in the RED.

References:

Human and Environmental Risk Assessment (HERA). 2004. Linear Alkylbenzene Sulphonate (CAS No. 68411-30-3). May 2004. http://www.heraproject.com/RiskAssessment.cfm

Human and Environmental Risk Assessment (HERA). 2002. Human and Environmental Risk Assessment on the ingredients of European household cleaning products. Alcohol Sulphates Human Health Risk Assessment. Draft. December 2002.
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JohnsonDiversey 2004. Memorandum from F. Heitfeld to L. Amadio. Toxicity Review of Sulfonated Oleic Acid, Sodium Salt. September 2, 2004.