Re-Review of
Sodium α-Olefin Sulfonates
as Used in Cosmetics

Status:	Re-Review for Panel Review
Release Date:	November 15, 2013
Panel Meeting Date:	December 8-9, 2013

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Cosmetic Ingredient Review

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MEMORANDUM

November 15, 2013

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: November 15, 2013

Subject: Re-Review of Sodium α-Olefin Sulfonates As Used In Cosmetics

In 1998, the CIR Expert Panel published a safety assessment on four sodium α-Olefin sulfonates with a conclusion of safe as used in rinse-off products and safe up to 2% in leave-on products. The concentration of the gamma sultone impurity of any formulation (leave-on or rinse-off) is limited to unsubstituted alkane sultones ≤ 10 ppm; chlorosultones ≤ 1 ppm; and unsaturated sultones ≤ 0.1 ppm.

No additional cosmetic ingredients were identified that might be added to this safety assessment. A literature search uncovered no new published data. However, the European Chemicals Agency (ECHA) database had a file on "sulfonic acids, C14-16 (even numbered)-alkane hydroxy and C14-16 (even numbered)-alkene, sodium salts". The data that was determined to not be included in the original report were summarized and included in this report.

The Panel is to review the new data and decide if there is cause to re-open this safety assessment. If not, then the Panel is to confirm the conclusion.

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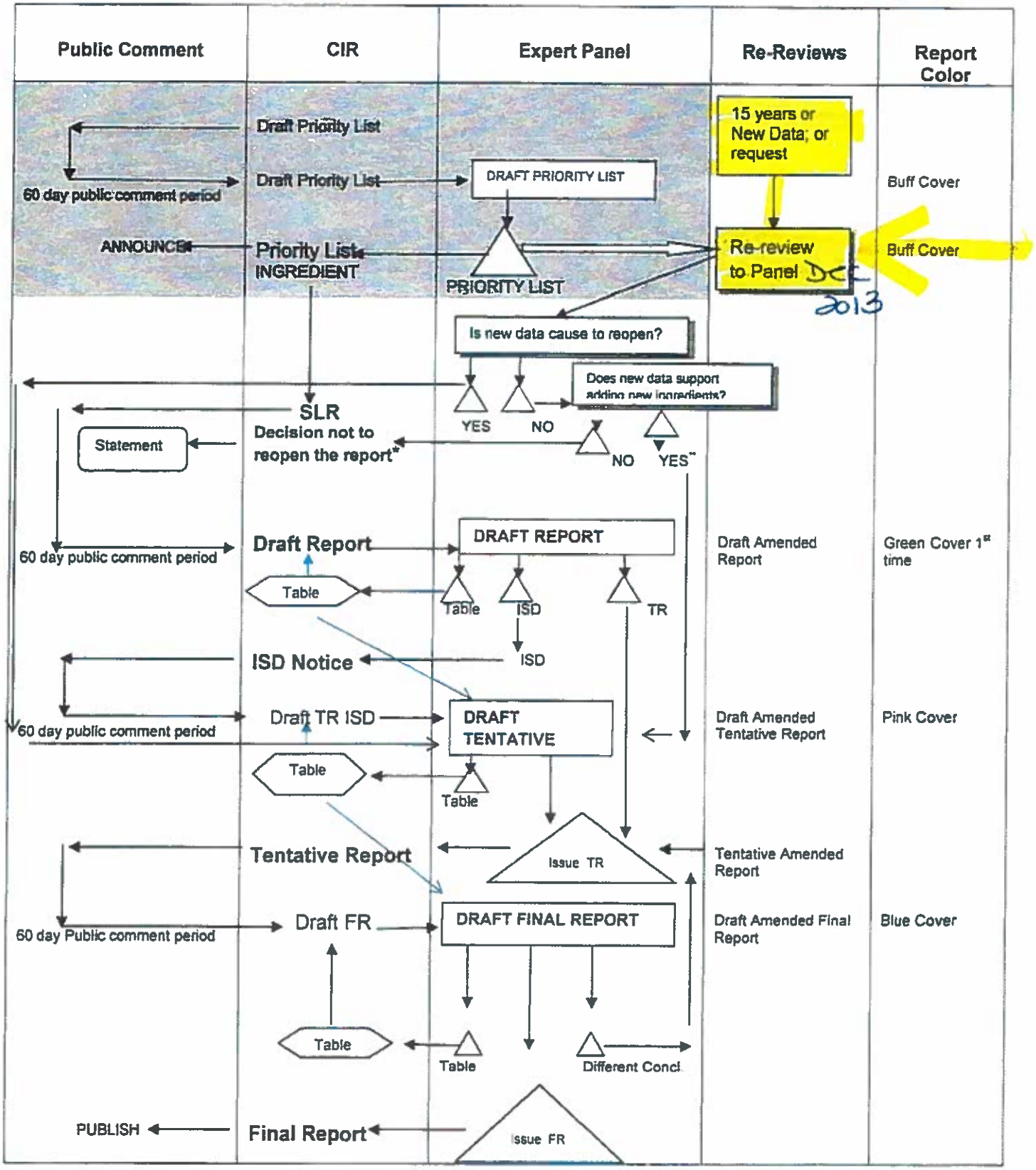
SAFETY ASSESSMENT FLOW CHART

Sodium α-olefin Sulfonates

Dec 2013



Sodium α-Olefin Sulfonates – History

1998 – Safety assessment published. Conclusion: safe as used in rinse-off products and was limited to 2% in leave-on products. Concentrations of the gamma sultone impurity of any formulations is limited to: unsubstituted alkane sultones, ≤10 ppm; chlorosultones, ≤ 1 ppm; and unsaturated sultones, ≤ 10 ppm.

December, 2013 – Panel examines re-review.

Search Strategy for Sodium Olefin Sulfonates

Scifinder - CAS Nos. and name search. Nothing useful.

PubMed – CAS Nos. and name search. Nothing useful.

HPVIS - CAS Nos. and name search. No hits.

Google Search - CAS Nos. and name search. Nothing useful.

ECHA – CAS Nos. and name search. Data found for Sulfonic acids, C14-16 (even numbered)-alkane hydroxy and C14-16 (even numbered)-alkene, sodium salts. Culled through for data not included in the original report.

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The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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INTRODUCTION

This is a re-review of the sodium α-olefin sulfonates as used in cosmetics. In 1998, a safety assessment of these ingredients was published.[1] The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded that these ingredients were safe as used in rinse-off products and safe use was limited to 2% in leave-on products. Concentrations of the gamma sultone impurity of any formulations are limited to: unsubstituted alkane sultones, ≤10 ppm; chlorosultones, ≤ 1 ppm; and unsaturated sultones, ≤ 10 ppm.

The ingredients in this re-review are:

- Sodium C14-16 Olefin Sulfonate
- Sodium C12-14 Olefin Sulfonate
- Sodium C14-18 Olefin Sulfonate
- Sodium C16-18 Olefin Sulfonate

These ingredients function in cosmetics as surfactant – cleansing agents (Table 1).

There were no data discovered during a literature search for this re-review. No new data have been submitted by industry. However, data were discovered on the European Chemicals Agency (ECHA) database. Robust summaries, obtained from the ECHA database, of studies that were not included in the original safety assessment are presented below.

USE

Cosmetic

At the time of the original safety assessment, it was reported by industry that sodium olefin sulfonates, in general, were used up to 5% in cleansers and 16% in shampoos and bath and shower products.[2] Specifically, in 1995, it was reported by the Cosmetic, Toiletries, and Fragrance Association that sodium C14-16 olefin sulfonates was used at 3.6% in facial cleansing foams, > %5 – 10% in skin care preparations, and > 10% in personal cleanliness products. There were no concentrations of use reported uses for sodium C12-14 olefin sulfonate, sodium C14-18 olefin sulfonate, or sodium C16-18 olefin sulfonate in the original safety assessment.

In 2013, data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 2).[3] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for these ingredients also in 2013.[4]

Sodium C14-16 olefin sulfonate was reported to be used in 11 leave-on products, 247 rinse-off products, and 42 products that are diluted for bath.[3] These include 6 baby products, 36 hair products, 1 lipstick, and 171 personal cleanliness products.

Sodium C14-16 olefin sulfonate was reported to be used up to 13.2% in leave-on products, 19% in rinse-off products, and 10% in bath products.[4] These include up to 10% in bubble baths and bath soaps and detergents, 19% in shampoos, and 13.2% in other personal cleanliness products. There were no concentrations of use reported for any baby products.

Sodium C14-18 olefin sulfonate was reported to be used in 5 shampoos.[3] Sodium C14-18 olefin sulfonate is used up to16% in shampoos.[4]

According to the VCRP, there were no reported uses for sodium C12-14 olefin sulfonate.[3] The Council reported that sodium C12-14 olefin sulfonate is used up to 5% in rinse-off products, including shampoos, hair tints, and skin cleansing preparations.[4]

There were no frequencies or concentrations of use reported for sodium C16-18 olefin sulfonate.[3,4]

TOXICOLOGICAL STUDIES

Acute Toxicity

Oral – Non-Human

In three acute oral toxicity studies of sodium C14-16 olefin sulfonate, the LD_{50} for female rats was reported to be 1379, 2290, and 6314 mg/kg (Table 3).[5] For male rats, it was 2340 mg/kg.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

When C14-16-alkane hydroxy and C14-16-alkene sulfonic acids sodium salts were orally administered to rats, mice, and rabbits, no embryotoxic, fetotoxic, or teratogenic effects were observed in rats; but, embryotoxic, fetotoxic and teratogenic effects in mice and rabbits at were observed.[5] The effects were at doses that were already inducing maternal toxicity. No further details were provided, including dosage, method of administration, treatment regime, mating regime.

GENOTOXICITY

In Vitro

Sodium C14-16 olefin sulfonate was negative in the following genotoxicity assays: Ames assay, chromosomal aberration assay, and mammalian cell gene mutation assay (Table 4).

In Vivo

In a gene mutation assay using mice, four samples of sodium C14-16 olefin sulfonate (5000 mg/kg) were not mutagenic to injected *S. typhimurium* or *S. cerevisiae* (Table 4).

CARCINOGENICITY

Sodium C14-16 olefin sulfonate was not carcinogenic to rats in two oral studies, one lasting 105 weeks (Table 5).

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

There were mixed results in dermal irritation studies of sodium C14-16 olefin sulfonate (Table 6). Several studies were not irritating to rabbits up to 36.9% active ingredients. Other studies had conclusions of irritating at 38% and 40% active ingredients.

Dermal – Human

Sodium C14-16 olefin sulfonates (1% in water; reagent grade) was predicted to be dermally irritating.[5] Human cadaver skin was soaked in sodium olefin sulfonates (C10, 12, 14, 16, and 18) for 1, 3, 6, and 24 h and compared to skin soaked in distilled water for the same time period. The maximum swelling was greatest for C12 and C14 (Table 7). Human abdominal stratum corneum was isolated from vertical sections of male and female (25-80 years of age) autopsied subjects. Swelling values were expressed as percentage increase above the hydrated length of the skin samples (i.e., length after soaking overnight in distilled water).

Ocular

Sodium C14-16 olefin sulfonate, in concentrations as low as 10% active, was irritating when administered to the eyes of rabbits in several studies (Table 6). In one study, the conclusion was that sodium C14-16 olefin sulfonate at 38% active was not irritating because only very slight to moderate erythema and chemosis and slight iritis was observed. In an EpiOcular (in vitro) assay, sodium C14-16 olefin sulfonate (90% active) was predicted to be irritating.

Sensitization

Dermal – Non-Human

Sodium C14-16 olefin sulfonate (up to 38% active) was not sensitizing in multiple guinea pig maximization tests (Table 8).

TABLES AND FIGURES

Table 1. Definitions and functions of sodium α-olefin sulfonates in this re-review.[6]

Ingredient	Definition	Function(s)
Sodium C14-16 Olefin Sulfonate (68439-57-6)	A mixture of long chain sulfonate salts prepared by sulfonation of C14-16 alpha olefins. It consists chiefly of sodium alkene sulfonates and sodium hydroxyalkane sulfonates	Surfactant – cleansing agent
Sodium C12-14 Olefin Sulfonate	A mixture of long chain sulfonate salts prepared by sulfonation of C12-14 alpha olefins. It consists chiefly of sodium alkene sulfonates and sodium hydroxyalkane sulfonates.	Surfactant – cleansing agent
Sodium C14-18 Olefin Sulfonate	A mixture of long chain sulfonate salts prepared by sulfonation of C14-18 alpha olefins. It consists chiefly of sodium alkene sulfonates and sodium hydroxyalkane sulfonates.	Surfactant – cleansing agent
Sodium C16-18 Olefin Sulfonate (8815-15-6)	A mixture of long chain sulfonate salts prepared by sulfonation of C16-18 alpha olefins. It consists chiefly of sodium alkene sulfonates and sodium hydroxyalkane sulfonates.	Surfactant – cleansing agent

Table 2. Current and historical frequency and concentration of use of sodium α-olefin sulfonates according to duration and exposure.[2-4,7]

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2013	1996	2013	1996	2013	1996	2013	1996
	Sodium C14-16 olefin sulfonate				Sodium C14-18 olefin sulfonate			
Totals	**300**	**93**	**0.12-19**	**5-10**	**5**	NR	NR	NR
Duration of Use								
Leave-On	9	2	1.2-13.2	10	NR	NR	NR	NR
Rinse-Off	247	66	0.12-19	NR	5	NR	NR	NR
Diluted for (Bath) Use	42	25	2-10	NR	NR	NR	NR	NR
Exposure Type*								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	4	NR	NR	3.6[a]	NR	NR	NR	NR
Incidental Inhalation-Powder	3	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	260	64	0.12-13.3	10	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	35	28	0.8-19	NR	5	NR	16	NR
Hair-Coloring	2	NR	4.5	NR	NR	NR	NR	NR
Nail	NR	1	NR	NR	NR	NR	NR	NR
Mucous Membrane	214	50	0.12-13.2	NR	NR	NR	NR	NR
Baby Products	6	NR	NR	NR	NR	NR	NR	NR

Table 2. Current and historical frequency and concentration of use of sodium α-olefin sulfonates according to duration and exposure.[2-4,7]

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2013	1996	2013	1996	2013	1996	2013	1996
	Sodium C12-14 olefin sulfonate				Sodium C16-18 olefin sulfonate			
Totals	NR	NR	**0.28-5**	NR	**NR**	NR	NR	NR
Duration of Use								
Leave-On	NR	NR	NR	NR	NR	NR	NR	NR
Rinse-Off	NR	NR	0.28-5	NR	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type*								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	5	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	0.28	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	0.37	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

NR – no reported use

Table 3. Acute oral toxicity studies of sodium C14-16 olefin sulfonate submitted to ECHA.[5]

Species (n)	Dose	Results
	Acute oral	
Wistar rats (5/sex)	1600, 2000, 2500, 4000 mL/kg (25% in water; ~90% active) by gavage. Observed for 14 d.	LD_{50} - Female = 2290 mg/kg, male = 2340 mg/kg Mortality – female: 1600 mg/kg bw: 0/5, 2000 mg/kg bw: 1/5, 2500 mg/kg bw: 4/5, 4000 mg/kg bw: 5/5; male: 1600 mg/kg bw: 1/5, 2500 mg/kg bw: 2/5, 4000 mg/kg bw: 5/5. Clinical signs: males and females: hunched posture, hollow flanks, lateral position, quiet behavior, clonic convulsions (weak), negative startle reflex, ruffled fur, cyanosis, hypothermia, closure of palpebral fissure, mucous feces, irregular and intermittent breathing. Two females temporarily demonstrated increased sensitivity to touch; two males had distended abdomens on day 1 and 2. No reduction of body weight. Macroscopic examination of the deceased animals revealed damage to the gastrointestinal tract. The stomachs were tightly filled with brownish fluid and foam. The gastric mucosa showed a dark-red color with sporadic hemorrhages. The mucosa of colon and small intestines showed a dark-red color, sporadically with hyaline appearance. Blood vessels of the GI-tract were injected.
Wistar Rats (10 female)	910, 1149, 1438, 1807 mg/kg (34.1% in water; 34.1% active) after fasting 18 h by gavage	LD_{50} - 1379 mg/kg. Mortality – female: 910 mg/kg: 0/10, 1149 mg/kg: 1/10, 1438 mg/kg: 6/10, 1807 mg/kg: 10/10. All deaths occurred within the first 24h. Clinical signs: 910 mg/kg: no abnormalities; 1149 mg/kg: 4 animals with spasms; 1438 and 1807 mg/kg: moderate apathy, prone positioning, decreased reflexes after 8h. Body weight - no differences in the surviving animals. Gross pathology - minor petechial bleedings in the lung of the animals that died within the first 24h, no effects in the surviving animals.
Wistar rats (10 female)	4000, 5000, 6300, 8000, 10000, 15000 mg/kg (25% in water; ~90% active); after fasting 16 h; by gavage	LD_{50} - 6314 mg/kg. Mortality - 4000 mg/kg: 0/10; 5000 mg/kg: 1/10; 6300 mg/kg: 5/10; 8000 mg/kg: 9/10; 10000 mg/kg: 10/10; 15000 mg/kg: 10/10. 16 animals died 70-120 min post application, 19 in the following night Clinical signs - Animals died in prone and lateral positions. No abnormal changes in body weight. Gross pathology - Red gastric content observed.

Table 3. Acute oral toxicity studies of sodium C14-16 olefin sulfonate submitted to ECHA.[5]

Species (n)	Dose	Results
Repeated dose oral		
Crl:CD(SD)IGS BR rats (15 male)	70 mg/kg/d neat for 90 d. Subsets of 5 rats were killed and necropsied on days 14, 28 and 91. Noses were processed and examined microscopically.	No clinical signs were observed. Degeneration and atrophy of the olfactory epithelium and degeneration and regeneration in the respiratory epithelium. The authors suggest that olfactory lesions may be due to tissue susceptibility rather than deposition of test substance within the nasal cavity. Metabolism may be essential in this susceptibility and it appears that the lesions do not represent a localized effect, since no evidence of aspiration, such as cellular debris, was observed during the microscopic examination.

Table 4. Genotox studies of sodium C14-16 olefin sulfonate submitted to ECHA.[5]

Assay	Details	Results
In vitro		
Ames assay; *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 and *E. coli* WP2 uvr A with and without metabolic activation (n = 3)	Experiment 1: 0, 4, 20, 100, 500, 2500, 10000 µg/plate; Experiment 2: 0, 4, 20, 100, 500, 2500, 5000 µg/plate (40% active; ≤C12: max. 1%, C14: approx. 65%; C16: approx. 30%; ≥C18: max. 1.5%) 48 to 72 h	Genotoxicity negative for both species. Cytotoxicity *S. typhimurium* Starting at 500 µg/plate without S9 and at 2500 µg/plate with S9.
Ames assay; *S. typhimurium*	Not provided	Genotoxicity negative Cytotoxicity no
Chromosomal aberration assay; Chinese hamster lung fibroblasts (V79) with and without metabolic activation.	-S9: 7.5, 37.5, 75 µg/ml +S9: 20, 100, 200 µg/ml (40% active; : ≤ C12: max. 1%; C14: ~65%; C16: ~30%; ≥ C18: max. 1.5%); 4 h.	Genotoxicity negative Cytotoxicity from 250 µg/ml up to the limit of solubility
Mammalian cell gene mutation assay	Not provided	Genotoxicity negative Cytotoxicity no
In vivo		
Gene mutation; mice (n not provided)	5000 mg/kg of four samples (21%-38% active) administered i.m. Tissues and cells were examined. Injected *S. typhimurium* or *S. cerevisiae* recovered and examined.	The test substance was not mutagenic in bacteria and yeast when metabolized by mice.

Table 5. Carcinogenicity studies of sodium C14-16 olefin sulfonate submitted to ECHA.[5]

Assay; animal (n)	Dose; details	Results
In vivo		
Wistar rats (40/sex; control = 100)	1, 0.75, or 0.5% C14-C18 (500, 375, or 250 mg/kg body weight per day) In feed for 24-27 weeks	No increase in tumors at necropsy at the end of treatment.
Long-Evans rats (50/sex)	10% (1 mL/kg; 30.0%, 30.9% and 38.9% active in deionized water; 42 mg/kg/d) by gavage for 105 weeks. Necropsy at 24 months.	Higher incidence of yellow staining of anogenital fur in treated rats compared to controls, but could not be attributed to urinary excretion of sultones; no differences in mortality. Similar incidence of neoplastic lesions in test and control rats, predominantly of the type predominantly found in aging rats, with no carcinogenic effect attributable to percutaneous application of the test materials.

Table 6. Dermal and ocular irritation studies of sodium C14-16 olefin sulfonate submitted to ECHA.[5]

Species (n)	Dose; details	Results
New Zealand White rabbit (6)	0.5 mL (38% active; vehicle not provided) shaved, intact and abraded skin; for 24 h; under occlusion. Not washed when removed. Observed at 24 and 72 h.	Intact skin - very slight irritant effects for 5/6. 1/6 had well-defined erythema, fully resolved at 72 h. Abraded skin - well-defined erythema in 5/6 and edema in 1/6 at 24 h. Very slight erythema in 6/6 and edema in 2/6 after 72 h. The observed effects were not fully reversible within 72 hours on abraded skin.
New Zealand White rabbit (6)	5% (starting with 34.1% active in water) shaved back; under occlusion for 24 h. Not washed at removal. Observed at 24 and 72 h.	Not irritating.
Rabbit (6)	Assumed neat (36.9% active) duration not provided. Observed at 24, 48, and 72 h.	Not irritating.
New Zealand White rabbit (3)	0.5 g (activity not provided) for 1 h. Wiped off at removal. Observed at 24, 48, and 72 h.	Not irritating.
New Zealand White rabbit (6)	(38% active) under occlusion, shaved, intact and abraded skin; for 24 h; under occlusion. Not washed when removed. Observed at 24 and 72 h.	Moderate to severe reactions were apparent in 6/6, 3/6 had eschar formation, one with cracking of the treated skin at 72 h. Reactions were slightly worse in abraded skin. Conclusion – irritating.
New Zealand White rabbit (6)	(0.5 mL; 40% active in water) under semiocclusion to shaved skin for 4 h. Washed at removal. Observed for 7 d.	Irritation but no corrosive effects on the skin. Conclusion – Irritating.
Rats (strain and number not provided)	20% and 30% (99.5% active) administered daily for 15 d.	Histological examination of tissues from the 30% group indicated some withering of the horny skin layer of the back and pronounced withering of the oral mucosa (the animals were not restrained after surfactant application); the tongue was essentially normal in appearance.
Ocular irritation, in vivo		
New Zealand White rabbit (3)	(0.1 mL; 34.1% active) with and without washing. Observed at 1, 2, 8, 24, 48, 72 h and 4, 5, 6, and 7 d after administration.	No effects were observed on cornea and iris. Conjunctiva and chemosis scores up to 2/4 and 1.66/4, respectively. Only slight erythema of the conjunctivae (score 0.33). Conclusion – irritating.
New Zealand White rabbit (6)	(0.1 mL; 38% active) with and without washing at 5 sec. Observed at 24, 48, and 72 h.	Positive result in the eyes of 6 animals. Rinsing the eye reduced the level of irritancy and corneal damage. Effects were still evident at the end of the observation period. Conclusion – irritating.
New Zealand White rabbit (3)	(100 mg in saline; 0.08 mL; 90% active) with washing. Observed at 24, 48, and 72 h.	Up to 72 h, there were clearly injected vessels up to diffuse, beefy red erythema and slight to severe swellings of the conjunctivae. Circumcorneal injection of the iris and corneal opacity as well as discharge, starting with clear and colorless and changing to white and viscous. 1/6 was free of symptoms after 7 d. 2/6 had distinct edema and erythema, ranging from diffuse, crimson red up to diffuse, beefy red. White, viscous discharge was observed. At 14 and 21 d, obvious edema and clearly injected vessels or diffuse, crimson red erythema of the conjunctivae, and complete corneal opacity with advanced vascularization was observed. Conclusion – irritating.
New Zealand White rabbit (3/sex)	(0.1 mL; neat) without washing. Observed at 24, 48, and 72 h.	Only slight redness and very slight swelling were left in the animals after 7 days. This was assumed to be reversible because of the direction to decline. Conclusion – irritating.
New Zealand White rabbit (6)	(0.1 mL; 38% active) with and without washing. Observed at 24, 48, and 72 h.	Very slight to moderate erythema and chemosis and slight iritis in 6/6 animals Very slight erythema and in 6/6 and 4/6 animals, respectively. Slight iritis in 2/6 at 48 h. At 72 h, all effects had resolved except for very slight erythema in 1/6. In the rinsed eyes, the effects were even less pronounced. Conclusion – not irritating.
New Zealand White rabbit (3)	(0.1 mL; 10% active) without washing. Observed at 24, 48, and 72 h and up to 7 d.	Conclusion – irritating.
Rabbit (6)	(36.9% active)	Corneal, iris and conjunctival effects were observed with high scores are still present after 72h. The response was deemed reversible. Conclusion – irritating.
New Zealand White rabbit (3)	(0.1 mL) with and without washing. Observed at 24, 48, and 72 h and up to 7 d.	Conclusion – irritating.
New Zealand White rabbit (3)	(37%; 37% active in distilled water) with and without washing and 5%, without washing. Observed at 1, 2, 8, 24, 48, and 72 h and up to 7 d.	Irritating at both concentrations.
Ocular irritation, in vitro		
EpiOcular test using human-derived epidermal keratinocytes cultured to form a stratified squamous epithelium similar to that found in human cornea.	(0.1 mL; 90% active) for 2, 10, 30, and 60 min.	Irritating.

Table 7. Percentage increase in swelling of human abdominal soaked in sodium C14-16 olefin sulfonates compared to skin soaked in distilled water.

Alkyl chain length	1 h	3 h	6 h	24 h
C10	4	5	7	12
C12	12	19	23	29
C14	12	18	23	35
C16	5	10	15	25
C18	6	11	17	26

Table 8. Sensitization studies

Assay; species (n)	Dose	Results
Guinea pig maximization test; female Dunkin-Hartley; (10; control 4)	100% (38% active) intradermal and epicutaneous induction; 25% and 12.5% epicutaneous challenge under occlusion	Irritation and exudation of the injection site (induction site) in 1/10. Conclusion – not sensitizing.
Sensitization; male Hartley guinea pigs (10)	50% (starting with 39% active) epicutaneous and occlusive induction and challenge	At 24 h after challenge 9/10 exhibited weaker erythema and edema scores than average produced during induction phase. 1/10 had edema at 24 h slightly stronger than average edema reaction during sensitization phase. Clinical observations - At 48 hours after challenge 9/10 exhibited weaker erythema and edema scores than averages produced during sensitization phase. At 48 h, 1/10 was slightly stronger than the average edema reaction during sensitization phase. Only 10 % (1/10) of the animals in the test group exhibited a slightly positive edema response at 24 and 48 h after challenge. Conclusion – not sensitizing.
Guinea pig maximization test; male albino; (10; control 4)	3.75% (starting with 15% active) intradermal and epicutaneous induction; 1.63% epicutaneous challenge under occlusion	Not sensitizing.
Guinea pig maximization test; not provided; (not provided)	9 samples of the test substance tested at 3.75% (starting with 36.9% active) intradermal and epicutaneous induction; epicutaneous challenge under occlusion	Not sensitizing.

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Cosmetic Ingredient Review

Commitment & Credibility since 1976

MEMORANDUM

November 15, 2013

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: November 15, 2013

Subject: Re-Review Data of Sodium α-Olefin Sulfonates As Used In Cosmetics

Attached, please find the original safety assessment of sodium α-Olefin Sulfonates and the results of the Council's concentration of use survey.

No new data were submitted from the Council and no data was discovered in the literature. However, data were discovered in the ECHA database. Information from those robust summaries has been summarized for review.

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FINAL REPORT ON THE SAFETY ASSESSMENT OF SODIUM ALPHA-OLEFIN SULFONATES[1]

Sodium C_{14-16} Olefin Sulfonate, Sodium C_{12-14} Olefin Sulfonate, Sodium C_{14-18} Olefin Sulfonate, and Sodium C_{16-18} Olefin Sulfonate are the Sodium α-Olefin Sulfonates used in cosmetics as surfactant–cleansing agents. The highest concentration reportedly is 16% in shampoos and bath and shower products. These ingredients are a mixture of long-chain sulfonate salts prepared by sulfonation of α-olefins of various carbon chain lengths noted as subscripts. In the manufacture of these ingredients, delta and gamma sultones may be produced. Sodium α-Olefin Sulfonates are poorly absorbed through normal skin, but are significantly absorbed through damaged skin. Acute oral LD_{50} values were 1.3–2.4 g/kg in rats and 2.5–4.3 g/kg in mice. Short-term toxicity studies using rats showed no consistent effects, even with exposures in the 0.5–1.0 g/kg range. Concentrations above 10% produced moderate ocular irritation and a concentration of 5% produced mild ocular irritation in rabbits. In reproductive and developmental toxicity studies, fetal abnormalities were noted, but only at doses that were maternally toxic. Genotoxicity data were mostly negative and oral and dermal carcinogenicity studies were negative. Various animal and clinical studies found irritation and sensitization. Sensitization was attributed to low level gamma sultone residues. Because gamma sultones are demonstrated sensitizers at very low levels, it was concluded that any product containing Sodium α-Olefin Sulfonates should have very little gamma sultone residues. The gamma sultone levels should not exceed 10 ppm for saturated (alkane) sultones, 1 ppm for chlorosultones, and 0.1 ppm for unsaturated sultones. Sodium α-Olefin Sulfonates are otherwise considered safe for use in rinse-off products. Based on concerns about irritation, were Sodium α-Olefin Sulfonates to be used in leave-on products, it was concluded that concentrations should not exceed 2% for such uses.

Sodium α-Olefin Sulfonates are long-chain sulfonic acids which function as surfactants–cleansing agents. The following report is a compilation of experimental data concerning the safety of Sodium C_{14-16} Olefin Sulfonate (CAS No. 68439-57-6); Sodium C_{12-14} Olefin Sulfonate; Sodium C_{14-18} Olefin Sulfonate; and Sodium C_{16-18} Olefin Sulfonate (CAS No. 68815-15-6) which are the sodium alpha-olefin sulfonates used in cosmetics. Much of the information comes from an evaluation of α-Olefin Sulfonates (AOS) done for the Soap and Detergent Association (Arthur D. Little, Inc. 1993).

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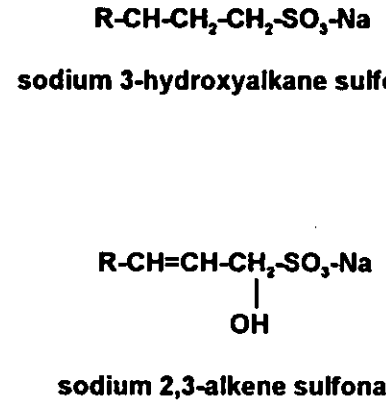

Figure 1. Chemical formulae for sodium hydroxyalkane and sodium alkane sulfonates.

CHEMISTRY

Definition and Structure

By definition, olefins are alkenes (unsaturated aliphatic hydrocarbons) obtained by cracking naphtha or other petroleum fractions at high temperatures. Alpha-olefins are particularly reactive because the double bond of the alkene is on the first carbon of the chain (Lewis 1993). Sodium AOS is a mixture of long chain sulfonate salts prepared by sulfonation of C(x–y) alpha-olefins where (x–y) represents the range of the carbon chain length (Wenninger and McEwen 1995a; 1995b). The mixture consists primarily of sodium hydroxyalkane sulfonates and sodium alkene sulfonates as shown in Figure 1 (Wenninger and McEwen 1995b; Arthur D. Little, Inc. 1993). Sodium C_{14-16} AOS is identified in Japan as sodium tetradecenesulfonate or sodium tetradecenesulfonate solution (Rempe and Santucci 1992).

Method of Manufacture

Although alpha-olefins can be produced by cracking of paraffin wax as noted, the limited availability of waxy crudes prevents large-scale use of the technique. For industrial use, α-olefins are synthesized by oligomerization of ethylene (Schoenberg 1980). Using continuous falling film techniques, the α-olefins are sulfonated with gaseous sulfur trioxide; typically a sulfur trioxide : olefin molar ratio between 1.0 to 1.2 is used. The sulfonation produces alkenylsulfonic acid and intermediate sultones as well as other by-products. At this stage of the process, the sultone content increases at the expense of alkylsulfonic acid upon standing. If the mixture ages too long, 1,4-sultone may be produced;

it is more difficult to hydrolyze than either 1,2 or 1,3-sultone (Kirk-Othmer 1983). The continuous falling film process limits contact time, temperature, molar ratio, and feed rates to eliminate undesirable side products formed during residence time (Schoenberg 1980). The acidic reaction mixture is neutralized and then hydrolyzed with an excess of sodium hydroxide to saponify the intermediate alkane sultones (some of which may be mild skin sensitizers) (Roberts and Williams 1983). The conditions of hydrolysis determine whether hydroxyalkane sulfonates or alkene sulfonates are the favored products. The process yields AOS mixtures of 60–65% alkene sulfonates, 30–35% hydroxyalkane sulfonates, and 5–10% disulfonates. Roberts et al. (1987) stressed that hypochlorite bleach should not be used in the manufacture of the Sodium AOS so as to avoid producing certain unsaturated and chlorosultones as by-products. These compounds are undesired by-products as they have been demonstrated to be highly potent skin sensitizers (Connor et al. 1975; Ritz, Connor, and Sauter 1975; Goodwin et al. 1983; see also Table 2). According to Ter Haar (1983), since 1973 the bleaching step in the production of AOS has been carried out at high pH to avoid the formation of hypochlorous acid (which subsequently reacts with alkene sulfonates to form chloro gamma and delta sultones), confirming the view of Roberts and Williams (1983) that knowledge of the chemistry of sultone formation allows them to be avoided in the manufacture of AOS.

Impurities

Stepan Company (1995) reports their internal specifications for Sodium AOS include a 31 ppm maximum for 1,4-sultones (delta sultones).

Techniques for sultone detection include separating and concentrating sultones from the surfactant via thin layer chromatography (TLC) followed by high performance liquid chromatography (HPLC) quantification. This technique has a sensitivity of 0.1 ppm and can go as low as 0.01 ppm when background does not interfere (MacMillan and Wright 1977). Another technique uses preparative HPLC followed by gas chromatography–mass spectrometry (GC–MS) and has a sensitivity of 2 ppb (Matsutani et al. 1986).

USE

Cosmetic

Sodium α-Olefin Sulfonates are used in cosmetic formulations as a surfactant–cleansing agent (Wenninger and McEwen 1995b). Data from the FDA (1996) indicates that Sodium C_{14-16} Olefin Sulfonate was used

Table 1. Reported use of Sodium C_{14-16} Olefin Sulfonate (FDA 1996)

Product category	No. formulations in category	No. containing ingredient
Bath oils, tablets and salts	147	1
Bubble baths	211	17
Other bath preparations	166	7
Rinses (noncoloring)	60	1
Shampoos (noncoloring)	972	26
Other hair coloring preparations	71	1
Other manicuring preparations	83	1
Bath soaps and detergents	372	22
Other personal cleanliness	339	3
Cleansing	820	13
Paste masks (mud packs)	300	1
1996 Total		**93**

in a total of 93 products (Table 1). There were no reported uses of the other three Sodium AOS. Concentrations of use are no longer reported to the Food and Drug Administration (FDA) (FDA 1992). However, data provided directly to CIR from the cosmetics industry indicate the following as the highest Sodium Olefin Sulfonates concentration used: 5% in cleansers and 16% in shampoos and bath and shower products. Data from industry specifically on Sodium C_{14-16} Olefin Sulfonates indicate use at 3.6% in facial cleansing foams; >5–10% in skin care preparations; and >10% in personal cleanliness products (CTFA 1995).

International

Sodium C_{14-16} AOS is listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category* (CLS). Sodium tetradecenesulfonate which conforms to the specifications of the Japanese Standards of Cosmetic Ingredients can be used without restrictions in all CLS categories except eyeliners and lipsticks and lip creams. Sodium tetradecenesulfonate solution which conforms to the standards of the *Japanese Cosmetic Ingredient Codex* can be used without restrictions in all CLS categories except eyeliners and lipsticks and lip creams, dentifrices and bath preparations (Yakuji Nippo, Ltd. 1994).

Noncosmetic

AOS and the ammonium, calcium, magnesium, potassium and sodium salts are approved by the FDA for use as indirect food additives. The

ruling specifies that the alkyl group be in the range of C_{10-38} with not less than 50% being in the range of C_{14-16} (Rothschild 1990).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism and Excretion

Oral

In a metabolism study, ^{14}C-AOS was administered as a single oral dose of 100 mg (50 μCi)/kg to three male Wistar rats. The radioactive AOS was a mixture of approximately 55% sodium 3-hydroxy alkane sulfonate [$C_{11}H_{23}CH(OH)CH_2{}^{14}CH_2SO_3Na$] and 45% sodium alkenyl(2) sulfonate [$C_{11}H_{23}CH{=}CH{}^{14}CH_2SO_3Na$]. The mixture was rapidly absorbed from the gastrointestinal tract (80% absorption) with peak activity in the blood at 3 hours after dosing. Within 12 hours, radioactivity in the bile accounted for 4.3% of the dose. At 24 hours postdosing, approximately 0.08% of the administered AOS was detected in the cecal content; the concentrations in other tissues were less than 0.02% dose/g. At that time, 72% of the dose had been excreted in the urine and 22% in the feces. No intact ^{14}C-AOS was detected in the urine. A metabolite more polar than AOS was detected (polarity determined by electrophoresis and equilibrium dialysis). The researchers suggested the metabolite was a hydroxylated or polyhydroxylated sulfonic acid with a shorter chain length than AOS (Inoue, O' Grodnick, and Tomizawa 1982).

Parenteral

Inoue, O' Grodnick, and Tomizawa (1982) conducted an intravenous metabolism study using the radioactive AOS described above. A single dose of 10 mg (5 μCi)/kg was administered to three male Wistar rats. Within 1 hour, half of the administered dose was excreted. By 6 hours postdosing, 90% of the administered dose had been eliminated. The concentrations of intact AOS in the liver and kidneys were comparable with blood concentrations. Therefore, the researchers proposed that, "intact AOS is distributed to about the same degree as the blood concentration in tissues." Similar to results from the oral studies, no intact AOS was detected in the urine. Because the concentration of the metabolites increased with time, the researchers proposed, "intact ^{14}C-AOS was metabolized in tissues, and therefore the transfer rate of metabolites from tissue to blood seems to be slightly slower than in urinary excretion rate." The researchers considered AOS to be rapidly absorbed and metabolized and the products excreted in the urine.

Dermal

The percutaneous absorption of ^{14}C-AOS in rats was investigated by Minegishi, Osawa, and Yamaha (1977). [The AOS was of the same composition and the radioisotopes at the same sites as in the study by Inoue, O' Grodnick, and Tomizawa (1982).] The solution was applied to the dorsal skin of groups of three male Wistar rats. The treatment groups were as follows: (1) intact skin dried naturally after application; (2) intact skin wiped off 0.5 hour after application; (3) intact skin wiped off 1.5 hour after application; (4) intact skin with a plastic cup containing the test substance (for continuous exposure); and (5) damaged skin (without stratum corneum) dried naturally. In the groups where the applied AOS was wiped off after a specified time (Groups 2 and 3), 60–70% of the applied radioactivity was recovered in the removal of the surfactant with wet cotton balls. Animals were killed at 24 hours. When 0.5 ml of a 0.2% ^{14}C-AOS solution was applied to the animals of Group 1, 0.33% was recovered in the urine, 0.08% in the bile, and 0.21% in the main organs 24 hours after application. It was estimated that 0.6% of the applied dose had been absorbed. Comparing results of Groups 1, 2, and 3, it was determined that the dermal absorption was almost complete by 1.5 hours postapplication. The excretion in the urine and bile approached the highest rate around 3 hours after application; excretion then decreased, but was still detectable at 70–90 hours postapplication. When the 0.2% dose was applied for continuous contact (Group 4), a small amount continued to be absorbed. In contrast, in damaged skin (Group 5), 36.26% of the applied dose was recovered in the urine, 1.83% in the bile, and 12.28% in the major organs 30 hours after application. Thus, 50% of the applied dose had been absorbed.

ANIMAL TOXICOLOGY

Oral Toxicity

Acute

Oral LD_{50} values for AOS range from 1300–2400 mg/kg in rats and 2500–4300 mg/kg in mice (Arthur D. Little, Inc. 1993). Ter Haar (1983) reported six samples of 36.9% C_{14-16} AOS had an average LD_{50} (rats) of 4000 mg/kg.

Short-Term

Rats were fed diets containing 0.625, 1.25, or 1.5% AOS (70% C_{14} : 30% C_{16}) for 7 days. At concentrations of 1.25 and 2.5%, a slight increase in the liver to body weight ratio was noted in males; at the 2.5% dose, a significant body weight depression was noted for 2 days in males and for

7 days in females. The "no effect" dosage was between 0.625 and 1.25% (Arthur D. Little, Inc. 1993).

In a 90-day feed study, groups of rats (number not specified) received AOS at doses of 40, 200, or 1,000 mg/kg/day. The AOS sample (89.7% active) contained 1.5% sultones and had been bleached and dried. A slight increase in the liver : body weight ratio was observed in animals of the high-dose group. No other changes in hematologic or biochemical parameters, feed consumption, gross or microscopic lesions were noted (Arthur D. Little, Inc. 1993).

In a 91-day feed study, groups of rats (number not specified) received C_{14-16} AOS (34% active) at doses of 50, 150, or 500 mg/kg. No treatment-related toxic or histopathologic changes were observed. Anomalies were noted in hematologic parameters. No further details were given. However, it was reported that similar changes were noted in rats which received C_{16-18} AOS (34% active) at doses of 50, 150, or 500 mg/kg also for 91 days. In that study red blood cell counts, but not hematocrit or hemoglobin values, were significantly higher for females of the high-dose group. Increased hemoglobin and hematocrit values were noted in females of the 150 mg/kg group, and significantly higher hematocrit values were noted in males of the 50 mg/kg AOS group (Arthur D. Little, Inc. 1993).

Acute Dermal Toxicity

Arthur D. Little, Inc. (1993) reported the following unpublished dermal LD_{50} values: two studies testing C_{14-16} AOS in rabbits, 1,130 mg/kg and 2,150 mg/kg, respectively; undiluted C_{14-18} AOS, 578 mg/kg. Ter Haar (1983) reported 36.9% C_{14-16} AOS had a dermal LD_{50} in rabbits of >6000 mg/kg.

Inhalation Toxicity

Acute

Groups of ten rats were exposed for 1 hour to a powdered aerosol of either C_{14-16} AOS flake (90% active) or a spray-dried formulation containing 17% C_{14-16} AOS at concentrations of 229 mg/L and 221 mg/L, respectively. No information regarding particle size was provided. All rats survived exposure and appeared normal clinically except for an increase in preening behavior. Five rats were killed and examined; mild petechial hemorrhages were noted in two animals exposed to the flake and in one animal exposed to the spray-dried formulation. The remaining animals were killed after 14 days; no treatment-related changes were noted at necropsy (Arthur D. Little, Inc. 1993).

Short-Term

Groups of 40 rats survived 20, 6-hour exposures (in 30 days) to either 0.9 or 10% C_{14-16} AOS flake (90% active). In the 0.9% group, no changes from control values were noted with respect to body weight, feed intake, blood chemistry, and gross lesions. At the 10% exposure level, a significant increase in gastric lesions was noted with 19/40 rats having edema and acute inflammation cell infiltration and 13/40 having ulceration of the squamous mucosa. The researchers attributed the lesions to stress factors (Arthur D. Little, Inc. 1993).

Ocular Irritation

Arthur D. Little, Inc. (1993) cited an unpublished report in which 1% AOS was not an ocular irritant to rabbits. At 5%, AOS was mildly to severely irritating and produced corneal necrosis. Imori, Ogata, and Kudo (1972a, b) reported 5% C_{14-19} AOS was mildly irritating. The review by the Soap and Detergent Association states that "there is general agreement that higher concentrations (10–40% of AOS) are moderately to severely irritating to rabbit eyes."

Using the Draize scoring system, two studies classified a 71.28% effective concentration of AOS in formulation (the formulation contained 79.2% of 90% AOS) as a moderate ocular irritant when tested on six rabbits (CTFA 1981).

Dermal Irritation

Acute

Referring to acute dermal irritation studies, Arthur D. Little, Inc. (1993) states "the majority of data concerned with the dermal irritation of AOS show it to be slightly to severely irritating to rabbit skin." In tests done on 20 AOS samples (of varying and sometimes similar carbon chain lengths), three AOS samples were classified as primary irritants according to the Draize procedure. These instances were as follows: a 25.7% C_{16-18} AOS sample had a Primary Irritation Index (PII) of 6.6 (maximum possible score is 8.0); a 10% sample of C_{16-18} AOS had a PII of 8.0; and a sample of 35% C_{17-20} AOS had a PII of 4.6. However, the results have varied from sample to sample and from study to study. For example, 10% sample of C_{14-16} AOS had a score of 6.2 in one assay (primary irritant), whereas another assay, using a sample from another manufacturer, had a score of 1.0 (slight irritant). The review stated, "such factors as AOS purity, method of production and/or variations in experimental technique may account for this inconsistency."

Repeated Exposure

Arthur D. Little, Inc. (1993), cites five unpublished studies that tested the dermal toxicity and irritation potential of AOS. In one study, 10 applications (in 14 days) of either 0.5 or 1.0% AOS produced no irritancy or skin fatigue in rabbits. In another study, 2 ml/kg/day of a 5% aqueous solution of AOS (34% active) was applied to the backs of six rabbits for 91 days. Mild to moderate skin irritation was noted (nonsuppurative dermatitis, parakeratosis, hyperkeratosis). One rabbit had a firm, swollen salivary gland which had changes of inflammation and hyperplasia. In the third study, twice daily application of open patches containing 2% aqueous C_{16-18} or C_{12} AOS (nine applications total) resulted in nil-to-slight and slight-to-moderate cumulative skin irritation in guinea pigs, respectively. In the fourth study, a 28-day dermal exposure to either 1% aqueous C_{14-16} AOS or a formulation containing 1% AOS produced no effect on intact rabbit skin. Questionable exfoliation and hyperemia were observed on abraded skin. The number of animals used was not reported. In the fifth study, an epilated guinea pig received two, 4-hour applications (24 hours apart) of either 2.4% AOS in a detergent or 8% aqueous C_{15-18} AOS. Both solutions were mildly irritating. Another dilution of the detergent (effective AOS concentration of 3.6%) was moderately irritating.

Dermal Sensitization

Table 2 lists guinea pig sensitization studies done on various sultones.

Arthur D. Little, Inc. (1993) cites unpublished studies regarding the sensitization potential of AOS. In one guinea pig assay, hydroxyalkane sulfonate C_{12-18} (21% active) and alkene sulfonate C_{12-18} (21% active), both used in the production of AOS, were nonsensitizers. The review states that commercial AOS should not contain unsaturated and chloro-1,3-sultones which are potent sensitizers, but may contain small amounts of alkane 1,4-sultones.

Ter Haar (1983) found that no sensitization occurred when guinea pigs were exposed to small amounts of C_{14} or C_{16} alkane 1,4-sultone. However, sensitization occurred in 50–60% of the animals when a sample with a 2% C_{14} 1,3-sultone content was used. Table 2 lists guinea pig sensitization studies done on various sultones.

Arthur D. Little, Inc. (1993) cites eleven unpublished studies which tested 64 AOS samples mostly derived from C_{14-18} α-olefins. Fifty-five of the samples were nonsensitizers. Of the nine sensitizers, two were photosensitizers. These latter two samples were a 44% active AOS paste (sensitized 6/6 animals) and an 80.7% active spray-dried AOS powder (sensitized 4/6 animals). Another two of the nine were aged samples;

Table 2. Guinea pig sensitization studies on sultones (Arthur D. Little, Inc. 1993)

No.	Sultone type		Concentration (ppm)	Sensitization rate	Comment/technique	Reference
Unsubstituted alkane 1,4-sultones (delta)						
1.	C_{16} 1,4-sultone	Injection:	10,000 (1%)		Magnusson-Kligman	Ter Haar 1983
		Topical:	50,000 (5%)		(induction includes	
		Challenge:	5,000 (0.5%)	zero	injection and topical exposure; challenge topical)	
2.	C_{16} 1,4-sultone	Injection:	20,000 (2%)		Magnusson-Kligman	Ter Haar 1983
		Topical:	100,000 (10%)			
		Challenge:	10,000 (1%)	zero		
3.	C_{14} 1,4-sultone	Injection:	20,000 (2%)		Magnusson-Kligman	Ter Haar 1983
		Topical:	100,000 (10%)			
		Challenge:	10,000 (1%)	zero		
4.	C_{14} 1,4-sultone	Injection:	20,000 (2%)			Ter Haar 1983
		Challenge:	100,000 (10%)	zero		
5.	C_{14} 1,4-sultone (2% 1,3-sultone)	Injection:	20,000 (2%)		Magnusson-Kligman	Ter Haar 1983
		Topical:	100,000 (10%)			
		Challenge:	10,000 (1%)	48%		
6.	C_{14} 1,4-sultone (2% 1,3-sultone)	Injection:	20,000 (2%)		Magnusson-Kligman	Ter Haar 1983
		Topical:	100,000 (10%)			
		Challenge:	10,000 (1%)	60%		
7.	Dodecane-1,4-sultone	Injection:	18,000 (1.8%)		Injection	CTFA 1995b
		Challenge:	10,000 (1%)	7/11		
			1,000 (0.1%)	1/11		
		Rechallenge:	10,000 (1%)	2/7		

Unsubstituted alkane, 1,3-sultones (gamma)						
8.	C_{14} 1,3-sultone	Injection:	20,000 (2%)		Magnusson-Kligman	Ter Harr 1983
		Topical:	100,000 (10%)			
		Challenge:	5,000 (0.5%)	24%		
9.	C_{14} 1,3-sultone	Injection:	20,000 (2%)		Magnusson-Kligman	Ter Harr 1983
		Topical:	100,000 (10%)			
		Challenge:	10,000 (1%)	zero		
10.	Dodecane 1,3-sultone	Induction:	22,000 (2.2%)		Injection	CTFA 1995b
		Challenge:	10,000 (1%)	14/15		
			1,000 (0.1%)	7/15		
			Rechallenge:			
		Dodecane-sultone:	10,000	1/14		
		1-Dodecene-sultone:	100	13/14		
Chlorosultones						
11.	3-Chlorotetra-decane-1,4-sultone (delta)	Injection:	20 (0.002%)		Magnusson-Kligman	Ter Harr 1983
		Topical:	100 (0.01%)			
		Challenge:	10 (0.001%)	zero		
12.	2-Chlorotetra-decane-1,3-sultone (gamma)	Injection:	20 (0.002%)		Magnusson-Kligman	Ter Harr 1983
		Topical:	100 (0.01%)			
		Challenge:	10 (0.001%)	50%		
13.	2-Chloro-1,3-dodecane sultone (gamma)	Induction:	20 (0.002%)			
		Challenge:	110 (0.011%)	12/13	Injection	CTFA 1995b
			11 (0.0011%)	7/13		
				1.1	4/13	
14.	2-Chloro-1,3-dodecane sultone (gamma)	Induction:	4,000 (0.4%)		Closed patch	CTFA 1995b
		Challenge:	120 (0.012%)	6/14		
				12	5/14	
				1.2	2/14	

(Continued on next page)

Table 2. Guinea pig sensitization studies on sultones (Arthur D. Little, Inc. 1993) *(continued)*

No.	Sultone type	Concentration (ppm)		Sensitization rate	Comment/technique	Reference
Unsubstituted alkane, 1,3-sultones (gamma)						
15.	1-Dodecene-1,3-sultone	Induction:	20 (0.002%)			Ter Haar 1983
		Challenge:	100 (0.01%)	29%		
16.	1-Tetradecene-1,3-sultone	Injection:	20 (0.002%)		Magnusson-Kligman	Ter Haar 1983
		Topical:	100 (0.01%)			
		Challenge:	10 (0.001%)	42%		
17.	1-Tetradecene-1,3-sultone	Induction:	100		Magnusson-Kligman	Inveresk Research
		Challenge:	100	10/15	same concentration used for	International 1985
		Rechallenge:	1	0/15	both (injection and topical) induction exposures	
18.	1-Tetradecene-1,3-sultone	Induction:	100		Magnusson-Kligman	Inveresk Research
		Challenge:	1	11/15	same concentration used for	International 1985
		Rechallenge:	0.1	0/15	both (injection and topical) induction exposures	
19.	1-Tetradecene-1,3-sultone	Induction:	50		Magnusson-Kligman	Inveresk Research
		Challenge:	10	14/15	same concentration used for	International 1985
		Rechallenge:			both (injection and topical)	
		(In acetone)	8	0/15	induction exposures	
		(In 5% AOS soln)	1	13/15		
20.	1-Tetradecene-1,3-sultone	Induction:	50		Magnusson-Kligman	Inveresk Research
		Challenge:	5	15/15	same concentration used for	International 1985
		Rechallenge:			both (injection and topical)	
		(In acetone)	5	0/15	induction exposures	
		(In 5% AOS soln)	1	0/15		

21.	1-Tetradecene-1,3-sultone	Induction: Challenge: (In acetone)	1 50 5	8/15; 3/15	Magnusson-Kligman same concentration used for both (injection and topical) induction exposures	Inveresk Research International 1985
22.	1-Tetradecene-1,3-sultone	Induction: Challenge: (In acetone)	0.1 50 5	0/15; 0/15	Magnusson-Kligman same concentration used for both (injection and topical) induction exposures	Inveresk Research Internaotinal 1985
23.	1-Tetradecene-1,3-sultone	Induction: Challenge: (In acetone)	0.01 50 5	0/15; 0/15	Magnusson-Kligman same concentration used for both (injection and topical) induction exposures	Inveresk Research International 1985
24.	1-Tetradecene-1,3-sultone	Induction: Challenge: (In acetone)	0.001 50 5	0/15; 0/15	Magnusson-Kligman same concentration used for both (injection and topical) induction exposures	Inveresk Research International 1985
25.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS sample)	Induction: Challenge:	0.01 0.01	1/ 20	Ritz-Buehler	Bay and Danneman 1985b
26.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS sample)	Induction: Challenge:	0.01 0.01	5/20	Ritz-Buehler	Bay and Danneman 1985b
27.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS sample)	Induction: Challenge:	0.01 0.01	5/20	Ritz-Buehler	Bay and Danneman 1985b
28.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS sample)	Induction: Challenge:	0.11 0.01	8/20	Ritz-Buehler	Bay and Danneman 1985b

(Continued on next page)

Table 2. Guinea pig sensitization studies on sultones (Arthur D. Little, Inc. 1993) *(continued)*

No.	Sultone type	Concentration (ppm)		Sensitization rate	Comment/technique	Reference
29.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS sample)	Induction: Challenge:	0.24 0.01	4/20	Ritz-Buehler	Bay and Danneman 1985b
30.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS sample)	Induction: Challenge:	0.09 0.05	3/20	Ritz-Buehler; AOS sample analyzed using HPLC or tandem mass spectrometry	Bay and Danneman 1985b
31.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS sample)	Induction: Challenge:	0.02 0.01	1/20	Ritz-Buehler; AOS sample analyzed using HPLC or tandem mass spectrometry	Bay and Danneman 1985b
32.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS sample)	Induction: Challenge:	0.09 0.01	3/20	Ritz-Buehler	Bay and Danneman 1985b
33.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS containing liquid laundry detergent)	Induction: Challenge:	0.04 0.02	2/20	Ritz-Buehler; ppm calculated	Bay and Danneman 1985b
34.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS containing "consumer product")	Induction: Challenge:	0.21 0.10	8/20	Ritz-Buehler; ppm calculated	Bay and Danneman 1985b
35.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS containing "consumer product")	Induction: Challenge:	0.12 0.05	1/20	Ritz-Buehler; ppm calculated	Bay and Danneman 1985b

36.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS containing "consumer product")	Induction: Challenge:	0.39 0.19	7/20	Ritz-Buehler; ppm calculated	Bay and Danneman 1985b
37.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS containing light duty liquid laundry detergent; bleach added)	Induction: Challenge:	0.1 0.1	1/20	Modified Ritz Buehler; ppm calculated	Bay and Danneman 1985b
38.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS containing light duty liquid laundry detergent; bleach added)	Induction: Challenge:	22.0 6.1	11/20	Modified Ritz Buehler; ppm calculated	Bay and Danneman 1985b
39.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS containing light duty liquid laundry detergent; bleach added)	Induction: Challenge:	122.2 11.0	2/9	Modified Ritz Buehler; ppm calculated	Bay and Danneman 1985b
40.	Combination of unsaturated gamma C_{12}, C_{14}, and C_{16} sultones (in an AOS containing light duty liquid laundry detergent; bleach added)	Induction: Challenge:	122.2 11.0	5/9	Modified Ritz Buehler; ppm calculated. Study repeated; same results	Bay and Danneman 1985b
41.	1-Tetradecene-1,3-sultone	Induction: Challenge: Rechallenge:	10 10 0.1 50	 0/15 0/15 0/15	Buehler	Inveresk Research International 1985

(Continued on next page)

Table 2. Guinea pig sensitization studies on sultones (Arthur D. Little, Inc. 1993) *(continued)*

No.	Sultone type		Concentration (ppm)	Sensitization rate	Comment/technique	Reference
42.	1-Tetradecene-1,3-sultone	Induction:	1		Buehler	Inveresk Research International 1985
		Challenge:	50	0/15		
			1	0/15		
43.	1-Tetradecene-1,3-sultone	Induction:	0.1		Buehler	Inveresk Research International 1985
		Challenge:	50	0/15		
			0.01	0/15		
44.	1-Tetradecene-1,3-sultone	Induction:	0.01		Buehler	Inveresk Research International 1985
		Challenge:	50	0/15		
			5	0/15		
45.	1-Dodecene-1,3-sultone	Induction:	4,000 (0.4%)	10/15	Closed patch	CTFA 1995b
		Challenge:	100 (0.01 %)	5/15		
			10 (0.001%)	2/15		
			1			
46.	1-Dodecene-1,3-sultone	Induction:	18		Injection	CTFA 1995b
		Challenge:	2	17/23		
		Rechallenge:	4	5/5		
			2	6/6		
			1	5/5		
			0.5	5/6		
			0.25	3/5		

unbleached, 10% active C_{14-16} *AOS (2 : 1) and bleached 10% active* C_{14-16} sensitized 5/10 and 6/10 animals, respectively. Sensitization was attributed to incomplete hydrolysis, but follow-up studies ruled out saponification and/or the presence of saturated sultones or residual oil as the causes. Two other bleached C_{14-16} AOS samples were also unexplained sensitizers. One of the two samples sensitized 7/10 guinea pigs in the first trial, but the results could not be duplicated. The seventh sample, C_{14-16} AOS (3 : 2) paste (29.4% active), sensitized 10/19 guinea pigs challenged with a 10% dilution; 5/10 had positive reactions with a 5% challenge. Similar findings were noted with a C_{16-18} (55 : 45) AOS paste (25.7% active) where positive reactions were noted in 2/20, 8/20, and 10/20 animals challenged with 7.5%, 15%, and 20%, respectively. In the ninth sample, repeated topical application of undiluted C_{16-18} sensitized 10/20 guinea pigs challenged with a 20% aqueous solution.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Palmer, Readshaw, and Neuff (1975) tested the teratogenic potential of C_{14-18} AOS using pregnant rats (20/dose), mice (20/dose), and rabbits (13/dose). The strains of animals used were not reported. Mice and rats were treated by gavage on days 6–15 of gestation; rabbits were treated on days 6–18. Doses were 0.2, 2, 300, and 600 mg/kg/day (the sultone content is unknown). No signs of maternal toxicity were observed in any of the treated rats. All rabbits given 600 mg/kg died; one dam of the 300 mg/kg group died. Anorexia, diarrhea, and body weight loss were observed prior to death. Six mice treated with 600 mg/kg died; five dams of this treatment group lost their litters. Six dams of the 300 mg/kg group lost their litters. Both mice and rabbits of the 0.2 and 2.0 mg/kg dose groups had initial reduction in body weight gain. Litter parameters (litter size, embryonic deaths, litter weight, mean pup weight) were unaffected at doses of 0.2 and 2.0 mg/kg in mice and rabbits and in all treated rats. No effects on the litters were noted at doses that were nontoxic or slightly toxic to dams. When total litter loss data were excluded, litter size and embryonic loss values for mice and rabbits of the two highest dose groups were comparable to control values. Pups of rabbits from the 300 mg/kg and pups of mice from the 600 mg/kg treatment group had lower (though not significant) mean body weight. At all doses of AOS, litter and mean pup weights of mice were lower than those of concurrent controls. However, the weights of pups of the treated groups were within the range for historical controls. Fetal abnormalities were noted in mice and rabbits at doses where maternal toxicity was noted. The incidence of minor skeletal anomalies in pups was high in rabbits of the 300 mg/kg group (23% vs. 7% for controls), and the proportion

of pups having an extra rib was significantly larger (87% vs. 59% for controls). There were no pups to examine from the 600 mg/kg group. In mice, cleft palates were observed in four pups of the 600 mg/kg group and in two of the 300 mg/kg group. (There was an exencephalic control pup.) A significantly high incidence of skeletal anomalies (mostly retarded ossification) was seen in pups of the 600 mg/kg group. However, it was stressed that the 1.0% incidence of abnormalities in controls was unusually low.

MUTAGENICITY

The reviews by the Soap and Detergent Association (Arthur D. Little, Inc. 1993) and by Oba and Takei (1992) cite several mutagenicity tests done using bacterial strains. Table 3 summarizes these tests. With one exception, all the tests were negative. In the exception, 283 mg/kg of C_{14-16} AOS (28.4% active) was mutagenic to *Salmonella typhimurium* TA 1530 (a point mutation) when tested in a rat host-mediated assay. (In a host-mediated assay, the animal is injected intraperitoneally with the bacterial strain and then immediately treated with the test substance via an intramuscular injection. After dosing, saline is injected intraperitoneally, and the fluid is withdrawn from the peritoneal cavity of the host. The mutation frequency in the recovered microorganisms is measured by counting viability [Oba and Takei 1992].) However, the Soap and Detergent Association review reported that in vitro assays with up to 1% C_{14-16} AOS were negative for the strain. Further, when the pH of the original test sample was neutralized and readjusted, a negative response was obtained in the host-mediated assay. The original sample was then extracted in ether and the aqueous fraction obtained was retested (210 mg/kg). The number of revertants was reduced from 1202 and >10,000 (two experiments) for the original sample to 477 revertants with the washed sample (Arthur D. Little, Inc. 1993).

CARCINOGENICITY

Hunter and Benson (1976) conducted a 104-week feeding study using CFY rats. The AOS used in the study was a mixture of alkenyl sulfonate and hydroxyalkane sulfonate present in a 60.4 : 39.6% ratio. The mixture was administered at dietary concentrations of 1000, 2500, and 5000 ppm to groups of 50 male and 50 female rats. No significant treatment-related differences were observed in the overall incidence of neoplasms, whether malignant or benign, between treated and control groups.

Table 3. Bacterial mutagenicity testing

AOS concentration (max.)	Assay (if indicated)	Strain tested	Result	Reference
In vitro				
10,000 ppm	Reversion Plate	*Salmonella typhimurium* TA 1535, 1536, 1537, 1538 *Escherichia coli* B/r WP try and try her	Negative (strains 1536 and 1538 had smaller colony size than His + strains but were *not* revertants)	Oba and Takei 1992
100 μg/plate	Ames	*S. typhimurium* TA 98, 100, 1535, 1537, 1538	Negative	Oba and Takei 1992
100 μg		*S. typhimurium* TA 98, 100	Negative	Oba and Takei 1992
2 mg/plate		*S. typhimurium* TA 1535, 1536, 1537, 1538 (7 preparations)		Arthur D. Little, Inc. 1993
		S. typhimurium TA 1535 (4 AOS compounds tested)	Negative	
In vivo				
283 mg/kg AOS C_{14-16} (28.4% active)	Host-mediated (rat)	*S. typhimurium* TA 1530, 1534	(+) in TA1530 (see text) (−) in TA 1534	Arthur D. Little, Inc. 1993
i.m. 0.1 ml/1% solution	Host-mediated (mouse)	*S. typhimurium* TA 1535	Negative	Oba and Takei 1992

Sultones have been proposed as potential carcinogens in laboratory animals (Slaga et al. 1973).

A skin painting study involving Swiss Webster mice was used to test AOS and C_{16} 1,4-sultone. Treatment groups (40/sex/group) were as follows: (1) 20% AOS (based on C_{14-18} α-olefin); (2) 25% AOS (from supplier used in Group 1); (3) 20% AOS (based on C_{14-16} α-olefin from another supplier); (4) 25% AOS (from supplier used in Group 3); (5) 6.7% C_{16} 1,4-sultone in acetone; (6) 8.3% C_{16} 1,4-sultone in acetone; (7) untreated control (shaved only); (8) water control; and (9) Acetone control. The test substance (0.02 ml) was applied to the interscapular region, three times a week for 92 weeks. Mean survival rate per group was 30%. Necropsy was performed. No toxic or carcinogenic effects of the two AOS products and sultone were observed in the skin painting study (Oba and Takei 1992).

A feeding study was also conducted using 11 groups of 40 male and 40 female MRC rats (Wistar derived). Treatment groups were as follows: (1) untreated control; (2) 1.0% AOS (based on C_{14-18} α-olefin); (3) 0.75% AOS (from supplier used in Group 2); (4) 0.5% AOS (from supplier used in Group 2); (5) 1.0% AOS (based on C_{14-16} from another supplier); (6) 0.75% AOS (from supplier used in Group 5); (7) 0.5% AOS (from supplier used in Group 5); (8) 0.33% C_{16} 1,4-sultone; (9) 0.25% C_{16} 1,4-sultone; (10) 0.16% C_{16} 1,4-sultone; and (11) extra control. The experiment was terminated when a mean survival point of 50% was reached. No toxic or carcinogenic effects related to treatment with AOS or sultone were observed (Oba and Takei 1992).

In a 92-week dermal exposure study, groups of Swiss Webster mice (40/sex) were treated three times a week with 0.02 ml of one of the following six treatments: (1) 20% C_{14-18} AOS; (2) 25% C_{14-18} AOS; (3) 20% C_{14-16} AOS; (4) 25% C_{14-16} AOS; (5) 6.7% C_{16} 1,4-sultone; and (6) 8.3% C_{16} 1,4-sultone. No significant toxicity or lesions attributable to AOS treatment were noted (Arthur D. Little, Inc. 1993).

In a 2-year dermal exposure study, groups of Long-Evans rats (50/sex/group) were treated with the following: (1) deionized water (vehicle control); (2) hydrolyzed, composite sample of C_{14-16} AOS and C_{16-18} AOS (30.0% active); (3) partially hydrolyzed sample of AOS, (same as Group 2 but containing residual level of sultone); and (4) commercial C_{14-16} AOS (38.9% active). The test substance was applied twice weekly to the clipped dorsal surface as a 10% active (v/v) aqueous solution at a dose of 1 ml/kg. Mean body weights, feed consumption, hematology, urinalysis, mortality, and gross lesions were comparable for all groups. Group 2 males had a slightly lower mean kidney weight and a significantly lower mean kidney to body weight ratio as compared to controls. The tests were negative for a carcinogenic effect attributable to the percutaneous application of the AOS test materials (Bio/Dynamics Inc. 1979).

Another study (Oba and Takei 1992) noted occasional dermatitis in Swiss-Webster mice (21 animals/group) treated for 2 years with twice-weekly applications of 5% aqueous solutions of either: (1) C_{15-18} AOS (90% active); (2) hexadecane 1,4-sultone; or (3) sultone concentrate (64% active) extracted from the sulfonation process of an α-olefin.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Magnusson and Gilje (1973) reported an outbreak of sensitization to a dishwashing detergent in Norway in the late 1960s. It was later established that ~ 22 ppm of unsaturated sultones was in the finished product (Connor et al. 1975). In a review of these findings, it was noted that the actual use exposure (allowing for a 500-fold dilution) was 0.044 ppm unsaturated sultones.

Bay and Danneman (1985a) reported that in a sensitization test, sodium C_{14-16} AOS paste and an AOS-containing dishwashing detergent did not induce sensitization in >900 panelists. AOS was tested at a maximum concentration of 0.06% with up to 0.002 ppm unsaturated sultones as an impurity. Although no induction of sensitization was observed, one case of pre-existing sensitization was detected. This individual reacted to a detergent containing ~0.002 ppm unsaturated sultones under patch and was positive to an AOS paste on rechallenge. The results from this individual helped to established an elicitation threshold for unsaturated sultones of 0.002 ppm under patch test conditions (Bay and Danneman 1985b).

Bay and Danneman (1985a, b) also reported that in diagnostic patch tests conducted using 542 panelists who had previous exposure to AOS-containing products, 15 had positive responses to 1.3 ppm unsaturated sultones in 0.046% sodium lauryl sulfate. None of the 15 patch-positive panelists reported any clinically significant skin problems following use of AOS (sultone)-containing products. Nonetheless, the results of the study suggested the possibility of pre-existing subclinical sensitization to unsaturated sultones, potentially attributable to consumer products containing low concentrations (<0.01–4.8 ppm).

In a separate product use test, sensitization to unsaturated sultones was induced and elicited in 2 of 264 subjects with no prior AOS exposure, after using an AOS-containing dishwashing detergent. Both developed hand dermatitis after use of the product; none of the 248 control subjects using a non-AOS detergent had hand dermatitis. The undiluted AOS detergent contained 0.5–1 ppm unsaturated sultones with in-use exposure at concentrations ~500-fold lower (Bay and Danneman 1985a, b).

In one unpublished study cited in the review by the Soap and Detergent Association (Arthur D. Little, Inc. 1993), 1 and 2% concentrations of AOS were nonirritating after 24-hour patch testing. In another study, 1 and 5% AOS were mild irritants, with reactions ranging from erythema to fissure formation accompanied by scaling. A 10-day occlusive patch test with 0.8% active AOS resulted in increasing irritation as the study continued.

In immersion studies, concentrations of 0.3% AOS caused negligible irritation following 30 1-minute immersions done in the course of 1 hour, and a 0.04% effective concentration of AOS (in a detergent formulation) was classified as a mild irritant after three 15-minute immersions done for up to 15 days. Half of the panelists were able to complete 12 immersions before reaching the predetermined irritation level (a score of "2") (Arthur D. Little, Inc. 1993).

Ter Haar (1983) reported no contact sensitization when 88 men were treated with an 8% aqueous AOS solution (occlusive patch applied three times a week for a total of 10 induction applications) and then challenged 2 weeks later with 4% AOS. (The challenge dose was reduced because of severe irritation.) Ter Haar (1983) also reported that sensitization occurred in 8 of 195 panelists treated three times a week for three weeks with 1% AOS (containing 28 ppm 1,3-sultones) and then challenged after a 1-week nontreatment period. Five of these eight reactors were also challenged with AOS containing 1 ppm of 1,3-sultone; 3/5 had positive reactions.

SUMMARY

Sodium AOS are a mixture of sodium alkene sulfonates and sodium hydroxyalkane sulfonates. Care should be taken in their manufacture to avoid producing alkene sultones and chlorosultones, some of which are potent sensitizers.

AOS are approved for use as indirect food additives. They function as surfactant–cleansing agents in cosmetic formulations. As of January 1996, there were 93 reported uses of sodium C_{14-16} olefin sulfonates.

AOS are rapidly absorbed, metabolized, and excreted (primarily in the urine) following oral or intravenous exposure. Dermal absorption was increased when AOS was applied to damaged skin.

Acute oral LD_{50} values for AOS range from 1300–2400 mg/kg in rats and 2500–4300 mg/kg in mice. No treatment related changes were noted in rats following a single 1-hour inhalation exposure to either an AOS flake (90% active) or a 17% AOS formulation, or after repeated exposure to 0.9 or 10% C_{14-16} AOS.

In a 7-day oral study in rats, the "no effect" dose was between 0.625 and 1.25%. One 91-day study noted hematologic changes in rats which

received up to 500 mg/kg of either C_{14-16} AOS or C_{16-18} AOS (both 34% active). In another 90-day oral study, a slight increase in the liver to total body weight ratio was found in animals of the highest dose group, 1000 mg/kg/day, but no changes in hematologic parameters were found at any dose. Concentrations of ≥10% AOS are moderately to severely irritating to rabbit eyes. In one study, mild irritation occurred after exposure to 5% C_{14-19} AOS.

Dermal irritation studies have recorded mild to moderate skin irritation in guinea pigs and rabbits after repeated exposure to ≥2% AOS of varying carbon lengths. Nine of 64 AOS samples produced sensitization in guinea pigs; in some, but not all cases, sensitization was attributed to the presence of unsaturated and chloro-1,3-sultones.

In teratogenicity studies, no signs of maternal toxicity or reproductive effects were found in pregnant rats treated with up to 600 mg/kg of C_{14-18} AOS on days 6–15 of gestation. Maternal toxicity and litter loss were observed in some mice and rabbits given 300 and 600 mg/kg; litter parameters were unaffected in mice and rabbits given 0.2 and 2.0 mg/kg. Fetal abnormalities were observed at treatment doses producing maternal toxicity.

With one exception, all mutagenicity assays conducted on AOS were negative. In the exception, 283 mg/kg of C_{14-16} AOS was mutagenic in a host-mediated assay conducted using rats; however, when the sample was neutralized or extracted in ether, the mutagenic capacity was diminished. Various oral and dermal carcinogenicity studies were negative.

Various clinical studies found irritation to AOS and sensitization to very low levels of sultones.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel was satisfied with results of toxicity, mutagencity, carcinogenicity, and reproductive/developmental studies cited in this report. The focus of the Panel's safety assessment of sodium AOS concerned the sensitizing potential of sultone impurities as indicated by guinea pig studies in Table 2.

Delta sultones (1,4-sultones) either in pure unsubstituted form (studies 1–3 in Table 2) or as a chlorosultone (Study 11 in Table 2) did not induce sensitization in Magnusson-Kligman maximization assays. Further, it is believed that AOS preparations contain 1,4-sultones at sufficiently low concentrations (<34 ppm) such that sensitization is not of concern.

Studies indicated that gamma sultones (1,3-sultones) were potent sensitizers at very small concentrations, though there was marked difference in the sensitization potential of the various gamma sultone types: unsubstituted alkane, chloro, and unsaturated (alkene).

With regard to unsubstituted alkane gamma sultones, studies employing either the Magnusson-Kligman (Study 8 in Table 2) or an injection technique (Study 10 in Table 2) indicated that a 2% induction concentration can induce sensitization. As no data were received regarding sensitization potential at lower induction concentrations, and a re-challenge concentration of 100 ppm elicited a response in virtually all animals tested (Study 8 in Table 2), the Panel elected to impose a significant safety factor and limit unsubstituted alkane gamma sultone concentrations to $\leq$10 ppm.

Gamma chlorosultones tested under either the Magnusson-Kligman (Study 12 in Table 2) or an injection technique (Study 13 in Table 2) indicated that 20 ppm was a sensitizer. No data were available on the sensitizing potential of gamma chlorosultones at induction concentrations less than 20 ppm. It was noted that Study 14 (in Table 2) which employed a closed-patch technique demonstrated a low response to challenge concentrations of 1.2 ppm following induction with 4,000 ppm. In view of these findings, the Expert Panel imposed a safety factor and limited gamma chlorosultone concentrations to $\leq$1 ppm.

With regard to unsaturated gamma sultones, it was noted that clinical safety data demonstrated induction/elicitation thresholds as low as 0.001–0.002 ppm (calculated but not measured) under certain conditions (Bay and Danneman 1985b). However, the Panel acknowledged that there has been only one clinically relevant sultone sensitization incident reported in the literature, despite broad use of AOS in the marketplace. In determining levels of safety for unsaturated gamma sultones, the CIR Expert Panel relied on Studies 17–24 (in Table 2) by Inveresk Research International (1985), which used the Magnusson-Kligman technique and demonstrated a dose-dependent response. In Studies 22 and 23 (in Table 2) no sensitization was produced by an induction concentration of 0.01 ppm. Sensitization was noted at 1 ppm, which was the next induction concentration tested (Study 21 in Table 2). Although additional studies using the Buehler technique demonstrated nonsensitization at higher induction concentrations (Studies 41–43 in Table 2), the Panel elected to use studies which employed the Magnusson-Kligman technique. In light of the sensitizing capacity of unsaturated gamma sultone at such small levels, the Panel was of the opinion that the stringent conditions of the Magnusson-Kligman technique (which combines injection and topical induction exposures) allowed for a more reliable measure of safety. Based on these data, the Expert Panel limited unsaturated gamma sultone concentrations to $\leq$0.1 ppm.

With the above limitations to guide manufacturers, the ability of certain gamma sultones to sensitize at very low concentrations remains. Thus, the Panel alerted producers of sodium α-olefin sulfonates to the possibility that testing in biological systems could be done in order

to make certain that commercially supplied preparations are not sensitizing.

The Panel acknowledged that because these ingredients are detergents, they would most likely be used in rinse-off products. Sodium AOS were considered to be safe for use in rinse-off products (provided gamma sultone impurities are limited to the above concentrations).

The Panel imposed a concentration limit of 2% in leave-on products, based on animal dermal irritation studies (provided gamma sultone impurities are limited to the above concentrations). A concentration of 2% aqueous C_{16-18} AOS produced nil-to-slight irritation in guinea pigs after nine dermal applications.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes Sodium α-Olefin Sulfonates (of chain lengths C_{12-14}, C_{14-16}, C_{14-18}, and C_{16-18}) to be safe as used in rinse-off products and safe up to 2% in leave-on products. The concentration of the gamma sultone impurity of any formulation (leave- on or rinse-off) is limited to unsubstituted alkane sultones $\leq$10 ppm; chlorosultones $\leq$1 ppm; and unsaturated sultones $\leq$0.1 ppm.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

TO: Lillian Gill, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 3, 2013

SUBJECT: Concentration of Use by FDA Product Category: Sodium Olefin Sulfonates

Concentration of Use by FDA Product Category

Sodium C12-14 Olefin Sulfonate
Sodium C14-16 Olefin Sulfonate
Sodium C14-18 Olefin Sulfonate
Sodium C16-18 Olefin Sulfonate

Ingredient	FDA Code†	Product Category	Maximum Concentration of Use
C12-14 Olefin Sulfonate	05F	Shampoos (noncoloring)	0.28%
C12-14 Olefin Sulfonate	06B	Hair tints	0.37%
C12-14 Olefin Sulfonate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	5%
C14-16 Olefin Sulfonate	02A	Bath oils, tablets and salts	2.5%
C14-16 Olefin Sulfonate	02B	Bubble baths	6.4-10%
C14-16 Olefin Sulfonate	02D	Other bath preparations	2-7.2%
C14-16 Olefin Sulfonate	05F	Shampoos (noncoloring)	0.8-19%
C14-16 Olefin Sulfonate	06A	Hair dyes and colors (all types requiring caution statement and patch test)	4.5%
C14-16 Olefin Sulfonate	07I	Other makeup preparations	1.2%
C14-16 Olefin Sulfonate	10A	Bath soaps and detergents	0.12-10%
C14-16 Olefin Sulfonate	10E	Other personal cleanliness products	3.9-13.2%
C14-16 Olefin Sulfonate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	4-13.3%
C14-16 Olefin Sulfonate	12C	Face and neck products not spray	13.2%
C14-16 Olefin Sulfonate	13A	Suntan products not spray	1.2%
C14-18 Olefin Sulfonate	05F	Shampoos (noncoloring)	16%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.
†Product category codes used by FDA

Information collected in 2013
Table prepared: September 3, 2013