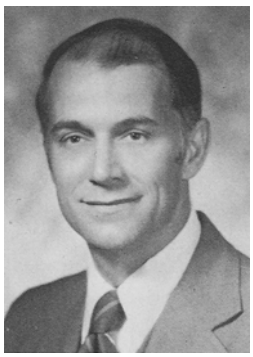
Technical News Feature

Safety of Alpha Olefin Sulfonates[1]



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Alpha olefin sulfonates (AOS) belong to the anionic surfactant class. They are efficient, readily biodegradable cleaning agents. This paper reviews the safety aspects of AOS, including acute toxicity, teratogenicity, animal sensitization, human sensitization, chronic toxicity and lifetime studies – cancer bioassay.

Acute Toxicity

Oral toxicity. Four groups of ten male rats were fasted overnight. Rats in each group were intubated with 36.9% C_{14-16} AOS (pH 7-8) from Ethyl Corporation. Animals were observed for 14 days after intubation, necropsied, and examined for gross pathological abnormalities. Six samples were tested, and all doses were expressed in terms of active ingredient, AOS. The data (Table I) show that AOS has a very low oral toxicity in rats, ca. 4,000 mg/kg.

Dermal toxicity. The dermal study used groups of four rabbits, two of which were first abraded. Various doses of the above AOS solution were injected under plastic sleeves wrapped around their clipped trunks. The material was allowed to remain in contact with the skin for 24 hr. All animals were observed for 14 days and examined for gross pathological abnormalities. The dermal toxicity of AOS was greater than 6,000 mg/kg (Table I).

Eye and skin irritation. Dermal and eye irritation tests were conducted on groups of six rabbits according to the method of Draize et al. (1). These studies also are summarized in Table I. The data show that concentrated AOS is a severe eye irritant, but not a skin irritant. Instillation of this material in the eyes of rabbits produces corneal, iris and conjunctival involvement. Although high scores are still present at 72 hr, the response is reversible.

While concentrated solutions of AOS are irritating, AOS concentrations near use levels are not eye irritants. Iimori et al. (2,3) report that 1% AOS solutions are not irritating to the eyes of the rabbits.

Teratology

Palmer et al. (4) studied the potential of AOS for teratogenic and embryotoxic effects in rats, mice and rabbits. Dosages of 0.2, 2, 300 and 600 mg/kg were used to evaluate effects. It was apparent that 600 mg/kg was an excessive dose and 300 to a lesser extent in mice and rabbits. They observed maternal toxicity and significant litter loss. Rats showed no effect at the highest dosage tested, 600 mg/kg. At levels not toxic to the mother, there was no evidence of an embryo toxic or teratogenic effect.

Animal Sensitization

Until late 1973, there was considerable controversy over whether AOS could sensitize guinea pigs and if so, why. At that time it was discovered that the sensitizing impurity 1,3-sultone, could on occasion be present in AOS when proper manufacturing practices were not followed.

Hypochlorite bleaching of AOS must be carried out at high pH to avoid the formation of hypochlorous acid. This

TABLE I

Acute Toxicity of AOS

Sample	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)	Eye	Irritation Skin (Draize score)
A	4,200 ± 290	6,300 ± 1,340	Severe	Negligible (.00)
B	4,000 ± 510	>16,000	Severe	Negligible (.00)
C	4,500 ± 400	10,000 ± 1,780	Severe	Negligible (.00)
D	4,500 ± 70	8,000 ± 2,900	Severe	Negligible (.00)
E	3,800 ± 240	13,500 ± 1,420	Severe	Negligible (.49)
F	4,200 ± 140	9,500 ± 1,600	Severe	Negligible (.04)

[1]Presented at the 56th Annual Meeting of The Soap and Detergent Association, Jan. 27-30, 1983, Boca Raton, Florida.

is necessary as hypochlorous acid will react with alkene sulfonates to form chloro-gamma and delta sultones. Since 1973, all production of AOS has been carried out with the bleaching step at a high pH.

Based on this knowledge, progress was made beginning late in 1973 in understanding the sensitization potential of AOS. Ethyl conducted guinea pig sensitization tests on commercial grade AOS late in 1973 and early 1974. Guinea pigs were tested according to the method of Magnusson and Klingman (5). Animals were induced by giving three single 0.1 mL intradermal injections of Freund's Complete Adjuvant (FCA) (Difco Laboratories, Detroit, Michigan), the test substance in a vehicle and the test substance emulsified in the adjuvant in a row along the left anterior nuchal region which was shaved. One week later, these animals were induced again by topical application of the test agent in the test vehicle which was spread over a 2 x 4 cm patch of Whatman No. 3MM filter paper. The patch was then covered by overlapping impermeable, plastic adhesive tape and secured firmly by an elastic adhesive bandage which was wound around the torso of the animal.

Two weeks after the topical application, the animals were challenged with the highest nonirritating concentration. After clipping the animals' flanks, the test agent was applied on a 2 x 2 cm piece of filter paper which was sealed to the flank for 24 hr and then removed.

Twenty-four hours after removal of the patch, the challenge site was evaluated and scored as follows: 0, no reaction; 1, scattered mild redness; 2, moderate and diffuse redness; and 3, intense redness and swelling. A score of one or more was considered to indicate sensitization.

Both positive and negative controls were used with each test. Sodium lauryl sulfate was used as the negative control and formalin was used as the positive control. The results (Table II) showed that commercial AOS is not a sensitizing agent. The investigators, on occasion, read one animal as responding. However, as is pointed out in the book, *Animal Models in Toxicology*, when less than 8% of the animals are interpreted as having shown a reaction, the authors conclude the following: "This indicates that the probability of sensitization at human exposures is very low."

We also have conducted some experiments using experimental samples. Although 1,3-sultones are not present in commercial AOS, there are small amounts of the slower hydrolyzing 1,4-sultones in the final commercial product. To establish the effect on this species, we tested the sensitization potential of pure 1,4-sultone.

When guinea pigs were administered pure C_{14} or C_{16} 1,4-sultone, no sensitization was observed. On the other hand, exposure to C_{14} 1,4-sultone containing 2% C_{14} 1,3-sultone produced sensitization in 50-60% of animals tested. Upon removal of the C_{14} 1,3-sultone impurity, no sensitization occurred.

Similar results occurred with the chloroalkane sultones. The pure 3-chlorotetradecane 1,4-sultone did not cause any reaction while the 2-chlorotetradecane 1,3-sultone was a sensitizer (Table III).

TABLE II

Sensitization Potential of Commercial AOS

Sample	Date	Responding animals/ total animals
9167	12-1-73	0/15
9443	12-1-73	1/15
9519	12-1-73	0/12
9625	1-14-74	1/13
9721	1-14-74	0/13
9816	1-14-74	0/14
9666	1-14-74	0/14
9820	1-14-74	0/15
0186	3-19-79	0/14

Human Sensitization

Given the severe nature of the guinea pig maximization test method which bypasses the potentially protective barriers of the skin, these animal results are contraindicative of any effect. On this basis, it was both reasonable and advisable to consider human sensitization studies as the next step in safety evaluation.

Dr. Howard Maibach in 1974 conducted, for Colgate, a standard Draize test on 111 male volunteers. For reasons unrelated to the experiment, 23 people were dropped from the study. There were ten applications to the same site at the rate of three times weekly (48 hours during the week and 72 hours on the weekend). The patch was an occlusive Johnson and Johnson square Band Aid. There then followed a rest (incubation) period followed by a 72-hr final elicitation at a fresh site.

The eight commercial samples of the same materials used for the guinea pig studies (Table II) were tested on each person. The sensitization series was carried out at 8% in water. Because of considerable irritation, the final challenge was made at 4%. Dr. Maibach stated, "There was no evidence of contact sensitization in this group of subjects" (personal communication).

The guinea pig studies indicated that it is possible to sensitize with 1,3-sultones. We studied this in 1978. We prepared a formulated detergent which was then bleached at a low pH. This procedure was known to produce 1,3-sultones. This formulated material was diluted in water to 1% AOS and contained 28 ppm 1,3-sultones. This is about the maximum level that could be expected if AOS were present in a home detergent and used with bleach under conditions to maximize sultone formation. Dr. Maibach conducted this study. A total of 195 subjects received ca. 0.2 mL of a 1% AOS solution under an occlusive patch on the skin. During the first three weeks, patches were applied three times a week. After a week of rest, a challenge application was applied. Eight out of 195 subjects were judged contact sensitized to this concentration of sultone in this detergent.

In a second test, Dr. Maibach challenged five of the sensitized subjects with AOS containing one ppm 1-3 sultone. Three out of five responded positively. These tests undoubtedly exaggerate the effect of the sultones.

Chronic Toxocity

Hunter and Benson (6) have published the results of a two-year feeding study of C_{14-16} AOS in rats. The 50 males and females in each group were fed 1,000, 2,500 and 5,000

TABLE III

Sensitization Potential of 1,3 and 1,4-Sultones

Sample	Test vehicle	Test concentration (%)	Sensitization rate (%)
Unsubstituted alkane, 1,4-sultones		I-T-C[c]	
1. C_{16} 1,4-sultone	Peanut oil	1-5-0.5	0
2. C_{16} 1,4-sultone	Peanut oil	2-10-1	0
3. C_{14} 1,4-sultone	DMF	2-10-1	0
4. C_{14} 1,4-sultone (2% 1,3-sultone)	Peanut oil	2-10-1	48[a]
5. C_{14} 1,4-sultone (2% 1,3-sultone)	DMF	2-10-1	60
6. C_{14} 1,4-sultone[b]	Peanut oil	2-10-1	0
Unsubstituted alkane, 1,3-sultones			
7. C_{14} 1,3-sultone	Peanut oil	2-10-0.5	24[a]
8. C_{14} 1,3-sultone	Peanut oil	2-10-1	0
Unsubstituted alkene, 1,3-sultones			
9. 1-Dodecene-1,3-sultone	T-80 Alcohol/20 H_2O C-Acetone	0.002-0.01	29[a]
10. 1-Tetradecene-1,3-sultone	T-80 Alcohol/20 H_2O C-Acetone	0.002-0.01-0.001	42[a]
Chloroalkane 1,3 and 1,4-sultones			
11. 3-Chlorotetra-decane-1,4-sultone	T-80 Alcohol/20 H_2O C-Acetone	0.002-0.01-0.001	0[a]
12. 2-Chlorotetra-decane-1,3-sultone	T-80 Alcohol/20 H_2O C-Acetone	0.002-0.01-0.001	50[a]

[a]Average of 2 tests on the same sample.
[b]Sample 4 processed to remove the 1,3-sultones (limit detectability 0.6%).
[c]Induction – Topical – Challenge.

ppm in the diet. The only adverse effects recorded were a significant reduction in body weight gain between weeks 14 and 26 of the study for both males and females receiving 5,000 ppm AOS and a marginally lower food intake during the first year in females receiving the 5,000 ppm diet. Blood chemistries, urinalyses, and histopathological findings were all comparable to control values. The authors calculated that the highest level of AOS in the two-year feeding study (representing about 0.5% of the diet) was at least 1,000 times the estimated maximum daily exposure to humans using AOS-containing products and therefore, AOS would not appear to represent a hazard to human health.

Lifetime Studies – Cancer Bioassay

Dermal application to rats and mice of AOS by both a "U.S." and "European" study has shown no carcinogenic activity. The study in the United States was conducted at Bio-Dynamics. The study was divided into two parts, both done under the technical direction of a SDA committee. The first part or SDA study used AOS supplied from several commercial and pilot plants. The second part, or Ethyl/Colgate study, used Ethyl olefin sulfonated in Colgate's commercial plant.

The SDA study involved a total of 300 Long-Evans rats divided into three groups of 50 animals/sex/group. Treatments were twice weekly for 105 weeks with a volume of 1.0 mL/kg applied to a shaved area of ca. 10% of the total body surface. Final necropsy was at 24 months.

Group I served as vehicle (deionized water) control; Groups II and III were tested with 30.0% and 30.9% active AOS dissolved in deionized water to yield a 10% v/v solution of active AOS.

The AOS samples tested by Bio-Dynamics in the SDA study were prepared from various C_{14} to C_{18} carbon number olefins produced by Ethyl, Gulf, Shell and Chevron and sulfonated by Witco, Colgate, Stepan and Lakeway. Stepan Chemical prepared and packaged the final composites. Sample analyses were conducted by Colgate and Ethyl for AOS, sultone levels, and other parameters.

Results from gross and histopathology examinations revealed no carcinogenic effects which could be attributed to the administration of AOS (7).

The second segment, or Ethyl/Colgate study, tested AOS samples produced solely by Ethyl and Colgate-Palmolive, based on C_{14}-C_{16} α-olefin from Ethyl sulfonated by Colgate.

A total of 200 Long-Evans rats were divided into two groups of 50 animals/sex/group. Treatments were also twice weekly for 105 weeks with a volume of 1.0 mL/kg applied to a shaved area of ca. 10% of the total body surface. Final necropsy was carried out at 24 months.

Group I served as vehicle (deionized water) control; Group II was tested with 38.9% active AOS dissolved in deionized water to yield a 10% v/v solution of active AOS. As with the SDA study, histopathology observations did not show any carcinogenic activity for AOS (8).

A study supported by a European group also has been completed. This European study conducted at Eppley Institute for Research in Cancer, consisted of dermal application to mice and oral feeding to rats. The study was coordinated by Unilever, Colgate-Palmolive, Ethyl, Farbwerke Hoechst, Henkel and Cie, ICI, Lion Corporation, Shell,

Witco, Gulf and Procter and Gamble. Applications were according to the following groupings.

Group I, 20% AOS (red label), (based on C_{14-18} α-olefin from Mitsubishi, sulfonated and hydrolyzed by Lion Corporation); Group II, 25% AOS (same as group I); Group III, 20% AOS (black label), (based on C_{14-16} α-olefin from Ethyl, sulfonated and hydrolyzed by Colgate-Palmolive); Group IV, 25% AOS (same as Group III); Group V, 6.7% C_{16} 1,4-sultone (Gulf/Henkel); Group VI, 8.3% C_{16} 1,4-sultone (Gulf/Henkel); Group VII, untreated control; Group VIII, water control; and Group IX, acetone control.

Treatments were carried out three times weekly for 92 weeks with a volume of 0.02 mL of test material applied to approximately 1 sq cm of exposed skin. Final necropsies were conducted at a mean survival of 30% per group (~19 mos). Again, histopathology failed to demonstrate carcinogenicity for either sample of AOS or for the 1,4-sultones (9).

Eppley Institute also carried out a rat feeding study. Five hundred male and 500 female Wistar rats were divided into eleven groups. There were 100 control males and females and 40 males and females in each treatment group and the extra control group. The rats were fed the materials in the diet as shown:

Group I, control; Group II, 1% red label; Group III, 0.75% red label; Group IV, 0.17% black label; Group V, 0.75% black label; Group VI, 0.33% C_{16} 1,4-sultone; Group VII, 0.25% C_{16} 1,4-sultone; Group VIII, 0.5% red label; Group IX, 0.5% black label; Group X, 0.16% C_{16} 1,4-sultone; and Group XI, extra control.

There was no evidence at any treatment level that AOS caused excess tumors compared to controls (9).

AOS has had limited use in the United States and Europe and extensive use in Japan in household detergents without any reports of problems. The data indicate that AOS can be safely used as a surfactant in personal care and household products.

Summary

Studies show AOS to have a very low acute oral and dermal toxicity. A lifetime study feeding AOS to rats at levels in the diet up to 5,000 ppm showed little effect. This study indicates repeated exposure of AOS to humans would create no hazard. Four separate studies, carried out for the lifetime of rats and mice to evaluate the potential of AOS to cause tumors were completed without effect. Rats, mice and rabbits have been dosed with AOS to study teratogenic effects. At levels not toxic to the mother, there was no evidence of an embryo toxic or teratogenic effect. Guinea pig skin sensitization tests show commercial AOS to be without sensitization potential. It is possible through improper hypochlorite bleaching techniques to produce 1,3-sultones that can cause sensitization. Human patch tests have shown that commercially prepared AOS does not cause sensitization. AOS detergents improperly used with hypochlorite bleach have the potential to produce 1,3-sultones which could cause human sensitization. AOS has been used safely for many years in Japan and to a lesser extent in the U.S.A. and Europe. There have been no reports of adverse health effects during this time.

REFERENCES

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4. Palmer, A.K., M.A. Readshaw and A.M. Neuff, Toxicology 3: 107 (1975).
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6. Hunter, B., and H.G. Benson, Toxicology 5:359 (1976).
7. A Twenty-Four Month Dermal Carcinogenicity Study of Experimental Sulfonated Compounds in Rats. Project 74-1094, Biodynamics, Inc., East Millstone, NJ, 1979. Submitted to The Soap and Detergent Association, New York.
8. Ibid. Project 74-1172, Bio-dynamics, Inc., East Millstone, N.J., 1979. Submitted to Colgate Palmolive Company, Piscataway, NJ.
9. Evaluation of the Carcinogenicity of Two Alpha Olefin Sulphonates and One Sultone. Epply Institute for Research in Cancer, University of Nebraska Medical Center, 1980.

Calendar

AOCS NATIONAL MEETINGS

May

Annual Meeting, 1983: May 8-12, Chicago Marriott, Chicago, IL.

Social Night, Midwest Chapter, Society of Cosmetic Chemists, week of May 23, 1983, to be announced. Contact: Kathleen A. Kochevar, Midwest Chapter, SCC, Jerome Laboratories Inc., 95 E. Bradrock Dr., Des Plaines, IL 60018.

October

Midwest Chapter meeting, Society of Cosmetic Chemists, Oct. 11, 1983, Museum of Science & Industry, Chicago, IL. Program speaker Dr. Derek R. Highley, Mary Kay Cosmetics. Contact: Kathleen A. Kochevar, Midwest Chapter, SCC, Jerome Laboratories Inc., 95 E. Bradrock Dr., Des Plaines, IL 60018.

1984

"Surfactants in Our World—Today and Tomorrow," CESIO Surfactant World Conference, May 6-10, 1984, Munich, Germany. Contact: CESIO, Avenue Louise 250, Boite 102, 1050 Brussels, Belgium.