AMENDED FINAL REPORT ON THE SAFETY ASSESSMENT OF DIOCTYL SODIUM SULFOSUCCINATE[1]

Dioctyl Sodium Sulfosuccinate is an anionic surfactant used in a wide variety of cosmetic formulations. In September 1994, the Cosmetic Ingredient Review (CIR) Expert Panel evaluated the ingredient to be safe up to 0.42% in cosmetic formulations. Since that time, CIR received a petition to re-open the safety assessment based on new clinical data. This amendment is a compilation of data contained in the original plus the data received in the petition; the latter appear at the end of this document. Studies conducted in the 1940's indicate that the oral LD_{50} in rats can be as low as 1.9 g/kg. Short-term subchronic and chronic animal studies of the same vintage found little toxicity at levels around 1% of the LD_{50} level. Inhalation studies likewise had few findings. Dioctyl Sodium Sulfosuccinate was minimally irritating to intact animal skin, but moderate to severely irritating to abraded skin. A concentration of 25% was a severe ocular irritant, but 10% produced little or no irritation. Mutagenesis tests were negative. A repeated insult patch test (RIPT) in 110 individuals produced no sensitization at a concentration of 5%. Erythema was noted during induction in a number of subjects at concentrations $\leq$5%. The CIR Expert Panel recognized that surfactants such as Dioctyl Sodium Sulfosuccinate would likely produce irritation under the conditions of a RIPT. The Panel cautioned that as the ingredient is a cumulative irritant, care should be taken to avoid irritancy in formulations intended for prolonged contact with the skin. The Panel concluded that Dioctyl Sodium Sulfosuccinate is safe for use in cosmetics.

Dioctyl Sodium Sulfosuccinate is an anionic surfactant used in cosmetics, in over-the-counter (OTC) and prescription drugs, as a food additive, and in a wide variety of other applications. The following report reviews the data available on Dioctyl Sodium Sulfosuccinate applicable to its cosmetic use.

In September 1994, the CIR Expert Panel evaluated the surfactant Dioctyl Sodium Sulfosuccinate (CAS No. 577-11-7) to be safe up to 0.42% in cosmetic formulations. Since that time CIR received a petition to re-open the safety assessment based on new clinical data. The following

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. The original scientific literature review was prepared by Lynn Willis, former Scientific Analyst and Writer. Additional information contained in this amendment was prepared by Bindu Nair, Scientific Analyst and Writer.

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is the original report plus the new clinical data received. The discussion section from the original report has been retained and expanded to include consideration of the new data.

CHEMICAL AND PHYSICAL PROPERTIES

Definition and Structure

Dioctyl Sodium Sulfosuccinate, CAS No. 577-11-7, is the sodium salt of the diester of a 2-ethylhexyl alcohol and sulfosuccinic acid that conforms to the formula (Wenninger and McEwen 1997) shown in Figure 1.

Other names for this compound include: 1,4-Bis(2-Ethylhexyl)Sulfobutanedioate, Sodium Salt; Butanedioic Acid, Sulfo-1,4-Bis(2-Ethylhexyl) Ester, Sodium Salt; Di-(2-Ethylhexyl)Sodium Sulfosuccinate; Docusate Sodium; Sodium Di-(2-Ethylhexyl)Sulfosuccinate; Sulfosuccinic Acid, Di-(2-Ethylhexyl) Ester, Sodium Salt; and Sodium Dioctyl Sulfosuccinate (Wenninger and McEwen 1997). In Japan it is referred to as Di(2-Ethylhexyl)Sodium Sulfosuccinate (Rempe and Santucci 1997).

Physical Properties

Dioctyl Sodium Sulfosuccinate has a molecular weight of 444.56 and appears as a waxy solid. It is soluble in both water and organic solvents, especially in water and water-miscible solvent combinations. Its water solubilities as a function of temperature are: 15 g/l at 25°C, 23 g/l at 40°C, 30 g/l at 50°C, and 55 g/l at 70°C. Acid and neutral solutions of Dioctyl Sodium Sulfosuccinate are stable; alkaline solutions hydrolyze (Budavari 1989). Results from mass, ^{1}H-NMR, and ^{13}C-NMR spectroscopy are available (Ahuja and Cohen 1983).

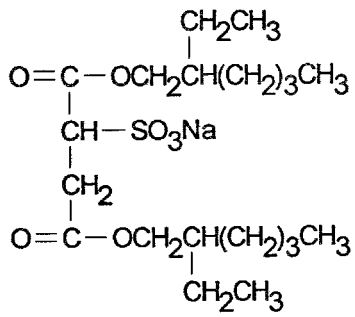

Figure 1. Chemical formula for dioctyl sodium sulfosuccinate.

Method of Manufacture

Maleic anhydride is reacted with 2-ethylhexanol to produce bis(2-ethylhexyl)maleate. This, in turn, is combined with sodium bisulfite under conditions conducive to the formation of the sulfonate structure through rearrangement with an accompanying saturation of the olefinic bond, producing Dioctyl Sodium Sulfosuccinate (Gennaro 1990).

Analytic Methods

Ahuja and Cohen (1983) described a number of methods available for the assay of Dioctyl Sodium Sulfosuccinate. Titration assays for anionic surfactants can be used to determine Dioctyl Sodium Sulfosuccinate: a two-phase mixed indicator titration using 2:3 (v:v) chloroform:1-nitropropane solvent system and an extractive titration technique using carbethopendecinium bromide. Colorimetric analysis methods involving extraction with ethyl violet, bis[2-(2-pyridylazo)-5-diethylaminophenolato] cobalt (III) ion, 1-(4-nitrobenzyl)-4-(4-diethylaminophenylazo)pyridinium bromide, and bis[2-(5-chloro-2-pyridylazo)-5-diethylaminophenolato] cobalt (III) chloride are also described. Turbidimetric, polarographic, and nitrogen blowing techniques are also available.

Impurities

According to the National Formulary (1980), calculated on an anhydrous basis, Dioctyl Sodium Sulfosuccinate should contain between 99 and 100.5% (inclusively) $C_{20}H_{37}NaO_7S$; water should be no more than 2.0%; arsenic, 3 ppm; heavy metals, 0.001%; bis(2-ethylhexyl)maleate, 0.4%.

USE

Cosmetic

Dioctyl Sodium Sulfosuccinate is a surfactant used as an emulsifier and a hydrotrope in cosmetic products (Wenninger and McEwen 1997). As of 1995, Dioctyl Sodium Sulfosuccinate is reported to be used in 38 cosmetic formulations (FDA 1995) (Table 1).

Concentrations of use are no longer reported to the FDA (FDA 1992). However, FDA data from 1984 reported that Dioctyl Sodium Sulfosuccinate was used in a variety of products at concentrations $\leq$5% (FDA 1984).

Table 1. Product formulation data for dioctyl sodium sulfosuccinate

Product category	No. formulations in category	Formulations containing dioctyl sodium sulfosuccinate
Bath oils, tablets, and salts	146	5
Eyeliner	588	5
Hair straighteners	59	1
Hair bleaches	112	5
Blushers (all types)	283	1
Foundations	333	3
Other Makeup preparations	155	1
Nail polish and enamel	108	2
Shaving cream	152	3
Cleansing	771	2
Body and hand (excluding shaving)	987	7
Moisturizing	873	1
Night	220	1
Paste masks (mud packs)	276	1
1995 totals		**38**

Source. FDA, 1995.

International

Dioctyl Sodium Sulfosuccinate is approved by Japan for use in cosmetics (Rempe and Santucci 1997).

OTC

The OTC Drug Review Ingredient Status Report (FDA 1989) reported on the use of Dioctyl Sodium Sulfosuccinate, listed as Docusate Sodium, in three different pharmaceutic or therapeutic use categories. It was generally recognized as safe and effective when used as a stool softener and when used to lower surface tension and produce a mucolytic effect. Dioctyl Sodium Sulfosuccinate, however, was not recognized as an effective pediculicide.

Prescription Drug

Dioctyl Sodium Sulfosuccinate is used in both generic and trade name prescriptions as a mild contact laxative. Usual dosage is 50 to 250 mg daily for adults and children over 12 and 50 to 150 mg for children ages 2 to 12 (AMA 1983).

Veterinary Drug

Dioctyl Sodium Sulfosuccinate is used as a stool softener and a surfactant in veterinary medicine. In addition, it is used to clean ear canals and to treat cattle bloat (Rossoff 1974).

Food

Dioctyl Sodium Sulfosuccinate has a number of applications as a food additive, which are regulated by the FDA. Used as a wetting agent in fumaric acid–acidulated foods, Dioctyl Sodium Sulfosuccinate is limited to a maximum of 15 ppm in finished gelatin desserts or 10 ppm in finished beverages or fruit-juice drinks. It is used in the production of unrefined cane sugar and can be detected in the final juice, syrup, or massecuite product at concentrations of 0.5 ppm per 1% sucrose. It may be used at a concentration of 25 ppm in molasses. Noncarbonated beverages containing cocoa fat may use Dioctyl Sodium Sulfosuccinate as an emulsifying agent, not to exceed 25 ppm in the finished beverage. Gums and hydrophilic colloids may be thickened with Dioctyl Sodium Sulfosuccinate, with a maximum concentration of 0.5% of gums or colloids by weight. As a diluent in color additive mixtures for food, Dioctyl Sodium Sulfosuccinate is limited to a concentration of 9 ppm in the finished product. Other regulated uses for Dioctyl Sodium Sulfosuccinate include: dispersing agent, diluent in color additive mixtures for egg shells, hair remover for hog carcasses, and a cooling and water retort treatment for the exterior of canned goods (Furia 1980).

Other Uses

Dioctyl Sodium Sulfosuccinate has a broad range of uses as a detergent and an emulsifier. Applications include: wetting agents, antifog preparations, emulsion and suspension polymerizations, industrial cleaning solutions, battery separators, and film coating products (McCutcheon's Division 1973).

GENERAL BIOLOGY

Cytotoxicity

Gaginella et al. (1977) studied the cytotoxic effects of intestinal secretagogues on epithelial cells. Cells were isolated from male Syrian hamsters using the methods of Harrison and Webster (1969). The viability of cells was established by the exclusion of trypan blue, and cells were counted and divided into 200- to 500-μl aliquots. For ^{51}Cr studies, cells were incubated with $Na_2{}^{51}Cr$ for 30 minutes at 37°C; a portion of these cells was

set aside for use as the control. The remaining cells were incubated with sample buffer alone or sample buffer and the test material for 15 minutes at 37°C. ^{51}Cr release was expressed as a percentage of dpm before and after test incubation. There was a dose-dependent release of ^{51}Cr with Dioctyl Sodium Sulfosuccinate: a 0.1% concentration effected an 18% release; 0.5% concentration, a 25% release; 1.0% concentration, a 30% release; 2.0% concentration, a 33% release; and 5.0%, a 42% release.

ANIMAL TOXICOLOGY

Oral and Intravenous

Acute

The oral LD_{50} in rats of a product containing 84% Dioctyl Sodium Sulfosuccinate was 3.69 g/kg (CTFA 1991).

Harlan albino mice were matched for sex, divided into groups of 10 and given varying doses of test compounds. For ingestion studies, doses were delivered by means of a stomach tube at different concentrations such that mice received 0.5 ml of solution per 20 g animal weight. Mice were observed for 72 hours after dosing. Using this method, the LD_{50} for a commercial product containing an unspecified amount of Dioctyl Sodium Sulfosuccinate as the active material was 4.8 g/kg. For intravenous studies, the same methods were used with the exception of a 24-hour observation period after intravenous injection. The LD_{50} for a commercial ingredient containing an unspecified amount of Dioctyl Sodium Sulfosuccinate as the active agent was 60 mg/kg (Hopper, Hulpieu, and Cole 1949).

Female albino rats weighing 135 to 180 g were used in an acute feeding study of a number of commercially available surfactants including Dioctyl Sodium Sulfosuccinate. Doses ranged from 0.25 to 7.95 g/kg, administered either by intubation as a 10% aqueous solution or as an emulsion. A 2-week period followed to determine mortality. The LD_{50} for Dioctyl Sodium Sulfosuccinate was 1.9 g/kg (Olson et al. 1962).

Short-Term

Hopper, Hulpieu, and Cole (1949) studied the subacute toxicity of surface-active ingredients in a commercial product containing an unspecified amount of Dioctyl Sodium Sulfosuccinate as the active ingredient. Harlan albino mice were intubated and received 0.1% of the LD_{50} concentration (previously determined) of test product daily, 6 days a week. There were 10 mice per group, and each group received a different number of doses per day such that the sum of the total exposure was equal to 0.1% of the LD_{50}. The group which received 5 doses of the commercial product had five deaths; 10 doses, seven deaths; 15 doses,

eight deaths; and 20 doses, eight deaths. The mortality for the group receiving 25 doses was not reported.

Subchronic

Bengalia et al. (1943) studied the subchronic toxicity of Dioctyl Sodium Sulfosuccinate in a commercial product in four animal species. Wistar rats were divided into six groups of five males and five females each. One group served as a control; the other groups received feed containing calculated doses of 0.25, 0.50, 0.75, 1.00, and 1.25 g of Dioctyl Sodium Sulfosuccinate/kg body weight. Actual doses, due to reduced consumption of feed, were 0.19, 0.37, 0.55, 0.75, and 0.87 g/kg, respectively. Animals were weighed and feed consumption was monitored twice a week. Blood samples were taken irregularly. All of the animals survived to the end of the 24-week experimental period. Mean weight gain for the test groups was about the same as controls. Erythrocyte and leukocyte counts were unaffected by the test material, although there was a small shift in differential counts: Neutrophils increased and lymphocytes decreased. During this period, the only clinical effect noted was the occasional occurrence of diarrhea. No lesions were found at necropsy.

Subchronic toxicity was studied in dogs: three dogs received a dietary dose of 0.10 g/kg of a commercial surfactant containing Dioctyl Sodium Sulfosuccinate as the active ingredient; three dogs received 0.25 g/kg. All dogs lived to the end of the 24-week period in good health. A decrease in animal weight was not considered to be due to any toxic effect of the test material. No lesions were found at necropsy (Bengalia et al. 1943).

In an experiment similar to that done with dogs, three monkeys received a 0.125 g/kg dose of the commercial preparation containing Dioctyl Sodium Sulfosuccinate. All three survived 24 weeks and had no lesions at necropsy (Bengalia et al. 1943).

Groups of five male Osborne-Mendel rats were fed 2, 4, and 8% Dioctyl Sodium Sulfosuccinate over a period of 4 months. These doses were considered by the investigators to be very toxic. Only rats in the 2% feeding group lived to the end of the experiment; their mean weight gain was 220 g as compared to 393 g in control animals (Fitzhugh and Nelson 1948).

Chronic

Groups of 12 male Osborne-Mendel rats were fed diets containing 0.25, 0.5, and 1% Dioctyl Sodium Sulfosuccinate. Controls received diets with no surfactant. Animals were studied for 2 years, with weekly bodyweight and feed-consumption determinations. All groups receiving Dioctyl Sodium Sulfosuccinate had 10 animals surviving after 1 year. The 0.25% dose animals had a 436-g mean weight gain; the 0.5% group, a 441-g mean weight gain; the 1% group, a 395-g mean weight gain. The

11 surviving control rats had a mean weight gain of 472 g (Fitzhugh and Nelson 1948).

Inhalation

Sprague-Dawley rats, 12 male and 12 female, were exposed to an aerosol of a product containing an effective Dioctyl Sodium Sulfosuccinate concentration of 0.21% (CTFA 1991). The concentration of exposure was 4.2 mg/m^3, and lasted 4 hours a day, 5 days a week, for 13 weeks. An equal number of rats were kept in a control chamber during this time. During week 7, two rats from each group were killed and necropsied. At the end of the 13 weeks, the remainder of the animals were killed and necropsied. There were no statistically significant differences in dosed and control groups, attributable to Dioctyl Sodium Sulfosuccinate, for the following parameters: mean body weight gain, survival, appearance and behavior, urinalysis values, and microscopic lesions. The following significant differences were noted in hematologic parameters in treated rats as compared to control rats: elevated erythrocytic values in male rats at 7 weeks and depressed mean corpuscular hemoglobin concentration values in male rats at 13 weeks. Significant differences between dosed and treated rats in clinical chemistry parameters included: elevated serum glutamic pyruvic transaminase (SGPT) values in males at 13 weeks, depressed SGPT values in females at 7 weeks, depressed serom alkaline phosphatase (SAP) values in females at 13 weeks, and elevated glucose values in both the 7- and 13-week females. For the male rats, there was a significant difference in relative brain, liver, and testis weights. In females, there was a significant difference in the absolute, but not relative, heart weight. At 7 weeks, the lungs of animals necropsied were examined and stained with Oil Red O. One dosed male rat had some scattered foci of neutrophils along with an increase in the number of free alveolar macrophages.

Nieman and Bredenberg (1985) studied the effects of inhaled Dioctyl Sodium Sulfosuccinate on pulmonary extravascular water volume. A 1% solution of a commercial detergent containing Dioctyl Sodium Sulfosuccinate was suspended in equal volumes of 95% ethanol and isotonic saline. The final concentration of the test material was 15 mg/kg. A volume of 1.5 ml/kg was administered to mongrel dogs which had previously been anesthetized with sodium pentobarbital and attached to a piston ventilator via an endotracheal tube. The dose was administered over a period of 30–45 minutes by an ultrasonic nebulizer connected to the ventilator. Blood pressure was monitored and blood was sampled throughout the dosing. Blood gases and hemoglobin were measured. Animals were killed at 30 minutes, 2 hours, and 4 hours; photographs were taken of the lungs and the pulmonary extravascular water volume

was measured. An extract of the lungs was prepared for surface tension measurements and light microscope examination. Any airway foam present in the distal trachea or large bronchi was similarly prepared. Changes in pulmonary structure and function present in Dioctyl Sodium Sulfosuccinate–dosed dogs, but not in vehicle-alone dogs included: atelectatic areas throughout the lungs, extensive nonhemorrhagic edema fluid appearing as foam, size change and collapse of some alveoli, high surface tension and narrowed hysteresis of the lungs, and pulmonary extravascular water volume increase. Microscopic evaluation indicated a preservation of pulmonary structure and no sign of destruction of the alveolar cells. The authors suggest that the inhaled test surfactant is capable of displacing the normal alveolar surfactant into the airway and resulting in increased alveolar surface tension and instability (Nieman and Bredenberg 1985).

The effect of Dioctyl Sodium Sulfosuccinate on the clearance of radioactive diethylene triamine pentaacetate (DTPA) was studied in rabbits. Rabbits were prepared in a manner similar to the dogs in the Nieman and Bredenberg study; six received 5% Dioctyl Sodium Sulfosuccinate in vehicle and six received vehicle alone for 5 minutes. Following dosing, ^{99m}Tc-DTPA was administered to the animals through the same method as before. A small amount of ^{99m}Tc-DTPA was then given intravenously to the animals for the purpose of background calibration. Radiation was measured with a gamma camera equipped with a converging collimator. The data indicated that animals given Dioctyl Sodium Sulfosuccinate cleared ^{99m}Tc-DTPA much more rapidly than those animals given vehicle alone. This effect increased over the 15 minute post-dose observation period. There were no observable changes in arterial oxygen pressure or compliance (Evander, Wollmer, and Jonson 1988).

Dermal

Acute

Draize, Woodard, and Calvery (1944) included Dioctyl Sodium Sulfosuccinate in an early study to develop irritation and toxicity tests. Rabbits were prepared by clipping the hair from their trunks. Areas on the back were designated for patches; half of these areas were abraded. Light gauze patches were taped over the skin where 0.5 ml of 2% Dioctyl Sodium Sulfosuccinate had been introduced. The skin irritation was evaluated after the 24-hour exposure and again after 72 hours. The final irritation score is the average of these two readings, with a maximum score of 8. The average score for the intact skin was 3.7; the score of the abraded skin was 1.7 (no explanation of data given).

The primary dermal irritation of a 10% solution of a product containing 84% pure Dioctyl Sodium Sulfosuccinate in propylene glycol was minimal in rabbits using a single insult occlusive patch test (CTFA 1991).

Short-Term

Heterogeneous-stock albino rabbits were shaved and abrasions were made to two areas of the caudal region of the belly. Cotton pads containing 5 ml of 1, 5, and 25% Dioctyl Sodium Sulfosuccinate were taped to the abraded areas. Dosed pads were replaced once a day for 3 days. A similar experiment was conducted on two areas of intact rabbit skin; fresh applications of dosed pads were made 10 times in 14 days. A third experiment was conducted on the intact skin of the external ear of a rabbit using the same concentrations of Dioctyl Sodium Sulfosuccinate in a similar application procedure. For the abdominal skin, the 1% solution had an index number of 4 (moderate hyperemia on intact skin, may or may not burn abraded skin), the 5% solution had an index of 5 (burn from two to four 24-hour applications to intact skin), and the 25% solution had an index of 6 (burn from one 24-hour application to intact skin). For the external ear, the 1% solution had an index number of 1 (essentially no irritation to intact skin), the 5% solution had an index of 4, and the 25% solution had an index of 6 (Olson et al. 1962).

Sub-Chronic

Eight female Sprague-Dawley rats (weighing 125–150 g) were used in a 13-week dermal toxicity test. An effective Dioctyl Sodium Sulfosuccinate concentration of 0.00126% (in formulation) was applied to a shaved site on the back, 5 days a week for 67 days. The solution was applied at a dose of 4 ml/kg; an untreated control group was maintained. Observations were made daily for the first two experimental weeks, weekly thereafter; blood and urine samples were obtained on weeks 7 and 13. While a statistically significant increase in white blood cell count was noted in week 13 and a decrease in serum glutamic oxaloacetic transaminase activities in week 7, the values remained within the range for historical controls. One dosed animal was noted to have fluid filled kidneys at necropsy. Body weight gain, organ weight, survival, and urinalysis parameters in dosed animals were not significantly different from control animals. Treated animals did, however, have minimal to moderate skin irritation sporadically throughout the study (CTFA 1991).

A study was conducted relating dermal irritancy and acanthosis. A commercially available product containing Dioctyl Sodium Sulfosuccinate was tested on guinea pigs at concentrations of 2, 10, and 20%. After repeated skin applications, a portion of skin was removed from test

and control animals and histologic slides were prepared. The acanthosis factor (AF) was calculated from the difference in the epidermal thicknesses, where 1 unit is equal to 2.7μm (Gloxhuber 1980). The 2% concentration of the product containing Dioctyl Sodium Sulfosuccinate had an AF of 1.8; the 10% concentration had an AF of 2.5; and the AF for the 20% concentration animals was 3.3 (Schaaf 1969).

Ocular

As well as dermal irritation, Draize et al. (1944) studied the effect of Dioctyl Sodium Sulfosuccinate on the rabbit eye. Three different concentrations of Dioctyl Sodium Sulfosuccinate, in a volume of 0.1 ml, were introduced into the conjunctival sac. Irritation readings were taken at 1 and 24 hours after application. At 1 hour, the eye receiving 0.5% Dioctyl Sodium Sulfosuccinate had an irritation score of 4.0; the score for the 2.0% solution was 9.0; and the score for the 10.0% solution was 26.0. At 24 hours, animals of the 0.5% group had an irritation score of 2.0; the score for 2.0% group was 2.0; and the score for the 10.0% group was 24.0.

The ocular irritation of a 10% solution of a product containing 84% Dioctyl Sodium Sulfosuccinate in propylene glycol was minimal in rabbits using the Draize classification (CTFA 1991).

Dioctyl Sodium Sulfosuccinate was instilled in rabbit eyes at 0.1, 0.25, 0.5, 1, and 100% concentrations. Doses were delivered in either a single instillation of two drops or in repeated dosings of two drops four times a day for 6 days for all concentrations except the undiluted test group, which received one dose a day for 6 days. The single application of the 0.1% concentration produced no effects; repeated use of this concentration produced mild conjunctival injection that disappeared within 24 hours after discontinuation of the doses. The single dose at 0.5% produced conjunctival hyperemia, edema, loosening of the epithelium, and minute corneal staining; repeated use intensified these effects, along with an appearance of mucoid discharge; eyes cleared; after 48 hours. A single instillation of the 1% concentration produced conjunctival hyperemia, edematous loosening of the epithelium, blepharospasm, and corneal haziness and staining which disappeared after 24 hours; the repeated instillation had similar effects, which cleared after 72 hours. The single application of the undiluted Dioctyl Sodium Sulfosuccinate induced conjunctival injection, edema, sloughing of the epithelium, corneal haziness and staining, and superficial punctate areas which disappeared in the majority of the tested eyes within 1 week (Leopold 1945).

Hopper, Hulpieu, and Cole (1949) studied the effects produced by a number of commercially available products containing surfactants. A solution of 1% of a product containing Dioctyl Sodium Sulfosuccinate was instilled into the conjunctival sac of the eye and observations of

effects were made at 5 min, 10 min, 1 h, and 24 h. The only effect noted was the presence of inflammation in six animals.

Drops of Dioctyl Sodium Sulfosuccinate were introduced into the conjunctival sac of both eyes of groups of three rabbits. The right eye was rinsed after a 30-second exposure, the left was left unrinsed. Both eyes were evaluated at 1 hour, 24 hour, 2 days, and 1 week. The 1% concentration produced little or no effect in both the rinsed and unrinsed eyes. The 5% concentration produced similar results in the rinsed and unrinsed eye: a slight effect, disappearing within a week, with no corneal damage. In the rinsed eye, the 25% concentration was just slightly more irritating than the 5% concentration. In the unrinsed eye, however, the 25% concentration produced a severe effect, consisting of corneal injury and impairment of vision (Olson et al. 1962).

Reproductive Effects

Mackenzie et al. (1990) conducted a three-generational study to determine the effects of oral administration of Dioctyl Sodium Sulfosuccinate on reproduction. Groups of 30 rats of either sex were fed diets containing 0, 0.1, 0.5, or 1.0% Dioctyl Sodium Sulfosuccinate. The males of this F_0 generation were maintained on such a protocol for 10 weeks, the females for 2; the diets were fed beginning at 7 weeks of age and continuing through mating, gestation, and lactation. The F_0 animals were mated to produce an F_1 generation. Groups of 30 males and females from the F_1 were fed the same diets as their respective F_0 parents for 10 weeks postweaning. The breeding program was repeated to produce an F_2 generation and again to produce an F_3 generation. Test diets were fed throughout the study; F_1 and F_2 animals were exposed to the test material in utero and while nursing, before being weaned to feed dosages. The study was terminated with the F_3 weanlings; necropsy and macroscopic examinations were performed. The researchers found decreased body weight in all parental males and in F_1 and F_2 females fed diets containing 0.5 or 1.0% Dioctyl Sodium Sulfosuccinate. The body weights of pups in all three generations were lower than those of corresponding controls. However, the reduced body weight did not interfere with normal reproductive development and performance. Dioctyl Sodium Sulfosuccinate at doses up to 1.0% had no effect on reproductive function and produced no treatment-related mortality and antemortem or macroscopic abnormality.

Mutagenicity

Dioctyl Sodium Sulfosuccinate, at concentrations up to 2500 μg/plate with S-9 activation and up to 1000 μg/plate without activation, did

not induce a statistically significant increase in revertant mutants in an Ames assay conducted on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 (Hazleton Microtest 1993).

A chromosomal aberration assay was conducted on Chinese hamster ovary cells (CHO). Duplicate plates of cells were incubated for 2 and 20 hours with 0.5 ml of a Dioctyl Sodium Sulfosuccinate dilution in the presence and absence of S-9 activation, respectively. Colchicine was added to the media prior to harvesting (20 hours after start of treatment) to arrest dividing cells in metaphase. Dioctyl Sodium Sulfosuccinate induced significant chromosomal aberrations in the presence of S-9 activation. Aberration values comparable to the positive control cyclophosphamide were first observed in the 120 μg/ml treatment plates where chromosomal aberrations were found in an average of 24/100 cells scored. The majority were abnormalities other than chromosomal gaps. The induction of toxicity was also demonstrated as a 62% reduction in mitotic activity at 120 μg/ml and complete toxicity at doses exceeding 140 μg/ml were observed. As a result, two subsequent attempts to repeat the above results were unsuccessful even when the dosing range was narrowed. In summary, there were no aberrations in the absence of toxicity. Cells treated for 20 hours with Dioctyl Sodium Sulfosuccinate in the absence of activation exhibited 52% mitotic inhibition at 55.29 μg/ml. In order to further test the mutagenic potential of the test agent, a delayed harvest was conducted in which cells were incubated for 44 hours with concentrations up to 130 μg/ml in the absence of S-9. The number of chromosomal aberrations in all assays treated without S-9 was within the range of the historical negative control (Hazleton Microtest 1994).

CLINICAL ASSESSMENT OF SAFETY

Sensitization and Photosensitization

Four separate 4-day mini-cumulative irritancy tests were performed testing various Dioctyl Sodium Sulfosuccinate formulations. The primary irritation index (PII) of each of four products containing an effective Dioctyl Sodium Sulfosuccinate concentration of 2.94% (3.5% solution of 84% Dioctyl Sodium Sulfosuccinate) was 0.25, 0.30, 0.80, and 0.38. The PIIs of two products containing a 0.25% solution of 84% Dioctyl Sodium Sulfosuccinate were 1.78 and 1.85 (separate studies). The PII of a product containing a 0.1% solution of 84% Dioctyl Sodium Sulfosuccinate was 0.04 (CTFA 1991).

A 21-day cumulative irritancy test was performed using seven volunteers and a product containing a 1.13% solution of Dioctyl Sodium Sulfosuccinate (84% pure). The test material was applied daily to the same

site using an occlusive patch. Areas were scored everyday on a scale of 0 (no reaction) to 4 (strong reaction). One volunteer was dropped from the study (no reason stated). The total irritation score was 324 out of a maximum score of 578 for all seven panelists over the 21-day period; the average score per panelist was 46.3 out of a maximum of 84. The lowest average reading for one panelist was 15; the highest reading was 73 (CTFA 1991).

A Repeated Insult Patch Test (RIPT) of a product containing an effective Dioctyl Sodium Sulfosuccinate concentration of 0.42% was conducted using 100 volunteers. An occlusive patch containing 0.2 ml of the product was applied to an area of the back. The patch was removed by the panelist after 24 hours. Application of induction patches was repeated for a total of nine exposures over a period of 3 weeks. After a 2-week nontreatment period, a nonspecified site was challenged with the same dose. Sites were scored before application of another patch. Four panelists had mild erythema covering most of the patch area in the last weeks of the study. None of the volunteers had a reaction to the challenge (CTFA 1991).

The above described method was used in four other RIPT studies. The challenge site was a previously untreated site. Of 119 volunteers tested with 0.21% Dioctyl Sodium Sulfosuccinate, eight had barely perceptible to mild erythema at the dose site during the induction phase; two had barely perceptible erythema during the challenge phase. Of 117 volunteers tested with a product which also had an effective Dioctyl Sodium Sulfosuccinate concentration of 0.21%, eight had barely perceptible to mild erythema at the dose site during the induction phase; three had barely perceptible erythema during the challenge phase. Of 94 volunteers tested with a product also containing 0.21% Dioctyl Sodium Sulfosuccinate, 27 had barely perceptible to mild erythema at the dose site during the induction phase; five had barely perceptible erythema during the challenge phase. Of 99 volunteers tested with a product containing 0.1% Dioctyl Sodium Sulfosuccinate (84% pure), 11 had barely perceptible to mild erythema at the dose site during the induction phase; one had mild erythema during the challenge phase. Of 94 volunteers testing a product also containing 0.1% Dioctyl Sodium Sulfosuccinate (84% pure), four had barely perceptible erythema at the dose site during the induction phase; there were no reactions during the challenge phase (CTFA 1991).

A photocontact allergenic potential study of a product containing 0.25% Dioctyl Sodium Sulfosuccinate (84% pure) was conducted using 25 volunteers. During the pretesting phase, the midback of volunteers was irradiated with a xenon arc solar simulator, 150 watt, with a UV-reflecting dichroic mirror and filtered with a 1-mm thick Schott WG-320 filter, in order to determine the minimal erythema dose (MED). During the induction phase, 10 μl/cm of the test material was applied

to a 2 × 2 cm^2 area and then covered by an occlusive patch. After 24 hours, the patch was removed, the area was wiped dry, and the site was irradiated with 3 MEDs. This was repeated twice a week for a total of six exposures. Ten to 14 days later, the same dose was applied in duplicate to nontreated sites. After 24 hours, the patches were removed and the sites wiped dry. One of the areas was then irradiated with 4 J/cm^2 ultraviolet A radiation, obtained by filtering the previous light source with a 1-mm thick UG5 filter. The duplicate site served as a control. There were no reactions in either the induction or challenge phase attributable to Dioctyl Sodium Sulfosuccinate (CTFA 1991).

Contact Dermatitis Case Study

Irritation coinciding with the application of a plaster-of-Paris cast lined with an orthopedic wool was observed in six patients. Staniforth and Lovell (1981) patch tested these patients with the four chemicals used to process the wool at 1, 10, and 100% concentrations along with gypsona (100%), benzalkonium chloride (0.1%), and cetrimide (0.1%). Only the chemical containing Dioctyl Sodium Sulfosuccinate gave a positive reaction in all patients. Gypsona, benzalkonium chloride, and cetrimide produced irritation in three patients. None of the other chemicals tested affected an irritant reaction. Following this, a product containing Dioctyl Sodium Sulfosuccinate was patch tested using eight volunteers with normal skin and ten volunteers with noninflammatory skin disease. The 1 and 10% concentrations produced neither irritation nor allergic reactions. The undiluted product caused an irritant reaction in 12 of the 18 volunteers (Staniforth and Lovell 1981).

A single 24-hour occlusive patch containing 2.5% Dioctyl Sodium Sulfosuccinate in formulation was applied to the upper back or arm of 50 panelists. No reactions were noted at the time of patch removal or after an additional 24 and 48 hours (GTLF 1994).

An RIPT was conducted on 110 panelists (demographically separated into two groups of 55) to determine the sensitization potential of 1, 3, and 5% Dioctyl Sodium Sulfosuccinate (TKL Research Inc. 1994). During the induction phase, semiocclusive patches containing 0.2 ml of the test material was applied to the back with the instruction to remove them after 24 hours. Evaluation of the treatment site and application of successive patches were done every 48 hours until a total of nine patches had been applied. A 14-day nontreatment period followed. During challenge, a 24-hour patch of the test material was applied to a previously unexposed site. The challenge site was evaluated at the time of patch removal and after additional 24- and 48-hour periods (i.e., 48 and 72 hours after application). With successive induction patch applications,

the 1% solution produced questionable reactions defined as "minimal or doubtful response, slightly different from surrounding normal skin" in an increasing number of panelists. At the ninth application, 17 panelists had such a reaction. Other reactions noted during early induction included four cases of "definite erythema, no edema" (scored +), "definite erythema, no edema with damage to epidermis; oozing, crusting, and/or superficial erosions" (scored +D), or "definite erythema, minimal or doubtful edema" (scored +*). These reactions were notably less severe by the final induction. There were no reactions during challenge. Similarly, the 3% solution produced questionable reactions in two panelists after application of the first induction patch and in 32 panelists by the ninth application. Reactions graded (+), (+D), and/or (+*) were noted in five panelists at various evaluations. There were no reactions during challenge. The 5% solution produced questionable reactions in eight panelists after application of the first induction patch and in 65 panelists by the ninth application. Reactions graded (+), (+D), and/or (+*) were noted in 16 panelists at various evaluations during induction. There were no reactions during challenge.

A second RIPT study was conducted on 107 panelists using a 50/50 dilution (with distilled water) of an eyebrow pencil containing 2.5% Dioctyl Sodium Sulfosuccinate (effective DSS concentration: 1.25%). During induction, patches containing the test material were applied to the back three times a week for 3 weeks for a total of 10 exposures. The patches remained on the skin for 48 hours; sites were evaluated at the time of patch removal, prior to application of the successive patch. A 12-day nontreatment period followed induction. During challenge, a 48-hour patch was applied to a previously untreated site on the back. Reactions were evaluated at 48 and 72 hours postapplication. During induction, 20 panelists had at least one reaction defined as "erythema throughout the entire patch area." (Ten of the twenty panelists had reactions noted at one to three evaluations, the other ten had reactions noted during at least five, and at up to eight, evaluations.) Erythema, edema, and vesicles were noted in another individual during observation 5. No reactions had been observed in this panelist during previous evaluations and further patch application was discontinued. There were no reactions during challenge (International Research Services Inc. 1995).

SUMMARY

Dioctyl Sodium Sulfosuccinate is an anionic surfactant used in a variety of leave-on and rinse-off cosmetic products. It is an approved OTC ingredient, prescription drug, and food additive. Dioctyl Sodium Sulfosuccinate had a dose-dependent cytotoxic effect on epithelial cells.

In one study using rats, the oral LD_{50} of Dioctyl Sodium Sulfosuccinate was 1.9 g/kg. Results of subchronic toxicity testing indicated little, if any, toxic effects below the LD_{50}. Mice receiving Dioctyl Sodium Sulfosuccinate orally for 2 years had reduced body weight gain as compared to controls.

Rats exposed to an aerosol containing Dioctyl Sodium Sulfosuccinate had changes in some hematology and clinical chemistry parameters. Dogs dosed similarly had significant gross, but not microscopic, changes of the lungs.

Dioctyl Sodium Sulfosuccinate was found to be minimally irritating at 10% on intact skin. Abraded skin of rabbits had moderate to severe irritation reactions to 1, 5, and 25% Dioctyl Sodium Sulfosuccinate. A 13-week dermal toxicity test using a 0.21% solution of Dioctyl Sodium Sulfosuccinate produced sporadic irritation throughout the study.

At concentrations of 25% or higher, Dioctyl Sodium Sulfosuccinate was a severe ocular irritant. Concentrations of 10% and less produced little or no irritation.

A three-generation study in rats found oral administration of up to 1.0% Dioctyl Sodium Sulfosuccinate did not affect the reproductive function nor produced treatment-related abnormalities in progeny.

Dioctyl Sodium Sulfosuccinate was nonmutagenic in an Ames assay, but with S-9 activation, it did induce chromosomal aberrations in CHO cells at treatment doses close to threshold toxicity.

The PIIs of a 2.94% solution of Dioctyl Sodium Sulfosuccinate were 0.25, 0.30, 0.80, and 0.85 in four separate studies. A 5% solution of Dioctyl Sodium Sulfosuccinate was not sensitizing in an RIPT study. However, irritation reactions were noted during induction. Irritation to Dioctyl Sodium Sulfosuccinate in orthopedic wool has been reported in six patients.

DISCUSSION

The CIR Expert Panel previously determined that a conclusion for Dioctyl Sodium Sulfosuccinate could be based on the available experimental data. A concentration of 0.42% was the highest level for which there was sufficient data to substantiate safety. This level was found not to induce sensitization in a human RIPT. While no effect was found in a clinical 21-day cumulative assay testing at a higher concentration (approximately 1%), the assay used seven panelists whereas the RIPT had 100 participants. In the absence of current data on concentration of use for this ingredient, the Expert Panel was unable to suggest how these experimental concentrations relate to actual use. This ingredient may be safe as currently used, but in the absence of use data, the Expert Panel concluded that a concentration limit is necessary.

In addition, the Panel recognized that positive results in the CHO mutagenicity assay were only found with toxicity. Thus, the findings are of questionable significance.

After reviewing additional data, the CIR Expert Panel decided that there was sufficient evidence to eliminate the need for a limit on concentration. The Panel considered Dioctyl Sodium Sulfosuccinate to be safe used in cosmetic formulations. It was acknowledged that under the exaggerated exposure conditions of the two RIPTs (continuous occlusive patch testing), the ingredient is a cumulative irritant, though not a sensitizer. The Panel recognized that a surfactant would most likely produce irritation under such conditions. The Panel stressed that care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin.

CONCLUSION

Based on the available data, the CIR Expert Panel concluded Dioctyl Sodium Sulfosuccinate to be safe as used in cosmetic formulations.

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