Safety Assessment of Dialkyl Sulfosuccinate Salts as Used in Cosmetics

Status: Tentative Amended Report for Public Comment
Release Date: June 20, 2013
Panel Meeting Date: September 9-10, 2013

All interested persons are provided 60 days from the above release date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to Dr. Lillian Gill.

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, 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 F. Alan Andersen, Ph.D. This re-review document was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer, and Bart A. Heldreth, Ph.D., Chemist.
# TABLE OF CONTENTS

Abstract...................................................................................................................................................................................................................................1
Introduction.................................................................................................................................................................................................................................1
Chemistry.................................................................................................................................................................................................................................1
  Definition and Structure..........................................................................................................................................................................................1
  Physical and Chemical Properties......................................................................................................................................................................1
  Method of Manufacture...........................................................................................................................................................................................2
  Impurities...............................................................................................................................................................................................................................2
Use.................................................................................................................................................................................................................................2
  Cosmetic ...........................................................................................................................................................................................................................2
  Non-Cosmetic ...............................................................................................................................................................................................................2
Toxicokinetics..............................................................................................................................................................................................................3
  Absorption, Distribution, Metabolism, and Excretion.........................................................................................................................................................3
  Penetration Enhancement......................................................................................................................................................................................3
Toxicological studies .........................................................................................................................................................................................................4
  Single Dose (Acute) Toxicity...................................................................................................................................................................................4
    Dermal ...........................................................................................................................................................................................................................4
    Oral ..............................................................................................................................................................................................................................4
  Repeated Dose Toxicity ................................................................................................................................................................................................4
    Dermal ..........................................................................................................................................................................................................................4
    Oral ..............................................................................................................................................................................................................................4
    Inhalation ...............................................................................................................................................................................................................4
  Ocular Irritation.........................................................................................................................................................................................................5
Reproductive and Developmental Toxicity ..................................................................................................................................................................5
Genotoxicity.................................................................................................................................................................................................................................6
Carcinogenicity..................................................................................................................................................................................................................6
  Effect on Colorectal Carcinogenesis .................................................................................................................................................................6
Irritation and Sensitization ................................................................................................................................................................................................6
  Dermal Irritation and Sensitization.........................................................................................................................................................................6
    Non-Human ........................................................................................................................................................................................................6
    Human ..........................................................................................................................................................................................................................6
  Phototoxicity/Photoallergenicity ..................................................................................................................................................................................6
    Human ..........................................................................................................................................................................................................................6
Summary...............................................................................................................................................................................................................................6
Discussion.............................................................................................................................................................................................................................7
Conclusion..............................................................................................................................................................................................................................8
Figures...............................................................................................................................................................................................................................2
  Structures..........................................................................................................................................................................................................................2
Tables...............................................................................................................................................................................................................................4
    Table 1. Data from the previous review of diethylhexyl sodium sulfosuccinate.................................................................................................4
    Table 2. Data on constituent alcohols.................................................................................................................................................................5
    Table 3. Definitions and Functions...................................................................................................................................................................5
    Table 4. Physical and chemical properties .....................................................................................................................................................6
    Table 5. Current and historical frequency and concentration of use of diethylhexyl sodium sulfosuccinate according to duration and exposure............7
References......................................................................................................................................................................................................................8
ABSTRACT
The CIR Expert Panel assessed the safety of eight dialkyl sulfosuccinate salts for use in cosmetics, finding that these ingredients are safe in cosmetic formulations in the present practices of use and concentration when formulated to be non-irritating. The dialkyl sulfosuccinate salts primarily function as surfactants in cosmetics. The Panel reviewed the new and existing available animal and clinical data in making its determination of safety. The Panel found it appropriate to extrapolate the data on diethylhexyl sodium sulfosuccinate to assess the safety of the entire group because all of the diesters are of a similar alkyl chain length, all are symmetrically substituted, and all have similar functions in cosmetic formulations.

INTRODUCTION
Diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate) was reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel in 1994, and a safe concentration limit of 0.42% was established. A petition to open the report to review new clinical data was received, and in 1998, the Panel amended the report to conclude that this ingredient is safe as used in cosmetic formulations. In the discussion, the Panel stressed that care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin.

In addition to diethylhexyl sodium sulfosuccinate, there are seven additional dialkyl sulfosuccinate salts listed in the International Cosmetic Ingredient Dictionary and Handbook. All eight ingredients are anionic surfactants, and the Panel determined that the data on diethylhexyl sodium sulfosuccinate can be extrapolated to support the safety of these salts:

- Ammonium Dinonyl Sulfosuccinate
- Diamyl Sodium Sulfosuccinate
- Dicapryl Sodium Sulfosuccinate
- Diheptyl Sodium Sulfosuccinate
- Dihexyl Sodium Sulfosuccinate
- Disobutyl Sodium Sulfosuccinate
- Ditridecyl Sodium Sulfosuccinate

Published literature that has become available since the CIR safety assessment was issued in 1998 are presented in this review. Data from 1998 report on diethylhexyl sodium sulfosuccinate are summarized in Table 1; because data from the existing safety assessment are included in Table 1, only new data will be included in the body of this safety assessment. CIR has not reviewed and concluded on the safety of any of the individual alcohol constituents that make up the sulfosuccinate salts. However, data on caprylic, isobutyl, and ethylhexyl alcohols, which are constituent of a few of the dialkyl sulfosuccinate salts, have been summarized in previous CIR reviews. Accordingly, these data are provided in Table 2.

CHEMISTRY
Definition and Structure
The ingredients proposed for this review are the salts of diesters of 2-sulfosuccinic acid. The ingredients all share a sulfosubstituted, succinic acid, core; accordingly, these salts are sulfosuccinates. For example, diheptyl sodium sulfosuccinate consists of a seven-carbon alkyl chain (heptyl), bonded to the sulfosuccinate core via an ester linkage, and followed by an ester linkage to an additional seven-carbon alkyl chain. (Figure 1.)

![Figure 1. Diheptyl Sodium Sulfosuccinate](image)

Due to the ester linkage, these sulfosuccinate ingredients are theoretically sensitive to hydrolysis, especially under acidic conditions.
The dialkyl sulfosuccinate salts included in this assessment are defined in Table 3, and the structures are depicted following the text of this document.

Physical and Chemical Properties
Little published physical and chemical properties data were found. The data that were available are provided in Table 4.
Method of Manufacture

Diethylhexyl Sodium Sulfonate

Refer to Table 1 for summary information from the original safety assessment on the method and manufacture of diethylhexyl sodium sulfosuccinate.

In the production of diethylhexyl sodium sulfosuccinate, malic acid and 2-ethylhexanol are reacted to form the diester, which is sulfonated using sodium metabisulfite. The reaction takes place in a closed system that is opened only for the addition of the reactants.

Dialkyl Sodium Sulfosuccinate

The dialkyl sodium sulfosuccinates are prepared by the action of the appropriate alcohols on maleic anhydride followed by the addition of sodium bisulfite.

Impurities

Diethylhexyl Sodium Sulfosuccinate

The Food Chemicals Codex has the following acceptance criteria for diethylhexyl sodium sulfosuccinate: not less than (NLT) 98.5% C_{20}H_{37}NaO_{7}S; not more than (NMT) 2 mg/kg lead; NMT 0.2% bis(2-ethylhexyl)maleate; NMT 2.0% loss on drying; 15.5-16.2% residue on ignition. The United States Pharmacopeia acceptance criteria are: NLT 99.0% and NMT 100.5% C_{20}H_{37}NaO_{7}S calculated on the anhydrous basis; NMT 2.0% water; NMT 0.001% heavy metals; NMT 0.4% bis(2-ethylhexyl)maleate; and 15.5-16.5% residue on ignition, calculated on the anhydrous basis.

USE

Cosmetic

The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA in 2013, and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council), indicate that diethylhexyl sodium sulfosuccinate is the only dialkyl sulfosuccinate salt in use.

The current and historical frequency and concentration of use data for diethylhexyl sodium sulfosuccinate are provided in Table 5. The frequency of use increased from use in 38 cosmetic formulations (1995 data) to use in 62 cosmetic formulations (2013 data). The use concentration appears to not have changed. According to a survey conducted by the Council in 2013, the maximum concentration of use reported for diethylhexyl sodium sulfosuccinate is 4.4% in eyebrow pencil formulations; the 1998 safety assessment stated that although concentration of use data were no longer reported to the FDA, 1984 data indicated that diethylhexyl sodium sulfosuccinate was used in a variety of product-types at concentrations of ≤5%.

Diethylhexyl sodium sulfosuccinate is used in hair spray formulations at a concentration of 0.15% in an aerosol and at 0.25% in pump spray formulations. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles <10 µm compared with pump sprays. Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.

All of the dialkyl sulfosuccinate salts named in this report are listed in the European Union inventory of cosmetic ingredients.

Non-Cosmetic

Sodium 1,4-dialkyl sulfosuccinates are exempt from the requirement of a tolerance for residues when used as an inert ingredient in pesticide formulations for pre-harvest and post-harvest uses, as well as for application to animals under 40 CFR 180.910 and 40 CFR 180.930, respectively. This regulation eliminates the need to establish a maximum permissible level for residues of the sodium 1,4-dialkyl sulfosuccinates.

Diethylhexyl Sodium Sulfosuccinate

Diethylhexyl sodium sulfosuccinate is generally recognized as safe and effective as a laxative drug product for over-the-counter use. (58 FR 46589, Sept 2, 1993).

Diethylhexyl sodium sulfosuccinate is included in the Listing Of Color Additives Exempt From Certification; it is used as a diluent in color additive mixtures for food use exempt from certification, and has a limitation of <9 ppm. (21CFR 73.1) It is approved as the direct food additive “cocoa with dioctyl sodium sulfosuccinate for manufacturing,” whereby the amount of diethylhexyl sodium sulfosuccinate does not exceed 75 parts per million of the finished beverage (21CFR 172.520). Diethylhexyl sodium sulfosuccinate is also allowed as a multi-purpose food additive when it meets the specifications of the
Diethylhexyl sodium sulfosuccinate is approved for the following used as an indirect food additive: in adhesives (21 CFR 175.105); in resinous and polymeric coatings (21 CFR 175.300), in resinous and polymeric coatings for polyolefin films (21 CFR 175.320); as a component of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170); in defoaming agents used in the manufacture of paper and paperboards (21 CFR 176.210); in cellophane (21 CFR 177.1200); in polymers in textile and textile fibers (21 CFR 177.2800); in sanitizing solutions for use on food-contact articles (21 CFR 178.1010); and in emulsifiers and/or surface-active agents in adjuvants, production aids, and sanitizers (21 CFR 178.3400).

**Diamyl, Dihexyl, and Diisobutyl Sodium Sulfosuccinate**

Diamyl, dihexyl, and diisobutyl sodium sulfosuccinate are used as wetting agents, and diamyl sodium sulfosuccinate is used as an emulsifier in emulsion polymerization.\(^5\)\(^7\)

### TOXICOKINETICS

**Absorption, Distribution, Metabolism, and Excretion**

The metabolism and excretion of diethylhexyl sodium sulfosuccinate was determined in rats in several studies; limited details were available. Albino rats were given a single oral dose of 50 mg/kg bw \(^{[15S]}\)diethylhexyl sodium sulfosuccinate in an alcohol and water (1:1) solution.\(^{18}\) More than 85% of the diethylhexyl sodium sulfosuccinate was excreted within 24-48 h after dosing, and all was excreted within 96-120 h. The majority of the radioactivity, 66%, was excreted in the feces. Only 25-35% of the dose was excreted in the urine, and that was within 24-48 h after dosing. At 96-168 h after dosing, only trace amounts of radioactivity were found in the tissues.

However, in other studies, the feces were not the primary route of excretion. In a study in which two rats were given a single oral dose of 5 or 10 mg diethylhexyl sodium sulfosuccinate in water, and two rats were given a single intravenous (i.v.) dose of 10 mg diethylhexyl sodium sulfosuccinate, the animals dosed orally with 5 and 10 mg excreted 18.6% and 15.5% of the total dose and the animals dosed i.v. excreted 12.3-15.5% of the dose in the urine in 24 h.\(^{18}\) The rats dosed orally excreted 0.9 and 8.7% of the dose in the feces in this time period; however, the animals that were dosed intravenously did not excrete any of the dose in the feces. The 24-48 h urine samples were analyzed for 2-ethylhexanol and no detectable levels were found. (Use of radiolabel was not specified.)

In a study in which a male rat was dosed by gavage with 10 mg/kg bw \(^{[14C]}\)diethylhexyl sodium sulfosuccinate, 64.1% of the radioactivity was excreted in the urine and 37.4% in the feces in the first 24 h, and then only approximately 1% in the urine and 0.9% in the feces in the next 24 h.\(^{18}\) The researchers stated that diethylhexyl sodium sulfosuccinate must undergo extensive metabolism in the rat because no unchanged diethylhexyl sodium sulfosuccinate was found in the urine, and only a small amount was present in the feces.

Metabolism and excretion was also determined in rabbits and dogs; as with the rat studies, limited details were available. One female rabbit and one male Beagle dog were each given a single oral dose, and one of each species was given a single i.v. dose of 4 mg \(^{[14C]}\)diethylhexyl sodium sulfosuccinate.\(^{18}\) In the rabbits, within 24 h, 87% and 69.7% of the radioactivity was excreted in the urine following oral and i.v. dosing, respectively, and similar patterns of metabolites were found with both routes of administration.

In the dogs, similar excretion patterns and metabolic profiles were observed for both routes of dosing. Approximately 21% of the radioactivity was excreted in the urine in the first 24 h. The majority of the radioactivity, approximately 70%, was excreted in the feces at 24-48 h post-dosing. Blood samples were analyzed for 2-ethylhexanol compounds; with i.v. administration, the blood levels fell rapidly during the first hour, and none was found after 8 h. Similarly, following oral administration, small amounts of 2-ethylhexanol was found in the blood after 1 h, and none was found after 8 h.

### Penetration Enhancement

Surfactants can enhance the permeation rate of various compounds, inducing a concentration-dependent biphasic action with respect to altering skin permeability.\(^{19}\) Surfactant molecules must diffuse through the lipid region of the stratum corneum in order to interact with the deeper protein-rich areas. Anionic surfactants can solubilize the less-soluble protein, or they can remain on the skin due to formation of chemical compounds with skin keratin, and they can interact strongly with both keratin and lipids. If exposure time is short, permeation through the stratum corneum by anionic materials is generally poor; however, permeation increases with a longer exposure time.

The effect of a diethylhexyl sodium sulfosuccinate microemulsion on the distribution of the polyphenols curcumin and resveratrol between the epidermis and dermis was examined in excised guinea pig and Yucatan micropig (YMP) skin.\(^{20}\) The microemulsion consisted of 150 mM saline solution, isopropyl palmitate, diethylhexyl sodium sulfosuccinate, and ethanol, with a weight ratio of 20.2:31.3:33.3:15.2, and the mean particle size was 16.6 ± 1.8 nm. Franz-type diffusion cells were used, and 0.5 ml (guinea pig skin) or 1 ml (YMP skin) of the vehicle containing each polyphenol was added to the donor compartment as saturated concentration; the available diffusion area was approximately 0.62 cm\(^2\). Vehicles consisting of a Tween 80 microemulsion or isopropyl myristate were also evaluated. Treatment time was 20 h for guinea pig skin and 40 h for YMP skin.
for YMP skin. The accumulation of the polyphenols in guinea pig and YMP skin was statistically significantly increased using diethylhexyl sodium sulfosuccinate microemulsion as the vehicle, as compared to that found with the Tween 80 microemulsion or isopropyl myristate. Approximately 1.7% curcumin and 2.2% resveratrol added to donor compartments were incorporated into the skin by the diethylhexyl sodium sulfosuccinate microemulsion. Skin accumulation of curcumin in the diethylhexyl sodium sulfosuccinate microemulsion was approximately 1.9 µmol/g skin in guinea pig skin and approximately 0.24 µmol/g skin in YMP skin; in the isopropyl myristate vehicle, almost no curcumin accumulated in either skin-type. Skin accumulation of resveratrol in the microemulsion was approximately 12 µmol/g skin in guinea pig skin and approximately 3 µmol/g skin in YMP skin; in the isopropyl myristate vehicle, approximately 1 µmol/g skin accumulated in guinea pig skin and 0.1 µmol/g accumulated in YMP skin. In determining the distribution in guinea pig and YMP skin, it was found that diethylhexyl sodium sulfosuccinate, curcumin, and resveratrol penetrated deep in the skin. In YMP skin, the distribution ratio of the polyphenols between the dermis and epidermis decreased with increased molecular weight.

**TOXICOLOGICAL STUDIES**

**Single Dose (Acute) Toxicity**

**Dermal**

The dermal LD$_{50}$ of undiluted diethylhexyl sodium sulfosuccinate in rabbits was >10 g/kg.\(^4\) Occlusive patches of 10 g/kg of the test material were applied to the clipped, unabraded, skin of five male New Zealand white rabbits. Skin fissuring, desquamation, and coriaceousness were observed.

**Oral**

Refer to Table 1 for a summary of single-dose oral toxicity data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

The oral LD$_{50}$ of diethylhexyl sodium sulfosuccinate was 2.64 g/kg bw in male albino ARS/ICR mice\(^21\) and approximately 0.65 g/kg bw in guinea pigs.\(^22\)

**Repeated Dose Toxicity**

**Dermal**

Refer to Table 1 for a summary of repeated-dose dermal toxicity data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

**Oral**

Refer to Table 1 for a summary of repeated-dose oral toxicity data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

A group of 20 male and 20 female albino rats were fed a diet containing 1% diethylhexyl sodium sulfosuccinate (100% pure) for 90 days, and controls were given untreated feed.\(^4\) All animals survived until study termination. There were no clinical signs of toxicity, and no dosing-related macroscopic or microscopic findings. Differences in body weights or organ weights compared to controls were not statistically significant.

Twelve rats/group were fed a diet containing 0, 0.5, 1.04, or 1.5% diethylhexyl sodium sulfosuccinate for 26 wks.\(^23\) Body weight gains of females of the 1.04 and 1.5% dose groups were decreased during wk 3. Two control animals and 4 animals of the 1.5% group died during the study; two of the four animals of the 1.5% group had hemorrhagic gastroenteritis. No other effects were noted. The no-observable adverse effect level (NOAEL) was 0.5%, and the lowest-observable adverse effect level was 1.04%.

Groups of four male and four female Beagle dogs were dosed orally with tablets containing 30 mg/kg bw diethylhexyl sodium sulfosuccinate, 10 mg/kg bw diethylhexyl sodium sulfosuccinate + 5 mg/kg bw 1,8-dihydroanthraquinone (DHA), or 30 mg/kg bw diethylhexyl sodium sulfosuccinate + 15 mg/kg bw DHA, daily, for 1 yr.\(^21\) A control group was given a placebo tablet. Urinalysis was performed, and hematological and clinical chemistry parameters were measured at various intervals. No signs of toxicity were observed in any of the groups. Diethylhexyl sodium sulfosuccinate, alone and in combination with DHA, did not have any adverse effects on urinalysis, hematological or clinical parameters, or body weights, and it did not induce any gross or microscopic lesions. The NOAEL was >30 mg/kg bw.

**Inhalation**

Refer to Table 1 for a summary of repeated-dose inhalation toxicity data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

Fluorescent latex particles, 0.63 µm diameter, were administered in aerosol form to 30 rabbits.\(^24\) Six rabbits were killed immediately after administration of the fluorescent particles (baseline group); 12 rabbits were given a diethylhexyl sodium sulfosuccinate aerosol prepared as a 2% solution in equal volumes of ethanol and physiological saline (detergent group) and 12 were given vehicle aerosol (control group). The detergent and control aerosols were administered as 200 pressure-controlled breaths at a frequency of 40/min, resulting in deposition of approximately 10 µl of fluid in the lungs; aerosol administration was repeated after 90 min. Groups of six animals from the detergent and control groups were then exposed to large
tinal volume ventilation (LTVV) or conventional ventilation for 3 h. The total number of particles in the alveoli and ducts were similar for all groups, except for a statistically significant decrease in the control LTVV group. All test groups had reduced number of single particles in the alveoli as compared to the baseline group. The number of clustered particles was statistically significantly increased in the alveoli + ducts in the detergent-LTVV group, as compared to the baseline group. Rabbits were administered [99mTc]diethylene triamine pentaacetaete (99mTc-DTPA) using a nebulizer, and the effect of diethylhexyl sodium sulfosuccinate on the absorption of this compound from the lungs was examined. The alveolo-capillary transfer of 99mTc-DTPA was measured for 30 min, and the rabbits were then nebulized with 0.2% solution of diethylhexyl sodium sulfosuccinate for 5 min. Thirty min later, the rabbits were nebulized with a 2% diethylhexyl sodium sulfosuccinate solution for 5 min. Diethylhexyl sodium sulfosuccinate greatly enhanced the alveolar absorption of 99mTc-DTPA.

Ocular Irritation
Refer to Table 1 for a summary of ocular irritation data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

Diethylhexyl sodium sulfosuccinate, 0.1 g, was instilled into the conjunctival sac of the eyes of six rabbits. The eyes were scored for irritation after 24, 48, and 72 h, and the following scores were reported: 11.66, 12.50, and 4.16, respectively, (cornea); 1.66 at all three times (iris); and 5.33, 4.33, and 1.66, respectively (conjunctiva). No destruction or irreversible changes of the tissue in 24 h were reported.

Diethylhexyl sodium sulfosuccinate, 10%, was used as a positive control in a Draize eye irritancy test. One-tenth ml of the test substance was instilled into the conjunctival sac of one eye of each of three rabbits for 2 sec; the eyes were rinsed. Diethylhexyl sodium sulfosuccinate, 10%, was severely irritating to rabbit eyes, inducing perforated damages. Diisobutyl sodium sulfosuccinate is irritating to eyes and mucous membranes. (Details were not provided.)

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY
Refer to Table 1 for a summary of reproductive developmental toxicity data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

In developmental toxicity studies, groups of 20 gravid female mice and 20 gravid female rats were dosed by gavage with 0, 16, 80, or 400 mg/kg bw of a test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate. The mice were dosed on days 6-15 and killed on day 17 of gestation and the rats were dosed on days 5-19 of gestation and killed on day 20 of gestation. The NOAEL for maternal toxicity and teratogenic effects for both mice and rats was 400 mg/kg bw of the test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate.

Groups of 20-39 gravid female Sprague-Dawley rats were fed a diet containing 0, 1, or 2% diethylhexyl sodium sulfosuccinate (equivalent to 0, 1074, and 1983 mg/kg bw, respectively) on days 6-15 of gestation, and the dams were killed on day 21 of gestation. No adverse effects on maternal or fetal parameters were observed in the 1% test group. In the 2% test group, significant incidences of resorptions and gross abnormalities, primarily exencephaly and, at times, spina bifida, anophthalmia, and associated skeletal defects, were reported. The NOAEL for maternal toxicity and teratogenic effects was 1%.

Groups of 30 female rats were dosed by gavage with 0, 16, 80, or 400 mg/kg bw of a test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate once daily for 14 days prior to mating with untreated males; one-half of the animals in each group were dosed until day 13 of gestation, at which time the animals were killed, and the remaining animals were dosed until parturition and were not killed. No effects on reproductive parameters, fertility, or pup weight and condition were observed. The parental NOAEL was 400 mg/kg bw of the test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate.

A three-generation study was performed in which male and female CFE rats were continuously fed a diet containing 0.5 and 1% of a test substance containing 50% diethylhexyl sodium sulfosuccinate in aq. beverage-grade ethanol; the control group was untreated. The number of animals per group was not stated. Dosing was initiated at weaning of rats of the F₀ generation; these rats were mating twice to produce the F₁a and F₁b generation. Rats of the F₁b generation were mated to produce the F₂ generation, and the F₂ generation was mated twice to produce the F₃a and F₃b offspring. F₁a and F₃b offspring were the only pups weaned directly to the test diets. Because of a high incidence of pup mortality, all other dams were given a control diet on the last expected day of gestation. Necropsy and microscopic examination were performed only on pups from the first mating of the F₂ animals that died or were killed at weaning.

Up until the F₂ generation, body weights in parental males were 6-10% lower than control body weights. There were no significant treatment-related effects on mean litter size and the mean number of viable pups in each litter or on fertility or gestational indices. For all pups of the F₁a generation, including controls, the number of pups weaned and the average body weight of those pups at weaning was reduced; however, greater reductions were seen in the test groups than in the control group. The viability indices of the F₃b pups receiving the test diet were reduced. The researchers stated the most remarkable result of the study was the reduced number of offspring surviving from day 5 until weaning; it was hypothesized that pups
stopped nursing because they could taste the test article. A no-observed effect level (NOEL) for parental toxicity and effects on pups was not established; the NOEL for reproduction was 1%.

**GENOTOXICITY**

Refer to Table 1 for a summary of genotoxicity data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

**CARCINOGENICITY**

Effect on Colorectal Carcinogenesis

A group of 84 inbred male F344 rats was fed a diet containing 1% diethylhexyl sodium sulfosuccinate, and the control group was fed untreated feed. As part of a rodent model for colon carcinogenesis, rats of both groups were given a subcutaneous injection of 20 mg/kg bw of 1,2-dimethylhydrazine, once weekly for 20 wks. Twenty rats per group were killed after 3, 4, 5, and 6 mos. The test group tolerated the diethylhexyl sodium sulfosuccinate feed well. There was no statistically significant difference between the test and control group in the percentage of rats bearing tumors, and the number of tumors per rat increased progressively throughout the study. However, at 5 and 6 mos, each rat in the test group had fewer tumors of all histologic types (combined), at all organ sites, compared to controls; this difference was statistically significant for the duodenum, colon, rectum, and total number of gastrointestinal tumors at 5 mos.

**IRRITATION AND SENSITIZATION**

Dermal Irritation and Sensitization

Non-Human

Refer to Table 1 for a summary of non-human dermal irritation and sensitization data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

Occlusive patches containing 0.5 ml diethylhexyl sodium sulfosuccinate were applied to intact and abraded skin of six rabbits; the duration of exposure was not stated. For intact skin, the mean Draize scores for erythema and edema were 2.33 and 2.50, respectively, after 24 h and 1.66 and 1.0, respectively, after 72 h. For abraded skin the mean scores for erythema and edema were 2.50 and 2.50, respectively, after 24 h and 1.66 and 1.60, respectively, after 72 h.

Human

Refer to Table 1 for a summary of human dermal irritation and sensitization data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

Diethylhexyl sodium sulfosuccinate produced irritation, but it was not a sensitizer. For induction, a 15 mm occlusive patch containing 0.30 g of 2.5% ethylhexyl sodium sulfosuccinate in petrolatum was applied to the backs or forearms of 100 subjects; the patches were applied for 10 alternate 24-h periods. Challenge patches containing 0.30 g diethylhexyl sodium sulfosuccinate were applied to a previously untreated site on the back or forearm following a 7-day non-treatment period. The challenge sites were scored upon patch removal and 24 h later. During induction, the following observations were made: mild erythema in 11 subjects on days 3-10 and in 1 subject on days 3-7; mild erythema on all days except day 7 and intense erythema on day 7 in one subject; mild erythema on days 3-6/7 followed by intense erythema on days 6/7-10 in 6 subjects. No reactions were observed at challenge.

In a case report, a female subject had allergic contact dermatitis from diethylhexyl sodium sulfosuccinate that was an ingredient in a topical corticosteroid. In patch testing, the patient had a +++ reaction to 1% aq. diethylhexyl sodium sulfosuccinate on day 2 and day 4. The researchers noted that this was a rare reaction.

Phototoxicity/Photoallergenicity

Human

Refer to Table 1 for a summary of human phototoxicity data from the original safety assessment on diethylhexyl sodium sulfosuccinate.

**SUMMARY**

Diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate), an anionic surfactant, was reviewed by the CIR Expert Panel in 1994, and the report was amended in 1998. In 1998, the Panel concluded that diethylhexyl sodium sulfosuccinate is safe as used in cosmetic formulations. Since the 1998 report was issued, the number of reported uses in cosmetic formulations has increased from 35 to 62 uses. However, the concentration of use has not changed. The data that were available for the 1998 report indicated that diethylhexyl sodium sulfosuccinate was used in a variety of product-types at concentrations of ≤5%; current information report that the maximum use concentration is 4.4% in eyebrow pencil formulations.

The Panel has determined that the data included in the original safety assessment, as well as in this re-review document, support the safety of an additional seven dialkyl sulfosuccinate salts. These salts, which are diesters of 2-sulfosuccinic acid,
all share a sulfo-substituted, succinic acid core; all contain an ester linkage, and are theoretically sensitive to hydrolysis, especially under acidic conditions; and all are anionic surfactants.

Metabolism and excretion studies have given mixed results on the primary route of excretion of diethylhexyl sodium sulfosuccinate; it does appear that diethylhexyl sodium sulfosuccinate is metabolized prior to excretion, and most of the dose is excreted within 24 h of dosing. In one oral study in rats, 66% of the radioactivity was excreted in the feces and only 25-35% in urine, within 24-48 h after dosing. In other rat studies, with oral and i.v. administration, the majority of the radioactivity was excreted in the urine, rather than in the feces. Studies were also performed in rabbits and dogs, and again conflicting results were obtained. In rabbits, 87% and 69.7% of the radioactivity was excreted in the urine following oral and i.v. dosing, respectively; in dogs, approximately 70% of the radioactivity was excreted in the feces at 24-48 h after oral and i.v. dosing.

Diethylhexyl sodium sulfosuccinate increased the penetration of curcumin and resveratrol, in vitro, through excised guinea pig and Yucatan micro-pig skin.

The dermal LD_{50} of undiluted diethylhexyl sodium sulfosuccinate in rabbits was >10 g/kg; skin irritation was observed following the single dermal dose of 10 g/kg test material. The oral LD_{50} was 2.64 g/kg bw in male albino ARS/ICR mice and approximately 0.65 g/kg bw in guinea pigs.

In repeated-dose oral studies in which rats were given feed containing 1% diethylhexyl sodium sulfosuccinate for 90 days or up to 1.5% for 26 wks, and in studies in which Beagle dogs were given tablets containing 30 mg/kg bw/day diethylhexyl sodium sulfosuccinate for 1 yr, no remarkable toxic effects were reported. In an inhalation study in rabbits, a 5-min exposure to 0.2% DSS, followed 30 min later by a 5 min exposure to 2% diethylhexyl sodium sulfosuccinate, greatly enhanced the alveolar absorption of 99mTc-DTPA.

Diethylhexyl sodium sulfosuccinate was used as a positive control in a Draize ocular irritation study; 10% diethylhexyl sodium sulfosuccinate was severely irritating to rabbit eyes, inducing perforated damages.

Numerous studies examining the effect of the oral administration of diethylhexyl sodium sulfosuccinate, both dietary and by gavage, on the reproductive and developmental toxicity in rats were performed; one study was performed in mice. In a developmental study in mice and rats of a test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate, the NOAEL for maternal toxicity and teratogenic effects for both mice and rats was 400 mg/kg bw. In another developmental toxicity study in rats, the parental NOAEL was 400 mg/kg bw for a test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate. In a study in which gravid female Sprague-Dawley rats were fed a diet containing up to 2% diethylhexyl sodium sulfosuccinate, no adverse effects on maternal or fetal parameters were observed in the 1% test group, but in the 2% test group, significant incidences of resorptions and gross abnormalities, primarily exencephaly and, at times, spina bifida, anophthalmia, and associated skeletal defects, were reported. The NOAEL for maternal toxicity and teratogenic effects was 1%. In a three-generation study in which rats were fed a diet containing up to 1% of a test substance containing 50% diethylhexyl sodium sulfosuccinate in aq, beverage-grade ethanol, a NOEL for parental toxicity and effects on pups was not established because of reduced body weight gains in the parents and reduced viability indices in the pups, but the NOEL for reproduction was 1%; the reduced viability index most likely was attributed to the pups discontinuing nursing because they could taste the test article.

In rats, a diet containing 1% diethylhexyl sodium sulfosuccinate did not have an effect on 1,2-dimethylhydrazine-induced colorectal carcinogenesis.

In clinical studies, 2.5% diethylhexyl sodium sulfosuccinate was an irritant, but not a sensitizer.

**DISCUSSION**

The Expert Panel determined that the safety assessment on diethylhexyl sodium sulfosuccinate should be expanded to include the seven dialkyl sulfosuccinate salts that are listed in the International Cosmetic Ingredient Dictionary and Handbook. Although data were not available on most of these additional ingredients, the Panel found the existing data on diethylhexyl sodium sulfosuccinate to be sufficient to support the safety of this entire family of ingredients, stating that diethylhexyl sodium sulfosuccinate is a reasonable representative of all of the diesters; all of the diesters are of a similar alkyl chain length, all are symmetrically substituted, and all have similar functions in cosmetic formulations. In contrast to oral exposure, these esters are not expected to absorb through the skin to any significant extent, and the reproductive effects observed in test animals orally exposed to diethylhexyl sodium sulfosuccinate are not likely effects of topical application of cosmetics containing these ingredients. Consistent with this view, the Panel noted that acute dermal toxicity of undiluted diethylhexyl sodium sulfosuccinate was quite low, with a dermal LD_{50} of >10 g/kg in rabbits.

The Expert Panel recognized that the dialkyl sulfosuccinate salts may enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.
In addition, the Panel confirmed its original discussion, acknowledging that under the exaggerated exposure conditions of the two repeated insult patch tests (RIPTs; continuous occlusive patch testing) presented in the original safety assessment of sodium diethylhexyl sulfosuccinate, the ingredient is a cumulative irritant, though not a sensitizer. The Panel recognized that a surfactant would most likely produce irritation under such conditions. Therefore, Expert Panel specified that products containing dialkyl sulfosuccinate salts must be formulated to be non-irritating.

Finally, the Panel discussed the issue of incidental inhalation exposure from hair sprays. The limited data available from short-term pharmaceutical studies in test animals exposed to diethylhexyl sodium sulfosuccinate aerosols suggest little potential for respiratory effects. This ingredient is reportedly used at concentrations up to 0.25% in cosmetic products that may be aerosolized. The Panel noted that 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical properties and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for the dialkyl sulfosuccinate salts to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, genotoxicity and carcinogenicity. They noted the lack of systemic toxicity in several acute and subchronic oral exposure studies, little or no irritation or sensitization in tests of dermal and ocular exposure, the absence of genotoxicity in Ames tests, and the lack of carcinogenicity in a subchronic oral exposure study. A detailed discussion and summary of the Panel’s approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the following eight dialkyl sulfosuccinate salts are safe in the present practices of use and concentration in cosmetics described in this safety assessment when formulated to be non-irritating.

- Ammonium Dinonyl Sulfosuccinate*
- Diamyl Sodium Sulfosuccinate*
- Dicapryl Sodium Sulfosuccinate*
- Diethylhexyl Sodium Sulfosuccinate
- Diheptyl Sodium Sulfo succinate*
- Dihexyl Sodium Sulfosuccinate*
- Diisobutyl Sodium Sulfosuccinate*
- Ditridecyl Sodium Sulfosuccinate*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.
Structures

1. Ammonium Dinonyl Sulfosuccinate

\[
\text{NH}_4^+ \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{S} \quad \text{O}^- \quad \text{CH}_3
\]

2. Diamyl Sodium Sulfosuccinate

\[
\text{Na}^+ \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{S} \quad \text{O}^- \quad \text{CH}_3
\]

3. Dicapryl Sodium Sulfosuccinate

\[
\text{Na}^+ \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{S} \quad \text{O}^- \quad \text{CH}_3
\]

4. Diethylhexyl Sodium Sulfosuccinate

\[
\text{Na}^+ \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{S} \quad \text{O}^- \quad \text{CH}_3
\]

5. Diheptyl Sodium Sulfosuccinate

\[
\text{Na}^+ \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{S} \quad \text{O}^- \quad \text{CH}_3
\]
6. Dihexyl Sodium Sulfosuccinate

7. Diisobutyl Sodium Sulfosuccinate

8. Ditridecyl Sodium Sulfosuccinate
females of the 0.5 and 1.0% test groups were decreased, and the body weights of pups of (2 iethylhexyl sodium sulfosuccinate for 2 yrs.

Sensitization – Human

Dermal Irritation and Sensitization – Non-Human

Genotoxicity

Dermal Irritation and Sensitization – Human

Photoallergenicity

Table1. Data from the previous review of diethylhexyl sodium sulfosuccinate

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Summary data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of Manufacture</td>
<td>Maleic anhydride is reacted with 2-ethylhexanol to product bis(2-ethylhexyl)maleate, which is then combined with sodium bisulfite under conditions conducive to the formation of the sulfonate structure through rearrangement with an accompanying saturation of the olefinic bond</td>
</tr>
<tr>
<td>Single-Dose Toxicity - Oral</td>
<td>The oral LD&lt;sub&gt;50&lt;/sub&gt; in rats of a product containing 84% diethylhexyl sodium sulfosuccinate was 3.69 g/kg, and the LD&lt;sub&gt;50&lt;/sub&gt; of a commercially available diethylhexyl sodium sulfosuccinate, administered as a 10% aq. solution or as an emulsion, was 1.9 g/kg in female rats. In mice, the oral LD&lt;sub&gt;50&lt;/sub&gt; for a commercial product containing an unspecified amount of diethylhexyl sodium sulfosuccinate as the active ingredient was 4.8 g/kg, and the i.v. LD&lt;sub&gt;50&lt;/sub&gt; for the product was 0.06 g/kg.</td>
</tr>
<tr>
<td>Repeated Dose Toxicity - Dermal</td>
<td>Four ml/kg of a test article containing an effective dose of 0.00126% diethylhexyl sodium sulfosuccinate in formulation was applied to the backs of rats, 5 days/wk, for 67 wks. (It is not stated whether the applications were covered.) No remarkable toxic effects were noted. However, minimal to moderate skin irritation was observed sporadically throughout the study.</td>
</tr>
<tr>
<td>Repeated Dose Toxicity - Oral</td>
<td>Repeated dose oral toxicity studies were performed in the 1940s on diethylhexyl sodium sulfosuccinate in rats, dogs, and monkeys. No remarkable toxic effects were found in rats fed ≤1.25 g/kg bw for 24 wks, in dogs fed 0.10 or 0.25 g/kg bw of a commercial surfactant containing diethylhexyl sodium sulfosuccinate as the active ingredient for 24 wks, or in monkeys fed 0.125 g/kg of the same preparation for 24 wks. However, in a study in which male rats were fed 2, 4, or 8% diethylhexyl sodium sulfosuccinate for 4 mos, the researchers found these doses to be very toxic. Reduced body weight gains were reported in rats fed ≤1% diethylhexyl sodium sulfosuccinate for 2 yrs.</td>
</tr>
<tr>
<td>Repeated Dose Toxicity - Inhalation</td>
<td>Rats exposed to an aerosol of a product containing an effective diethylhexyl sodium sulfosuccinate concentration of 0.21% at an exposure concentration of 4.2 mg/m³, 4 h/day, 5 days/wk, for 13 wks, had significant changes in hematology and clinical chemistry parameters as compared to controls. Mongrel dogs were exposed for 30-45 min to a 1% solution of a commercial detergent containing diethylhexyl sodium sulfosuccinate in equal volumes of 95% ethanol and isotonic saline, at a final concentration of 15 mg/kg of the test material, and then killed 30 min, 2 h, or 4 h after exposure. Gross, but not microscopic changes in pulmonary structure and changes in pulmonary function were observed; the researchers suggested that the test article was capable of displacing the normal alveolar surfactant into the airway and resulted in increased alveolar surface tension and instability.</td>
</tr>
<tr>
<td>Ocular Irritation</td>
<td>In the eyes of rabbits, concentrations of ≥25% diethylhexyl sodium sulfosuccinate were severely irritating, and concentrations of ≤10% produced little or no irritation.</td>
</tr>
<tr>
<td>Reproductive and Developmental Toxicity</td>
<td>In a three-generation study, rats were fed 0, 0.1, 0.5, or 1.0% diethylhexyl sodium sulfosuccinate. Body weights of all parental males and in F&lt;sub&gt;1&lt;/sub&gt; and F&lt;sub&gt;2&lt;/sub&gt; females of the 0.5 and 1.0% test groups were decreased, and the body weights of pups of all three generations were decreased compared to controls. No effects on reproductive parameters, and no gross lesions or treatment-related mortalities, were observed.</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>Diethylhexyl sodium sulfosuccinate was not mutagenic in an Ames test, but with metabolic activation, it did induce chromosomal aberrations in Chinese hamster ovary cells at treatment doses close to threshold toxicity.</td>
</tr>
<tr>
<td>Dermal Irritation and Sensitization – Non-Human</td>
<td>In rats, a 24-h patch of 2% diethylhexyl sodium sulfosuccinate resulted in an irritation score of 3.7/8 for intact skin and 1.7/8 for abraded skin. In a single-insult occlusive patch test, a 10% solution of a product containing 84% diethylhexyl sodium sulfosuccinate in propylene glycol was minimally irritating to rabbit skin. In a 2-wk study, 10 applications of 1% diethylhexyl sodium sulfosuccinate to intact abdominal skin in rabbits resulted in moderate hyperemia; a test concentration of 5% produced a burn from two to four 24-h applications and of 25% produced a burn with one 24-h application. Application of 1, 5, and 25% diethylhexyl sodium sulfosuccinate to abraded rabbit abdominal skin for 3 days was moderately to severely irritating. In a study examining acanthosis following repeated (number not stated) dermal applications of 2, 10, and 20% diethylhexyl sodium sulfosuccinate, an acanthosis factor (AF) was calculated from the difference in epidermal thickness, with 1 unit being equivalent to 2.7 µm. The AFS were 1.8, 2.5, and 3.3, respectively.</td>
</tr>
<tr>
<td>Dermal Irritation and Sensitization – Human</td>
<td>In a 50-subject study, a single 24-h occlusive patch of a formulation containing 2.5% diethylhexyl sodium sulfosuccinate was not an irritant. In mini-cumulative irritancy tests, the primary irritation index (PII) of four products containing a 3.5% solution of 84% diethylhexyl sodium sulfosuccinate ranges from 0.25 – 0.80; the PIIs of two products containing a 0.25% solution of 84% diethylhexyl sodium sulfosuccinate were 1.78 and 1.85; and the PII of a product containing a 0.1% solution of 84% diethylhexyl sodium sulfosuccinate was 0.04. In a 21-day cumulative irritancy test of a product containing 1.13% solution of diethylhexyl sodium sulfosuccinate performed in 7 volunteers, the total irritation score was 324/578 for abraded skin. In a single 24-h occlusive patch of a formulation containing 2.5% diethylhexyl sodium sulfosuccinate in 25 subjects, there were no reactions during the induction or the challenge phase that were attributable to ethylhexyl sodium sulfosuccinate.</td>
</tr>
</tbody>
</table>
Table 2. Data on constituent alcohols

<table>
<thead>
<tr>
<th>Caprylic Alcohol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal Irritation – Non-Human</td>
<td>caprylic alcohol applied full strength to intact or abraded rabbit skin produced a mild irritation</td>
</tr>
<tr>
<td>Dermal Irritation and Sensitization – Human</td>
<td>tested in at a concentration of 2% in petrolatum, caprylic alcohol produced no irritation in a 48 h closed-patch test in 25 human subjects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isobuty1 Alcohol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated Dose Toxicity - Inhalation</td>
<td>rats (10/sex/group) were exposed via inhalation to isobutyl alcohol vapor concentrations of approximately 0, 770, 3100, or 7700 mg/m3, for 6 h/day, 5 days/week, for 14 weeks; the functional observational battery was conducted along with endpoints of motor activity, neuropathology and scheduled-controlled operant behavior; a slight reduction in responsiveness to external stimuli was observed in all treated groups during exposure; this effect resolved upon cessation of exposure to isobutyl alcohol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethylhexyl Alcohol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicokinetics</td>
<td>in vitro dermal absorption rates were determined for ethylhexyl alcohol in rats and humans; in rats, the rate was 0.22 mg/cm²/h and in the human it was 0.038 mg/cm²/h; accordingly, the human rate of ethylhexyl alcohol absorption was 5.78 times slower than the rate in the rat</td>
</tr>
<tr>
<td>Dermal Toxicity</td>
<td>in three different acute dermal toxicity studies on rabbits with ethylhexyl alcohol, the LD₅₀ values reported were 2380, &gt;2600 and &gt;5000 mg/kg bw; 10 rats were dosed with 2 ml/kg bw/day (1600mg/kg/day) via single application on shaved backs; absolute and relative thymus wts, liver granulomas, bronchiectasis in the lung, renal tubular epithelial necroses, edematous heart and testes, and spermatogenesis, all decreased; 10 rats/sex were dosed with 0, 500, or 1000 mg/kg bw/day (5 days occlusive, 2 days untreated, 4 days treated); 500 and 1000 mg treated rats exhibited minimal exfoliation, decreased spleen wt and increased serum triglycerides in females</td>
</tr>
<tr>
<td>Ocular Irritation</td>
<td>in three different acute dermal toxicity studies on rabbits with ethylhexyl alcohol, the LD₅₀ values reported were 2380, &gt;2600 and &gt;5000 mg/kg bw; 10 rats were dosed with 2 ml/kg bw/day (1600mg/kg/day) via single application on shaved backs; absolute and relative thymus wts, liver granulomas, bronchiectasis in the lung, renal tubular epithelial necroses, edematous heart and testes, and spermatogenesis, all decreased; 10 rats/sex were dosed with 0, 500, or 1000 mg/kg bw/day (5 days occlusive, 2 days untreated, 4 days treated); 500 and 1000 mg treated rats exhibited minimal exfoliation, decreased spleen wt and increased serum triglycerides in females</td>
</tr>
<tr>
<td>Dermal Irritation – Non-Human</td>
<td>ethylhexyl alcohol was applied under occlusion to the skin of 3 male rabbits for 4 hours and found to be irritating; in another study with rabbits, 0.5 ml of ethylhexyl alcohol was applied under occlusion on intact skin for 1, 2, 4, and 24 hours; irritation was considered high, and effects seen after 7 days were not reversible</td>
</tr>
<tr>
<td>Dermal Irritation and Sensitization - Human</td>
<td>tested at a concentration of 4% in petrolatum, ethylhexyl alcohol produced no irritation in a 48 h occlusive-patch test in 29 male volunteers; in a maximization study, ethylhexyl alcohol did not induce any sensitization reactions</td>
</tr>
<tr>
<td>Reproductive and Developmental Toxicity</td>
<td>a group of female rats was exposed for 7 h/day to 850 mg/m³ of ethylhexyl alcohol on gestation days 1-19; dams were sacrificed at day 20; ethylhexyl alcohol reduced maternal feed intake, but did not produce any malformations; the estrogenic activity of 2-ethylhexanoic acid was examined using an E-SCREEN assay using T47D human breast cancer cells; weak estrogenic activity was observed; additional details were not provided</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>in vitro, ethylhexyl alcohol was negative in a number of Ames assays, a liquid suspension assay, mouse lymphoma assay, and unscheduled DNA synthesis assay; in a ³H-thymidine assay, there was a dose-dependent inhibition of ³H-thymidine incorporation into replicating DNA, with a dose-dependent increase in the ratio of acid-soluble DNA incorporated into the thymidine; the urine of rats dosed orally with 1000 mg/kg bw ethylhexyl alcohol was not mutagenic; in vivo, ethylhexyl alcohol was not genotoxic in a mouse micronucleus test or a transformation assay</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>B6C3F₁ mice (50/sex/group) were administered 0, 50, 200, or 750 mg/kg bw/day via gavage, 5 days/wk for 18 mos; at the 750 mg/kg dose, weak hepatocellular carcinoma increased in females, bw gain decreased and mortality increased; F344 rats (50/sex/group) were administered 0, 50, 150, or 500 mg/kg bw/day via gavage, 5 days/wk for 24 mos; rats dosed ≥150 mg/kg were characterized with bw gain decrease, lethargy and unkemptness; at 500 mg/kg, mortality in females was at 52%</td>
</tr>
</tbody>
</table>

Table 3. Definitions and Functions

<table>
<thead>
<tr>
<th>Ingredient/CAS No.</th>
<th>Definition¹</th>
<th>Function²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyhexyl Sodium Sulfo succinate 377-11-7</td>
<td>the sodium salt of the diester of 2-ethylhexyl alcohol and sulfosuccinic acid</td>
<td>surfactant – cleansing agent; hydrotrope</td>
</tr>
<tr>
<td>Ammonium Dinonyl Sulfo succinate 27501-55-9</td>
<td>the ammonium salt of a nonyl alcohol diester of sulfosuccinic acid</td>
<td>surfactant – cleansing agent</td>
</tr>
<tr>
<td>Diamyl Sodium Sulfo succinate 922-80-5</td>
<td>the sodium salt of the diester of amyl alcohol and sulfosuccinic acid; the amyl or 1-methylbutyl diester of the monosodium salt of sulfosuccinic acid or a mixture of both</td>
<td>surfactant - hydrotrope</td>
</tr>
<tr>
<td>Dicapryl Sodium Sulfo succinate 1639-66-3</td>
<td>the sodium salt of the diester of an capryl alcohol and sulfosuccinic acid</td>
<td>surfactant - hydrotrope</td>
</tr>
<tr>
<td>Diheptyl Sodium Sulfo succinate 4680-44-8</td>
<td>the sodium salt of the diester of a heptanol and sulfosuccinic acid</td>
<td>surfactant - hydrotrope</td>
</tr>
<tr>
<td>Diethylamyl Sodium Sulfo succinate 6001-97-4</td>
<td>the sodium salt of the diester of 1-methylamyl alcohol and sulfosuccinic acid; the bis(1-methylamyl) ester of sulfosuccinic acid monosodium salt, perhaps in an admixture with the diethyl ester</td>
<td>surfactant - hydrotrope</td>
</tr>
</tbody>
</table>
### Table 4. Physical and chemical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ammonium Dinonyl Sulfosuccinate</strong></td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>molecular wt</td>
<td>467.66</td>
<td></td>
</tr>
<tr>
<td>physical appearance</td>
<td>mixture of white, hard pellets and powder</td>
<td></td>
</tr>
<tr>
<td>molecular wt</td>
<td>444.56</td>
<td></td>
</tr>
<tr>
<td>melting point</td>
<td>153-157°C</td>
<td>4</td>
</tr>
<tr>
<td>partition coefficient</td>
<td>approx., 3.95 (25°C; estimated)</td>
<td>23</td>
</tr>
<tr>
<td>density</td>
<td>1.1 g/m³</td>
<td>4</td>
</tr>
<tr>
<td>solubility</td>
<td>soluble in water and in organic solvents, especially in water and water-miscible solvent combinations</td>
<td>1</td>
</tr>
<tr>
<td>stability</td>
<td>stable in acid and neutral solutions; hydrolyzes in alkaline solutions</td>
<td>5</td>
</tr>
</tbody>
</table>

**Diamyl Sodium Sulfosuccinate**

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>molecular wt</td>
<td>445.57</td>
<td></td>
</tr>
<tr>
<td>physical appearance</td>
<td>waxy solid; usually in rolls of tissue-thin material</td>
<td></td>
</tr>
<tr>
<td>molecular wt</td>
<td>444.56</td>
<td></td>
</tr>
<tr>
<td>melting point</td>
<td>150-157°C</td>
<td>4</td>
</tr>
<tr>
<td>partition coefficient</td>
<td>approx., 3.95 (25°C; estimated)</td>
<td>23</td>
</tr>
<tr>
<td>density</td>
<td>1.1 g/m³</td>
<td>4</td>
</tr>
<tr>
<td>solubility</td>
<td>soluble in water and in organic solvents, especially in water and water-miscible solvent combinations</td>
<td>1</td>
</tr>
<tr>
<td>stability</td>
<td>acid and neutral solutions are stable; alkaline solutions hydrolyze</td>
<td>1</td>
</tr>
</tbody>
</table>

**Dicapryl Sodium Sulfosuccinate**

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>molecular wt</td>
<td>416.51</td>
<td></td>
</tr>
<tr>
<td>physical appearance</td>
<td>white, slightly hygroscopic, wax-like pellets</td>
<td></td>
</tr>
<tr>
<td>molecular wt</td>
<td>388.45</td>
<td></td>
</tr>
<tr>
<td>melting point</td>
<td>153-157°C</td>
<td>4</td>
</tr>
<tr>
<td>partition coefficient</td>
<td>approx., 3.95 (25°C; estimated)</td>
<td>23</td>
</tr>
<tr>
<td>density</td>
<td>1.1 g/m³</td>
<td>4</td>
</tr>
<tr>
<td>solubility</td>
<td>must be soaked to dissolve in cold water; dissolves rapidly in hot water</td>
<td>6</td>
</tr>
<tr>
<td>stability</td>
<td>stable in acid and neutral solutions; hydrolyzes in alkaline solutions</td>
<td>6</td>
</tr>
</tbody>
</table>

**Dihexyl Sodium Sulfosuccinate**

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>physical appearance</td>
<td>white, powder-like, easily grindable material</td>
<td></td>
</tr>
<tr>
<td>molecular wt</td>
<td>322.35</td>
<td>7</td>
</tr>
<tr>
<td>solubility</td>
<td>must be soaked to dissolve in cold water; dissolves rapidly in hot water</td>
<td>7</td>
</tr>
<tr>
<td>stability</td>
<td>stable in acid and neutral solutions; hydrolyzes in alkaline solutions</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 5. Current and historical frequency and concentration of use of diethylhexyl sodium sulfosuccinate according to duration and exposure

<table>
<thead>
<tr>
<th></th>
<th>2013¹</th>
<th>1995¹</th>
<th>2013¹</th>
<th>1984¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of Uses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>62</td>
<td>38</td>
<td>0.0002-4.4</td>
<td>5**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Duration of Use</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leave-On</td>
<td>34</td>
<td>21</td>
<td>0.0002-4.4</td>
<td>**</td>
</tr>
<tr>
<td>Rinse-Off</td>
<td>25</td>
<td>12</td>
<td>0.1-1.2</td>
<td>**</td>
</tr>
<tr>
<td>Diluted for (Bath) Use</td>
<td>3</td>
<td>5</td>
<td>NR</td>
<td>**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Exposure Type</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Area</td>
<td>14</td>
<td>5</td>
<td>0.06-4.4</td>
<td>**</td>
</tr>
<tr>
<td>Incidental Ingestion</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>**</td>
</tr>
<tr>
<td>Incidental Inhalation-Spray</td>
<td>NR</td>
<td>NR</td>
<td>0.15 (aerosol)</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.25 (pump spray)</td>
<td>**</td>
</tr>
<tr>
<td>Incidental Inhalation-Powder</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>**</td>
</tr>
<tr>
<td>Dermal Contact</td>
<td>28</td>
<td>30</td>
<td>0.0002-4.4</td>
<td>**</td>
</tr>
<tr>
<td>Deodorant (underarm)</td>
<td>2*</td>
<td>NR</td>
<td>0.0002</td>
<td>**</td>
</tr>
<tr>
<td>Hair - Non-Coloring</td>
<td>12</td>
<td>1</td>
<td>0.15-0.75</td>
<td>**</td>
</tr>
<tr>
<td>Hair-Coloring</td>
<td>10</td>
<td>5</td>
<td>NR</td>
<td>**</td>
</tr>
<tr>
<td>Nail</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>**</td>
</tr>
<tr>
<td>Mucous Membrane</td>
<td>3</td>
<td>5</td>
<td>NR</td>
<td>**</td>
</tr>
<tr>
<td>Baby Products</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>**</td>
</tr>
</tbody>
</table>

*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.

**Only the maximum reported concentration of use was reported in the 1998 safety assessment.

* It is not know whether or not these products are sprays.

NR – no reported use
REFERENCES


23. US Environmental Protection Agency. High Production Volume Information System (HPVIS). Detailed chemical results for butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt; CAS no. 577-11-7. N:\CIR\New N Drive\Production\Alkyl Sulfosuccinate Salts\Prelim data\High Production Volume Information System (HPVIS) OPPT US EPA_files\High Production Volume Information System (HPVIS) OPPT US EPA.htm. Date Accessed 4-23-2013.


