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Amended Safety Assessment of Dodecylbenzenesulfonate, Decylbenzenesulfonate, and Tridecylbenzenesulfonate Salts as Used in Cosmetics

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Abstract

Sodium dodecylbenzenesulfonate is one of a group of salts of alkylbenzene sulfonates used in cosmetics as surfactant-cleansing agents. Sodium dodecylbenzenesulfonate is soluble in water and partially soluble in alcohol, with dermal absorption dependent on pH. Dodecylbenzenesulfonate salts are not toxic in single-dose oral and dermal animal tests, and no systemic toxicities were observed in repeat-dose dermal animal studies. In dermal animal studies, no evidence of reproductive or developmental toxicity was reported. At 15% concentrations, sodium dodecylbenzenesulfonate was severely irritating to rabbit skin. The Cosmetic Ingredient Review Expert Panel concluded that the irritant properties of these ingredients are similar to those of other detergents, with severity dependent on concentration and pH. Products containing these ingredients should be formulated to ensure that the irritancy potential is minimized.

Keywords

safety, cosmetics, dodecylbenzenesulfonate, decylbenzenesulfonate, tridecylbenzenesulfonate salts

Introduction

The Cosmetic Ingredient Review (CIR) Expert Panel reviewed the safety of sodium dodecylbenzenesulfonate (SDDBS), triethanolamine-dodecylbenzenesulfonate (TEA-DDBS), and sodium decylbenzenesulfonate as used in cosmetics in an earlier report, with the conclusion that these ingredients were safe as cosmetic ingredients in the (then) present practices of use.[1] The summary of that report stated the following.

The oral median lethal dose (LD_{50}) for sodium dodecylbenzenesulfonate (SDDBS) in rats was 1.26 g/kg. No significant toxic effects were observed when rats were given oral doses of 1000 ppm SDDBS in water. No systemic toxicity was observed in rabbits given dermal applications of 10% or less SDDBS to abraded skin for 28 days; severe dermal irritation was observed at the application site. Mild necrosis of internal mucosa with hemosiderosis of the spleen, liver, and kidneys was observed in rats given a varying dosage of 2.5-5.0 mL/kg per d of a formulation containing 15% SDDBS for a total of 22 weeks; lesions were not observed for rats given 0.5 mL/kg per d. Renal damage was observed in rats dosed orally with 0.6% or less SDDBS for 6 months. For dogs fed 1000 mg/kg per d or less of a formulation containing 15% SDDBS in the diet for 6 months, hemorrhagic necrosis of the intestine and infiltration of inflammatory cells were observed at 10 mg/kg and hemosiderosis of the liver and spleen was observed at 100 and 1000 mg/kg. SDDBS, adjusted to 15% active and a pH of 7.0, applied to intact and abraded sites was severely irritating. A solution containing 1.9% SDDBS and 1.9% tallow alkyl ethoxylate sulfate was moderately irritating to the skin of rabbits. This compound was not a sensitizer when tested at low concentrations. Concentrations of 5% or greater linear alkylbenzene sulfonate (LAS) were irritants to the eyes of rabbits; 0.1% or less of LAS produced mild to no irritation. (LAS is a commercial preparation that has the average molecular weight of SDDBS.) No reproductive effects were produced by dermal application of LAS or TEA-DDBS or by oral administration of LAS. The results of mutagenic assays using SDDBS were

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Table 1. Cosmetic Ingredients With DEA, MIPA, or TEA Reviewed by CIR

Ingredient	Conclusion	Reference
DEA and TEA		
TEA and DEA	Safe in rinse-off products; safe at less than 5% in leave-on-products; should not be used where *N*-nitroso compounds could be formed	2
DEA-containing ingredients		
Cocamide DEA	Safe in rinse-off products; safe at less than 10% in leave-on products; should not be used where *N*-nitroso compounds could be formed	3
	Safe in rinse-off products; safe at less than 10% in leave-on products; should not be used where *N*-nitroso compounds could be formed	4
Isostearamide DEA	Safe in rinse-off products; safe at less than 40% in leave-on products (which would limit ethanolamines to 5%); should not be used where *N*-nitroso compounds could be formed	5
Lauramide DEA	Safe in rinse-off products; safe at less than 10% in leave-on products; should not be used where *N*-nitroso compounds could be formed	4
Linoleamide DEA	Safe in rinse-off products; safe at less than 10% in leave-on products; should not be used where *N*-nitroso compounds could be formed	4
Myristamide DEA	Safe in rinse-off products; safe at less than 40% in leave-on products (which would limit ethanolamines to 5%); should not be used where *N*-nitroso compounds could be formed	5
Stearamide DEA	Safe in rinse-off products; safe at less than 40% in leave-on products (which would limit ethanolamines to 5%); should not be used where *N*-nitroso compounds could be formed	5
TEA-containing ingredients		
TEA-Cocoyl	Safe as a cosmetic ingredient	6
Hydrolyzed collagen	Confirmed	7
TEA-EDTA	Safe as a cosmetic ingredient	8
TEA-lauryl sulfate	Safe up to 10.5%, formulate to not cause irritation	9
MIPA		
MIPA[a]	Safe as cosmetic ingredients	10
Monisopropanolamine	Confirmed	4

Abbreviations: CIR, cosmetic ingredient review; DEA, diethanolamine; TEA, triethanolamine; MIPA, monoisopropanolamine.
[a] Included diisopropanolamine, triisopanolamine, and mixed isopropanolamines.

negative. Dermal carcinogenicity studies using LAS and TEA-DDBS and oral carcinogenicity studies using SDDBS and LAS were negative. On the basis of the animal and clinical data presented in this report, it is concluded that sodium dodecylbenzenesulfonate, TEA-DDBS, and sodium decylbenzenesulfonate are safe as cosmetic ingredients in the present practices of use.

In a re-review of this earlier safety assessment, the CIR Expert Panel determined that the available data were sufficient to support the safety of the entire group of salts of sulfonated alkylbenzenes used in cosmetics. Accordingly, this safety assessment has been expanded to include the following:

- Ammonium Dodecylbenzenesulfonate,
- Calcium Dodecylbenzenesulfonate,
- DEA-Dodecylbenzenesulfonate,
- Isopropylamine Dodecylbenzenesulfonate,
- Magnesium Isododecylbenzenesulfonate,
- MIPA-Dodecylbenzenesulfonate,
- Potassium Dodecylbenzenesulfonate,
- Sodium Decylbenzenesulfonate,
- Sodium Dodecylbenzenesulfonate,
- Sodium Tridecylbenzenesulfonate,
- TEA-Dodecylbenzenesulfonate (TEA-DDBS), and
- TEA-Tridecylbenzenesulfonate.

Sodium dodecylbenzenesulfonate is an LAS. As described in the original safety assessment,[1] LAS is not a specific chemical name but the name used to describe the material studied in several publications. Linear alkylbenzene sulfonate can be considered to have an average molecular weight close to that of SDDBS but could contain some of alkyl groups of similar size. Also, the point of attachment of the benzene ring to the alkyl chain would be distributed along the chain, with attachment at the number 2 carbon being prominent; several isomers would be present. Data from 3 manufacturers reported in the original safety assessment, for example, demonstrated that a 12-carbon chain length moiety comprises 18.1% to 35.0% and a 10-carbon chain length moiety comprises 0.5% to 20.6% of commercial LAS products.

The CIR Expert Panel also has reviewed the safety of several ingredients that form a portion of the ingredient structures addressed in this safety assessment. These include diethanolamine (DEA), triethanolamine (TEA), and monoisopropanolamine (MIPA). Table 1 lists these and related ingredients and the conclusion regarding safety reached by CIR.

Table 2. Ingredient Names, CAS Numbers, Technical, and Other Names as Listed in the International Ingredient Dictionary and Handbook[11]

Ingredient (CAS No)	Technical/Other Names
Ammonium dodecylbenzenesulfonate (CAS No 1331-61-9)	Ammonium lauryl benzene sulfonate and benzenesulfonic acid, dodecyl- ammonium salt
Calcium dodecylbenzenesulfonate (CAS No 26264-06-2)	Benzenesulfonic acid, dodecyl- calcium salt, and dodecylbenzenesulfonic acid, calcium salt
DEA-dodecylbenzenesulfonate (CAS No 26545-53-9)	Benzenesulfonic acid, dodecyl-, compared with 2,2'-iminobis[ethanol](1:1) and diethanolamine dodecylbenzene sulfonate
Isopropylamine dodecylbenzenesulfonate (CAS No 26264-05-1)	Benzenesulfonic acid, dodecyl-, compared with 2-propanamine (1:1); dodecylbenzenesulfonic acid, compared with 2-propanamine (1:1); and sopropylammonium Dodecylbenzenesulfonate
Magnesium isododecylbenzenesulfonate (CAS No 27479-45-4)	None listed
MIPA-dodecylbenzenesulfonate (CAS No 42504-46-1, 54590-52-2)	Benzenesulfonic acid, dodecyl-, compared with 1-amino-2-propanol (1:1) and monoisopropanolamine dodecylbenzenesulfonate
Potassium dodecylbenzensulfonate (CAS No 27177-77-1)	Benzenesulfonic acid, dodecyl-, potassium salt, and dodecylbenzenesulfonic acid, potassium salt
Sodium decylbenzenesulfonate (CAS No 1322-98-1)	Benzenesulfonic acid, decyl-, sodium salt, and decylbenzenesulfonic acid, sodium salt
Sodium dodecylbenzenesulfonate (CAS No 25155-30-0)	Sodium lauryl benzene sulfonate; benzenesulfonic acid, dodecyl-, sodium salt; dodecylbenzenesulfonic acid, sodium salt; and sodium lauryl phenyl sulfonate
Sodium tridecylbenzenesulfonate (CAS No 26248-24-8)	Benzenesulfonic acid, tridecyl- sodium salt and tridecylbenzenesulfonic acid, sodium salt
TEA-dodecylbenensulfonate (CAS No 27323-41-7)	Benzenesulfonic acid; dodecyl-, compared with 2,2'2"-nitrilotris (ethanol [1:1]); dodecylbenzenesulfonic acid, compared with 2,2',2"-nitrilotris (ethanol [1:1]); and triethanolamine dodecylbenzenesulfonate
TEA-tridecylbenzenesulfonate (CAS No. 59599-58-5, 61886-59-7)	Benzenesulfonic acid, tridecyl-, compared with 2,2',2"-nitrilotris (ethanol [1:1]); tridecylbenzenesulfonic acid, compared with 2,2',2"-nitrolotris (ethanol [1:1]); and triethanolamine tridecylbenzenesulfonate

Abbreviations: CIR; cosmetic ingredient review; DEA, diethanolamine; TEA, triethanolamine; MIPA, monoisopropanolamine.

This safety assessment presents and discusses new data not previously considered by CIR.

Chemistry

Definition and Structure

The definitions and technical/other names of the cosmetic ingredients included in this assessment as given in the *International Cosmetic Ingredient Dictionary and Handbook*[11] are listed in Table 2. All of these ingredients are in the chemical class alkyl aryl (benzene) sulfonates and function as surfactant-cleansing agents (Figure 1).

Sodium decylbenzenesulfonate is also known as decyl benzene sodium sulfonate and sodium decylbenzenesulfonamide.[12]

Sodium dodecylbenzenesulfonate is also known as dodecyl benzene sodium sulfonate; dodecylbenzenesulphonate, sodium salt; sodium laurylbenzenesulfonate[12]; and dodecylbenzene sodium sulfonate.[13]

Triethanolamine-dodecylbenzenesulfonate is also known as LAS and triethanolamine salt.[14]

Chemical and Physical Properties

Sodium dodecylbenzensulfonate is commercially available as a yellow slurry or off-white dry product.[15] The slurry is usually 30% to 50% active (percentage activity defined as solids minus salts.[16] The dry product, which can be in the form of a powder, flake, or bead, is usually 40% to 90% active. The chemical and physical properties of SDDBS are summarized in Table 3.

Triethanolamine-dodecylbenzenesulfonate is a clear yellow liquid that is commercially available as 40% to 60% aqueous solutions.[17] Properties of TEA-DDBS are also summarized in Table 3.

Sodium decylbenzenesulfonate has a molecular weight of 320.46.[12] Chemical and physical properties were not available for the other ingredients in this safety assessment.

Manufacture and Production

Sodium dodecylbenzenesulfonate is made by reacting dodecylbenzene with sulfuric acid (oleum process) or air/SO_2 to produce dodecylbenzene sulfonic acid.[17] The dodecylbenzenesulfonic acid is then neutralized with sodium hydroxide. Sodium dodecylbenzenesulfonate is then sold as a slurry. It can be dried by a drum drier to form flakes and powders or dried by a spray drier to form beads.

Triethanolamine-dodecylbenzenesulfonate is made by reacting dodecylbenzenesulfonate with sulfuric acid (oleum process) and air/SO_2, to produce dodecylbenzene sulfonic

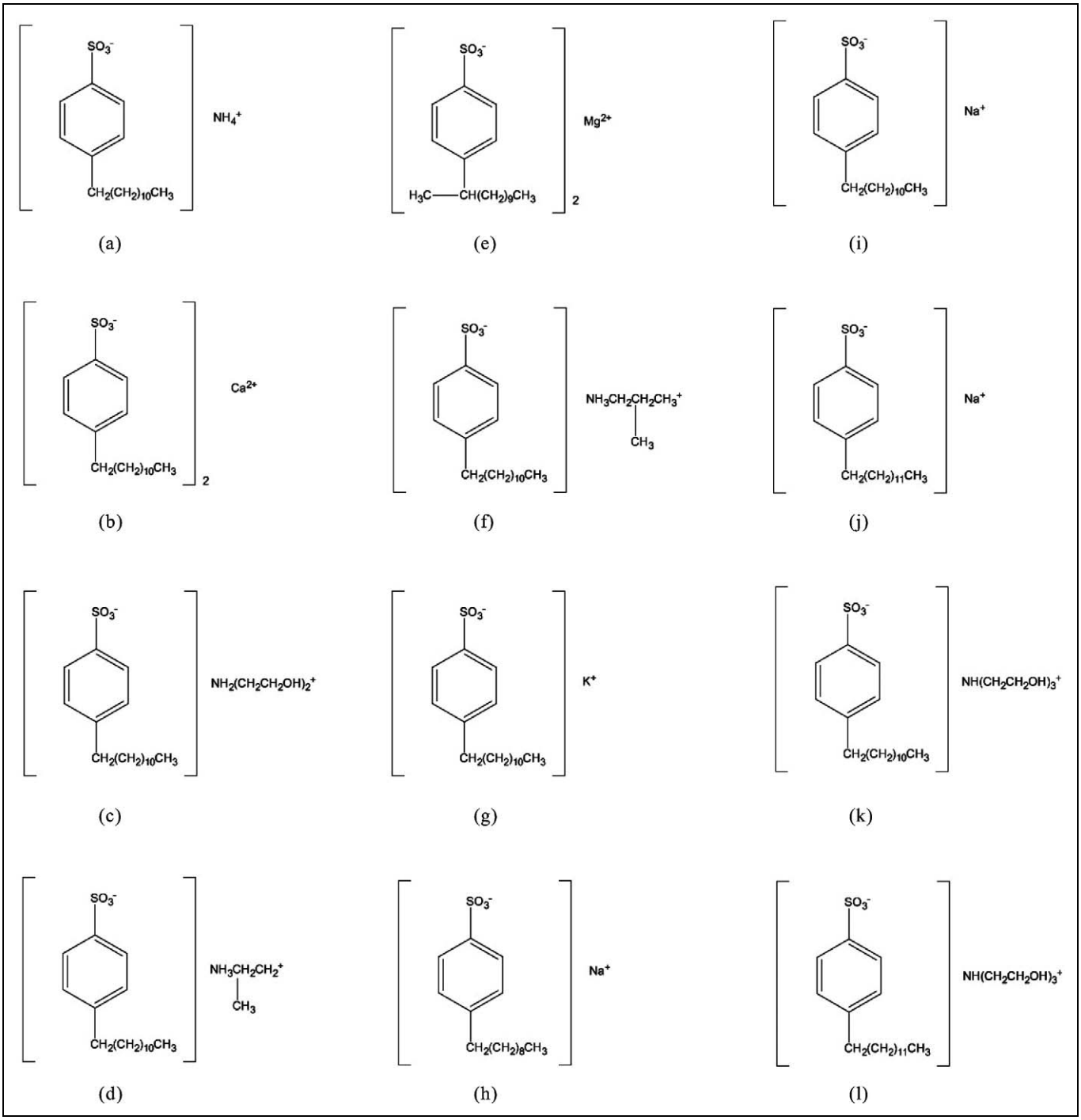

Figure 1. The structures of the cosmetic ingredients addressed in this safety assessment.

acid.[17] The dodecylbenzene sulfonic acid is then neutralized with triethanolamine.

Linear alkylbenzene sulfonate is made by the sulfonation of straight-chain alkylbenzenes prepared from petroleum distillates.[16] In 1987, approximately 2.15 billion pounds of LAS were used in North America, Western Europe, and Japan, with dodecylbenzenesulfonate being the most widely used.[17]

Analytical Methods

Sodium dodecylbenzenesulfonate was analyzed by high-pressure liquid chromatography (HPLC) and Karl Fisher titration.[18]

Two-phase titration can be used for the determination of total cationic or anionic surfactants in mixtures.[20,21]

Linear alkylbenzene sulfonate was determined by HPLC[22]; by spectroscopic methods, particularly HPLC with UV detection; by chromatographic techniques; by spectrophotometric

Table 3. Physical and Chemical Properties of Sodium Dodecylbenzensulfonate, Sodium Decylbenzenesulfonate, TEA-Dodecylbenzenesulfonate, and Linear Alkylbenzene Sulfonates

Property	Value	Reference
Sodium dodecylbenzenesulfonate		
Physical appearance	Yellow slurry or off-white dry product (powder, flakes, or beads)	(CTFA, unpublished data, 1991)
	Pale yellow paste or slurry, spray-dried powder, or as a flake	14
Odor	Bland	15
% Active slurry	30%-50%	(CTFA, unpublished data, 1991)
	Usually 30%-60%	14
Dried product	40%-90%	(CTFA, unpublished data, 1991)
	~90%	14
Molecular weight	349	(CTFA, unpublished data, 1991)
	348.52	12
	348.49	13
Solubility	Water dispersible, soluble at low concentrations	14
	Soluble in water; partially soluble in alcohol	15
Stability	Stable in the presence of a strong acid and base; generally nonreactive and does not polymerize	(CTFA, unpublished data, 1991)
Specific gravity (at 25°C)	Slurry: 1.02-1.05; dry product: 0.45-0.65	(CTFA, unpublished data, 1991)
pH		
10%	Slurry: 7-8; dry product: 7-9	(CTFA, unpublished data, 1991)
1% aqueous solution	7.0-9.0	15
Impurities		
Neutral oil	1% maximum	
Arsenic (as As)	3 ppm maximum	
Iron (as Fe)	10 ppm maximum	
Lead (as Pb)	20 ppm maximum	
Moisture	3.5% maximum	15
Ionic type	Anionic	14
Sodium decylbenzenesulfonate		
Molecular weight	320.46.	12
TEA-dodecylbenzenesulfonate		
Physical appearance	Clear yellow liquid	(CTFA, unpublished data, 1991)
	Clear yellow or amber liquid	14
	Clear, pale yellow viscous liquid	15
Odor	Mild, slightly oily	15
% Activity	40%-60%	(CTFA, unpublished data, 1991).
	50%-60%	14
Aqueous solution	60%	15
Molecular weight	475	(CTFA, unpublished data, 1991)
	476.77	12
Solubility	Soluble in water	14
	Soluble in water and alcohol	15
Stability	Stable under normal cosmetic use conditions	(CTFA, unpublished data, 1991)
Specific gravity (at 25°C/25°C)	1.08	15
pH		
10%	5.5-7.5	(CTFA, unpublished data, 1991)
At 25°C	6.8-7.5	15
Viscosity (at 25°C)	6.8-7.5	15
Assay (average molecular weight 462)	54%-60%	15
Impurities		
Sulfates (as TEA hydrosulfate)	4.0% maximum	15
Water	3%-42%	15
Linear alkylbenzene sulfonates		
Impurities	Dialkyltetralin, dialkylnaphthalene, and to a lesser extent dialkylindane may be present in the final product	(CTFA, unpublished data, 1992)

Abbreviation: TEA, triethanolamine.

methods, especially the assay for methylene blue active substances (MBAS); by volumetric methods; by potentiometric methods; and by physicochemical methods.[23]

Impurities

Sodium dodecylbenzenesulfonate contains impurities that include neutral oil (unsulfonated materials), arsenic (As), iron (Fe), and lead (Pb).[15]

Triethanolamine-dodecylbenzenesulfonate contains sulfates (as TEA hydrosulfate) at a maximum of 4.0%.[2]

Linear alkylbenzene sulfonates are produced by the alkylation of benzene, which results in a number of side reactions.[23] Some of the dialkylbenzenes that result from the side reactions could not be separated from the primary product with ease and, following sulfonation, remained in commercial LAS. Other dialkylbenzenes and the diphenylalkanes that form as products of the side reactions boil at temperatures sufficiently above the linear monoalkylbenzene, facilitating their removal.

Six samples of commercial LAS were analyzed for dialkyltetralins and dialkylnaphthalenes.[19] These compounds were detected as impurities in concentrations ranging from 0% to 15% and 0% to 0.25%, respectively. Gas chromatography and mass spectral analysis also revealed the presence of dialkyl indanes in these LAS samples; however, the concentration of these impurities amounted to only about 1/10 of that of alkyltetralins.

Ultraviolet Absorption

Three commercial samples of LAS, dissolved in water at concentrations up to 1.0 g/L, did not absorb in the UVB region of the spectrum. All absorption maxima were in the UVC region; λ_{max} 218 to 224, λ_{max} 254 to 255, and $\lambda_{shoulder}$ 260 to 261.[24]

Photodegradation

Murakami et al[25] reported that SDDBS exposed to a combination of ultraviolet radiation (UVR) and ozone for 4 hours breaks down into formaldehyde and glyoxal. When exposed to UVR and ozone for up to 10 hours, linear dodecylsulfonates decreased in a linear manner up to 5 hours, whereas the concentrations of formaldehyde and glyoxal increased until approximately 5 hours, then decreased. When exposed to ozone alone, linear dodecylsulfonates decreased in a linear manner for up to 15 hours and formaldehyde and glyoxal increased and leveled off at approximately 7 hours. The concentrations for formaldehyde and glyoxal were lower when exposed just to ozone and not UVR.

Murakami et al[26] reported that SDDBS (3490 μg/mL) exposed to UVR and ozone for 4 hours decreased to 16 μg/mL and formaldehyde was present at 63.0 μg/mL and glyoxal at 38.3 μg/mL.

Xia et al[27] reported that the photocatalytic degradation rates of SDDBS with titanium oxide (TiO_2) was affected by added anions. Cl^-, SO_4^{2-}, NO^{3-}, and HCO^{3-} as NaCl, $NaSO_4$, $NaNO_3$, and $NaHCO_3$ (12 or 36 mmol/L) retarded the rates of linear dodecylsulfonates degradation at different degrees. PO_4^{3-} increased the degradation rate at the lower concentration but not the higher. The authors concluded that the mechanisms for this effect were as follows: anions compete for the radicals, anions are absorbed on the surface of the catalyst, and lock the active site of the catalyst, and anions added to the solution change the pH value and influence the formation of ·OH radicals and the adsorption of linear dodecylsulfonates on the catalyst.

Use

Cosmetic

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Reporting Program (VCRP), SDDBS was used in a total of 45 cosmetic products in 1992. Use concentrations were not reported.[1]

The VCRP data indicated that SDDBS is used in 12 cosmetic products.[28] A survey of current use concentrations conducted by the Personal Care Products Council (Council) reported a range from 2% to 3%[29]

Based on VCRP data, TEA-DDBS was used in a total of 54 cosmetic products in 1992.[1] Currently, VCRP indicated that it is used in 39 products[28] at concentrations ranging from 0.002% to 3%.[29]

Sodium decylbenzenesulfonate is reported to be used at a concentration of 0.02%[29]

Available use and use concentration data are listed in Table 4.

There were no reported uses or use concentrations for ammonium dodecylbenzenesulfonate, calcium dodecylbenzenesulfonate, DEA-dodecylbenzenesulfonate, isopropylamine dodecylbenzenesulfonate, magnesium isodecylbenzenesulfonate, MIPA-dodecylbenzenesulfonate, potassium dodecyl-benzenesulfonate, sodium, and TEA-tridecylbenzenesulfonate.

Straight-chain sodium alkylbenzene sulfonate is on the list of quasi-drugs in Japan. [30]

Noncosmetic

Sodium dodecylbenzensulfonate is used as a detergent in hospitals[31] and as an industrial neutral cleansing agent.[32] Large quantities of dodecylbenzene sulfonates are used in household detergent and dishwashing products.[14] Almost 80% of the total US production of LAS is used in household products.[33]

Tsukatani et al[34] suggested that dodecylbenzenesulfonate anions have a possible use as a chelate extraction solvent.

Sodium *n*-dodecylbenzenesulfonate is used in the removal of heavy metals.[35]

Sodium dodecylbenzenesulfonate and LAS are generally recognized as safe (GRAS) as chemicals used in washing or to assist in the peeling of fruits and vegetables at levels not to exceed 0.2% in wash water (21 CFR Sec. 173.315).

General Biology

Absorption, Distribution, Metabolism, and Excretion

Linear alkylbenzene sulfonate. Michael[36] orally administered ^{35}S-labeled LAS (0.6, 1.2, 8.0, or 40.0 mg; 1.0 mL) to male

Table 4. Historical and Current Cosmetic Product Uses and Concentrations[a] for Ingredient Sodium Dodecylbenzenesulfonate, TEA-Dodecylbenzenesulfonate, and Sodium Decylbenzenesulfonate

Product Category (FDA 2008)	1992 Uses[1]	2007 Uses[26]	2008 Concentrations (Council, unpublished data, 2008) (%)
Sodium dodecylbenzensulfonate			
Baby products			
Other	—	—	3
Bath products			
Oils, tablets, and salts	—	1	—
Soaps and detergents	6	9	3
Bubble baths	33	1	—
Other personal cleanliness products	3	—	—
Eye makeup			
Eyeliners	3	—	2
Other	—	1	—
Total uses/ranges for sodium dodecylbenzenesulfonate	45	12	2-3
TEA-dodecylbenzenesulfonate			
Baby products			
Shampoos	—	—	0.02
Noncoloring hair care products			
Conditioners	—	—	0.01-0.02
Shampoos	18	6	0.002-5
Tonics, dressings, etc	—	—	0.003
Hair-coloring products			
Dyes and colors	36	31	—
Skin care products			
Skin cleansing creams, lotions, liquids, and pads	—	1	0.9
Moisturizers	—	1	—
Total uses/ranges for TEA-dodecylbenzenesulfonate	54	39	0.002-5
Sodium decylbenzenesulfonate			
Skin care products			
Moisturizers	n/a	—	0.02
Total uses/ranges for Sodium decylbenzenesulfonate	n/a	—	0.02

Abbreviations: FDA, food and drug administration; TEA, triethanolamine

[a] Concentration of use was not recorded at the time of the first assessment.

albino Charles River rats (n = 3 or 5) after fasting. The animals were housed individually and urine and feces were collected daily for 3 days. The rats were then killed, radioassayed, and necropsied. After 3 days, radioactivity from the test substance was detected in the urine at 40.2%, 57.7%, 40.2%, and 41.7% for 0.6, 1.2, 8.0, or 40.0 mg, respectively, and in the feces at 56.1%, 38.9%, 41.1%, and 43.5%, respectively. After 3 days, no ^{35}S residue (<0.1% of the dose) could be detected in the carcasses that received the 40-mg dose.

^{35}S-linear alkylbenzene sulfonate (40 mg) was administered to thoracic duct-cannulated rats (n = 3). Lymph was collected in a single 42-hour fraction. ^{35}S was detected in the lymph collected (1.6% of total). The author concluded that absorption was from the gastrointestinal tract and transported by some route other than the lymphatic system.

The ability of the rats to absorb LAS (1.2 mg) administered orally was determined in bile duct-ligated rats. The urine and feces were collected for 90 hours. The test substance (83% recovered) was excreted mostly in the urine (89% of ^{35}S recovered) and not the feces (11%). The author stated that this indicates absorption from the gastrointestinal tract.

In bile duct-cannulated rats (n = 2) fed ^{35}S-LAS (1.2 mg), 46% of the recovered test substance was detected in the urine, 29% in the feces, and 25% in the bile. Recovery was 90%.

In another experiment, the proximal end of the bile duct was cannulated on rat 1, which then fed into the distal end of the bile duct of rat 2. Rat 1 was then administered LAS (1.2 mg) by stomach tube. Bile was collected from an additional cannula in rat 2. Urine and feces were collected from both rats for 90 hours. The ^{35}S-containing compounds that were excreted in the bile of rat 1 and transferred to rat 2 were completely absorbed from the gastrointestinal tract of rat 2; nearly two thirds of this activity was excreted in the bile of rat 2. The author concluded that 89% to 90% of an oral dose of LAS was readily adsorbed from the gastrointestinal tract.[36]

Miscellaneous Studies

Organ effects. Gupta et al[37] orally administered LAS (50, 100, and 250 mg/kg) to developing male albino rats for 10 weeks. At the end of treatment, the rats were killed, the liver and kidneys removed, and enzyme activity measured. For the

livers, adenosine triphosphatase activity was decreased in all treatment groups ($P < .01$ and .001). Acid phosphatase activity was increased ($P < .001$) and glutamic pyruvic transaminase activity was reduced ($P < .01$) in the high-dose group. Alkaline phosphatase and glutamic oxaloacetic transaminase activity were unaffected.

In the kidneys, adenosine triphosphatase activity was decreased in the high-dose group ($P < .01$). Alkaline phosphatase activity was decreased in the mid- ($P < .01$) and high-dose ($P < .001$) groups. Acid phosphatase, glutamic oxaloacetic transaminase activity, and glutamic pyruvic transaminase were unaffected. The authors concluded that ingestion of LAS can affect enzymatic activity in the liver and kidneys, possibly due to cellular injury.[37]

Enzyme effects. Freeman et al[38] reported that a mixture of sodium alkylbenzene sulfonates inhibited activity of amylase, lipase, trypsin, pepsin, and phosphatase enzymes collected from a dog and a human.

Animal Toxicology

Acute Oral Toxicity

Sodium dodecylbenzenesulfonate. The oral LD_{50} of a detergent solution containing 15% SDDBS was 7.5 mL/kg for rats and 12.6 mL/kg for mice.[33] A lethal dosage for dogs was 400 mL/kg; 100 mL/kg had no effect.

Alkyl aryl sulfonate. Hine et al[39] orally administered a product containing alkyl aryl sulfonate (alkyl aryl sulfonate $\geq$40%, moisture $\sim$2%, unsulfonated oil $\sim$1%; 1.4, 1.8, 2.1, 2.4, or 2.5 g/kg) to Fisher albino mice (n = 10) and observed them for 6 days. Gelatinous diarrhea containing traces of blood was observed in 90% of the mice. There was a decrease in motor activity immediately after administration. Necropsy revealed bloody feces and slight hemorrhage in the pyloric mucosa. Mortality was 0, 2, 6, 8, and 10 for 1.4, 1.8, 2.1, 2.4, and 2.5 g/kg, respectively. All but 1 death in the high-dose group occurred within 12 hours.

The above experiment was repeated with Golden Syrian hamsters, young Long-Evans rats, and on adult albino Fisher rabbits. All animals had diarrhea and sluggishness. Mortality was dose dependent.[39]

Short-Term Oral Toxicity

Alkylbenzene sulfonate. Hine et al[39] incorporated a product containing alkylbenzene sulfonate (alkyl aryl sulfonate $\geq$40%, moisture $\sim$2%, unsulfonated oil $\sim$1%; 10%, 25%, or 50%) into the feed of young Long-Evans rats (n = 10) for 45 days. The rats were then killed and necropsied. All rats survived the treatment period. Feed consumption and weight gains were similar between groups. Pathological examinations were unremarkable. The authors concluded that alkylbenzene sulfonate was not classified as a toxic compound.

The authors applied the product (5% aqueous) to the backs of rats and rabbits 6 d/week for 30 days. There were no clinical signs. One rabbit showed a +1 erythema at day 11 which was clear by day 12.[39]

Sodium alkylbenzene sulfonate mixture. Freeman et al[38] orally administered a sodium alkylbenzene sulfonate (2.0, 3.0, or 4.0 g/d) mixture to dogs (25 to 30 lbs; breed not specified; n = 2) in capsules just before feeding for 1 month. The dogs were then killed and necropsied. The dogs in the high-dose group had decreased feed consumption after 1 week. One dog in the high-dose group died at 3 weeks. The other dog in the high-dose group and 1 in the mid-dose group were killed due to poor condition. One dog in the low-dose group developed anorexia that worsened over time. One dog in the mid-dose group vomited the first few days then developed anorexia and stopped eating during week 3. Both dogs in the high-dose group stopped eating by week 3. Necropsy revealed an excess of mucous and bile in the small intestine and liquid stools in the colons of 5 dogs. There was some accentuation of the lobular markings of the liver in the dogs that died at 3 weeks. Histological examination revealed only a few discrete foci of leucocyte infiltration in the cortex of the kidneys of 1 mid-dose dog.

In another experiment, the sodium alkylbenzene sulfonate mixture (0.5 g/100 g feed) was incorporated into the feed of rats (strain not specified; 21 days old; n = 21) for 65 days. Control rats received the basal diet. The rats were then killed and necropsied. The treated rats had slight weight loss for the first 3 days of treatment, then weights were similar to controls. Hemoglobin determinations at 35 and 65 days were similar. Macroscopic and microscopic examinations revealed no abnormalities.[38]

Short-Term Oral and Subcutaneous Toxicity

Linear alkylbenzene sulfonate. Heywood et al[40] simultaneously administered LAS to Rhesus monkeys (*Macaca mulatta*; n = 6; 3 males and 3 females) orally (0, 30, 150, 300 mg/kg per d in distilled water) and subcutaneously [SC] 0.1, 0.5, 1.0 mg/kg per d in saline) for 28 days. All the monkeys in the high-dose group vomited frequently, usually within 3 hours of dosing. There was also salivation and/or retching. In the mid- and high-dose group, there was an increase in frequency of passage of loose or liquid stool. Body weights and feed and water consumption were similar among groups. There was an increase in the occurrence of chronic inflammatory cell infiltration (mainly fibroblasts) at the SC injection sites in a dose-dependent manner. There were injection-associated pseudocysts, hemorrhage, and necrosis. There were no treatment-related findings with regard to ophthalmological, laboratory, and other pathological tests.

Subchronic Oral Toxicity

Sodium dodecylbenzenesulfonate. Industrial Bio-Test Laboratories, Inc[41] incorporated SDDBS (0.020%, 0.10%, or 0.50%) into the feed of weanling Sprague-Dawley albino rats (n =

20; 10 males, 10 females) for 90 days. After the test period, the rats were killed and necropsied. Two sets of controls (n = 20; 10 males and 10 females) were fed either the basal diet or the basal diet incorporated with sodium sulfate (0.125%). All rats were fed ad libitum. After the test period, the rats were killed and necropsied.

There were no mortalities or clinical signs observed during the test period. Body weights and weight gains were similar between groups; the high-dose male group had decreased growth but did not reach significance. The authors concluded that the decreased weight was due to palatability issues. There were no differences in the hematological studies and urinalysis among groups. There were no gross pathological findings attributable to SDDBS ingestion. Gross and microscopic histopathological studies were unremarkable.[41]

Industrial Bio-Test Laboratories, Inc[42] incorporated SDDBS (0%, 0.020%, 0.10%, or 0.50%) into the feed of Beagle dogs (n = 6; 3 males and 3 females) for 90 days. After the test period, the dogs were killed and necropsied. There were no mortalities during the test period. There were no differences between the controls and treatment groups with regard to weight, hematologic studies, urinalysis, or gross and microscopic pathology. There was no evidence of organ dysfunction. Feed consumption of the treatment groups was below that of the control group for the first few weeks of the experiment. It then increased but remained below that of the controls. The authors suggested that it was due to palatability and differences in the initial body weights between groups.

In two separate rat studies, [43,44] Industrial Bio-Test Laboratories, Inc incorporated SDDBS (0.020%, 0.10%, or 0.50%) into the feed of weanling Sprague-Dawley rats (n = 20; 10 males and 10 females) for 90 days. After the test period, the rats were killed and necropsied. Two sets of controls (n = 20; 10 males and 10 females) were fed either the basal diet or the basal diet incorporated with sodium sulfate (0.125%). All rats were fed ad libitum. After the test period, the rats were killed and necropsied. In both studies, there were no mortalities or clinical signs observed during the test period. There were no gross pathological findings attributable to SDDBS ingestion.

In the first study,[42] body weights and weight gains were similar between the controls and the low- and mid-dose groups; the high-dose male and female group had decreased growth rates that reached significance only in the females. The authors concluded that the depressed weight was likely due to palatability issues. There were no differences in the hematological studies and urinalysis among groups. Gross and microscopic histopathological studies were unremarkable. [43]

In the second study,[45] body weight and weight gains were similar among groups. The dogs in the high-dose group had generalized, comparative weakness and lack of activity. Body weights and weight gains were similar among the controls and the low- and mid-dose groups. The high-dose group had decreased body weights and weight gains, especially in the males. The dogs in the high-dose group had decreased feed consumption; the males in the mid-dose group had a slightly decreased feed consumption. There were lower values for hemoglobin, hematocrit, and erythrocyte counts in the high-dose group. There was microscopic evidence of hepatotoxic effects in the high-dose group; the livers of 4 dogs had mild degenerative changes in the form of slight hepatocellular edema without evidence of hepatic cell loss. A fifth dog that was killed early due to its poor condition had extensive hepatocellular degeneration associated with mononuclear infiltrates. Absolute organ weights were similar to controls. Organ/body ratios were increased among dogs in the high-dose group. The authors suggested that this was due to weight loss of this group.[42]

In 2 separate Beagle dog studies Sprague-Dawley rats,[43] Industrial Bio-Test Laboratories, Inc incorporated SDDBS (0.020%, 0.10%, or 0.50%) into the feed of Beagle dogs (n = 6; 3 males, 3 females) for 90 days. The control group was fed the basal diet incorporated with sodium sulfate (0.125%). After the test period, the dogs were killed and necropsied. In both studies, there were no mortalities or clinical signs during the test period. Gross and microscopic pathology were unremarkable. There were no differences in the hematological studies and urinalysis among groups.

In the first study,[44] all dogs in the test groups consumed less feed the first week of the test period, then increased consumption similar to the control group. There was no evidence of kidney or liver dysfunction.[43]

In the second study,[39] body weights and weight gains were similar between the controls and all treatment groups.

Rats (number, gender, and strain unspecified) received a formulation containing 15% SDDBS and 13% ammonium fatty alcohol polyglycolether sulfate in drinking water.[22] A slight decrease in growth rate was observed for male rats given 2.5 mL/kg per d for 9 weeks followed by 3.75 mL/kg per d for an additional 9 weeks. Rapid weight loss was observed when the dosage was increased to 5.0 mL/kg per d at 18 weeks. The animals were given untreated water after 22 weeks; an increase in body weight gain was observed and control values were attained by week 26. Mild necrosis of intestinal mucosa with hemosiderosis of the spleen, liver, and kidneys was observed at microscopic examination. These lesions were not observed for animals in the group given 0.5 mL/kg per d.

In a second experiment, dogs (number, gender, and strain unspecified) were fed 10, 100, or 1000 mg/kg per d of a formulation containing 15% SDDBS in the diet for 6 months. The only observation was a slight decrease in body weight gain for females of the 1000 mg/kg per d group compared with controls. There was no difference between treated and control groups in hematologic or urine chemistry values. At microscopic examination, hemorrhagic necrosis of the intestine and infiltration of chronic inflammatory cells were observed in dogs given 10 mg/kg and hemosiderosis of the liver and spleen was observed in dogs administered 100 and 1000 mg/kg.[22]

Sodium alkylbenzene sulfonate. Freeman et al[33] reported a no observed effects level (NOEL) of 1 g/d for 6 months for dogs orally administered sodium alkylbenzene sulfonate.

Woodard and Calvery[45] reported a NOEL of 0.2% sodium alkylbenzene sulfonate administered in drinking water for 6 months for guinea pigs.

Fitzhugh and Nelson[46] reported a NOEL of 1.0% sodium alkylbenzene sulfonate administered in feed for 16 weeks for rats. Rats fed 4% sodium alkylbenzene sulfonate had severe bloating and diarrhea, grew very little and died within the first week of the experiment.

Linear alkylbenzene sulfonates. Three groups of Sprague-Dawley rats (10 males and 10 females per group) were fed a diet containing 0.02%, 0.1%, or 0.5% LAS for 90 days.[47] A control group of 20 rats was fed untreated diet for the same time period. Body weights and feed consumption were measured weekly. Hematologic studies and urinalysis were performed on samples taken from 5 males and 5 females from each group prior to dose initiation and after 30, 60, and 90 days of testing. At study termination, all animals were killed and necropsied. The tissues of some animals were examined microscopically. No differences were observed in body weight, feed consumption, survival, hematologic values, urinalysis, organ weights, or organ-to-body weight ratios between animals of the treated and control groups, and there were no gross or microscopic lesions in examined tissues.

Wistar rats (number, gender, and strain unspecified) were fed LAS in the diet for 6 months.[48] A concentration of 0.07% LAS in the diet (~40 mg/kg per d) did not produce adverse effects. Minor histologic changes were observed in the kidneys of rats given a concentration of 0.2% LAS; the severity of the lesions increased at concentrations of 0.6% and 1.8% LAS. At the highest dosage (concentration not specified), a decrease in body weight gain, tissue damage in the cecum and liver, and increased severity of renal lesions, specifically glomerular atrophy and necrosis of renal tubules were observed.

Rats (number, gender, and strain unspecified) were fed approximately 5000 ppm (0.5%) LAS for up to 12 weeks.[49] No significant changes were observed.

Two groups of FDRL rats (15 males, 15 females per group) were fed a diet containing 0.05 or 0.25 g/kg/d LAS (expressed as active ingredient) for 12 weeks. Linear alkylbenzene sulfonates had a nominal chain length of 12 carbon atoms (range C_9-C_{12}), an average molecular weight of 346, and was 39.5% active. A control group was fed untreated diet. The rats were observed daily for signs of toxicity. Body weights and feed consumption of approximately 50% of the rats (males and females) were measured weekly. Hematology tests and urinalysis were performed on samples obtained from the remaining rats during week 6 and 12. At study termination, all animals were killed for necropsy. The tissues of some animals were examined microscopically. There was no difference in behavior between animals of the test and control groups. No differences were observed in body weight, feed consumption, survival, hematological values, or urinalysis. Liver-to-body weight ratios were increased for male and female rats of the 0.25 g/kg per d group compared with rats of the control group. No microscopic lesions were observed that were attributed to test article administration.[49]

Rats (number, gender, and strain unspecified) were dosed orally with 0.6% or less LAS for 6 months.[50] Slight renal damage was observed at a dose of 0.2%; this damage was increased at 0.6%.

Alkylbenzene sulfonate. Hine et al[34] incorporated a product containing alkylbenzene sulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 1, 10, or 2 ppm) into the feed of Long-Evans rats for 6 months. At the end of the treatment period, the rats were killed and necropsied. There were no clinical signs during the treatment period. One rat in the low-dose group died in week 3 due to nontreatment causes. Feed consumption and body weights were similar among groups. Hematological tests and urinalysis were unremarkable. Females in the high-dose group had increased kidney weights compared with controls; there was no evidence of kidney damage. There were no morphologic lesions caused by alkylbenzene sulfonate.

Sodium alkylbenzene sulfonate mixture. Freeman et al[33] orally administered a sodium alkylbenzene sulfonate mixture (1.0 g/d) to dogs (25-30 lbs; breed not specified; n = 5) in capsules just before feeding for 6 months. The dogs were then killed and necropsied. Four of the dogs gained weight (2.5-8.5 lbs) and 1 lost weight (1.0 lb). A liver function test at approximately 6 weeks showed no adverse effects. Gross and microscopic examination revealed 1 dog with bilateral cortical retention cysts or abscesses, one on the cortex of each kidney. Another dog had some pitting of the outer surface of the kidneys. There were few foci of leukocytic infiltration into the cortex in 3 dogs with occasional hyaline casts. The authors concluded that the kidney abnormalities were not related to treatment.

Chronic Oral Toxicity

Sodium dodecylbenzenesulfonate. Hazleton Laboratories (1956) incorporated SDDBS (0 ppm, 0% [n = 20 males, 20 females]; 200 ppm, 0.02% [n = 20 males]; 1000 ppm, 0.1% [n = 20 males, 20 females]; or 2000 ppm, 0.2% [n = 20 males]) in the feed of male and female albino rats (Carworth Farms strain) for 104 weeks. At the end of the treatment period, the rats were killed and necropsied. All rats that died during treatment were necropsied.

There were no behavioral or clinical signs in any of the treatment groups. Several rats in all treatment groups had rough coats, alopecia, bloody noses and eyes, dyspnea, and sores on the head or body. Hematological tests at baseline, 13, 52, 78, and 104 weeks showed no differences between control and treatment groups. Treated males in all groups had lower growth rates. The body weights and feed consumption for both treated males and females were not different from controls. Mortality was comparable among the control, 1000, and 2000 ppm groups. Mortality was higher in the 200-ppm group; this was probably not related to treatment. Pneumonitis was the cause

of death for most of the rats that died before the end of treatment. Gross necropsy results were comparable between controls and treatment groups. There were no characteristic findings through histopathology. Organ/body weight ratios were comparable between controls and treatment groups (Hazleton Laboratories 1956).

Industrial Bio-Test Laboratories, Inc[40] incorporated SDDBS (0.02%, 0.10%, or 0.50%) into the feed of Beagle dogs (n = 6; 3 males and 3 females) for 104 weeks. Due to poor palatability, the high dose was adjusted to 0.10% in the feed and the remaining dose was administered by capsule (the timing of this adjustment was not provided). The control group was fed the basal diet containing 0.050% sodium sulfate. At the end of the test period, the dogs were killed and necropsied.

The high-dose group was observed to have comparative weakness and lack of activity. There were no differences in body weights in the low- and mid-dose groups; there was reduced weight gain in the high-dose group. Feed consumption was decreased in the high-dose group throughout the test period. The male dogs in the mid-dose group also had decreased feed consumption but to a lesser extent. Hematologic studies revealed lower values for hemoglobin, hematocrit, and erythrocyte counts in the high-dose group. The high-dose group was anemic. The urinalysis revealed no differences among groups. There were no differences noted in gross pathologic examination.

Microscopic examination revealed that the livers of 4 of the dogs in the high-dose group had mild degenerative changes in the form of slight hepatocellular edema without evidence of hepatocyte loss. A fifth dog had extensive hepatocellular degeneration associated with a mononuclear infiltrate (this dog was killed shortly before the conclusion of the test period due to poor condition). Some organ/body ratios were increased in the high-dose group. The authors suggested that this was due to decreased body weights, as there were no differences in absolute organ weights.[40]

Sodium alkylbenzene sulfonate. Tusing et al[44] incorporated sodium alkylbenzene sulfonate (0%, 0.5%, or 0.1%) into the feed of albino rats (Carworth Farms; n = 80; 40 female and 40 male) for 104 weeks. Ten of the rats of each gender of each group were killed and necropsied at 26 and 52 weeks. Any rats that died during treatment were necropsied. At the end of the treatment period, the remaining rats were killed and necropsied.

In the feed study, there were no differences between control and treatment groups with regard to mortality, body weights, feed consumption, hematological tests, or biochemical tests. There were no lesions observed in the test groups. There were no pathological differences between control and test groups. There were no differences in organ weights that could be attributed to the test substance except for cecums in males at 104 weeks, which were heavier.

The authors conducted a parallel study to compare consumption from drinking water. The rats (n = 40, 20 females and 20 males) were fed the basal diet above. Their drinking water contained 0.1% sodium alkylbenzene sulfonate. However, the daily intake was not comparable to the 0.1% feed group. The amount in the drinking water was adjusted to 0.04% to 0.06% after 4 weeks.

The results in the drinking water study were similar to the feed study. There was an increase in consumption in the test groups with no other signs of stress. The liver/bodyweight ratio in males and the empty cecum/bodyweight ratio in females were increased compared with controls. However, there was no evidence in the blood chemistry of stress to the organs. The authors concluded that there was no evidence of toxicity by sodium alkylbenzene sulfonate at these levels.[44]

Ocular Irritation

Sodium alkylbenzene sulfonate. Maurer and Parker[45] conducted a modified Draize test where the test substance is applied directly to the cornea. Sodium alkylbenzene sulfonate (35.07% active; 10 μL) was instilled in the right eye of adult New Zealand albino rabbits (n = 6) and adult male Sprague-Dawley rats (n = 6). The eyelids were not held shut and the eyes were not washed. The eyes were observed after 3 hours. Half of each group was then killed and the eyes and eyelids removed and examined. The remaining animals were observed on days 1, 2, 3, 4, 7, 14, 21, 28, and 35, then killed and the eyes removed and examined.

At 3 hours, the overall mean score was 26.0 of 110 for rabbits and 24.2 of 110 for rats. There was mild damage to the cornea (10.0 of 80 and 15.0 of 80 for rabbits and rats, respectively), conjunctiva (11.0 of 20 and 5.0 of 20, respectively), and the iris (5.0 of 10 and 4.2 of 10, respectively). The days to recovery for the rabbits were 4 to 7 days and 3 to 7 days for the rats. Microscopic examination of the rabbit and rat corneas after 3 hours showed erosion and denudation of the epithelium and neutrophils in the substantia propria. Examination of the conjunctiva showed erosion and denudation of the epithelium as well as edema and neutrophils in the substantia propria. At 35 days, microscopic examination of the rabbit conjunctiva showed a decreased prominence of goblet cells in the rabbits. The authors concluded that sodium alkylbenzene sulfonate was a mild irritant.[41]

Maurer et al[46] performed the test described above on rats (n = 40). Sodium alkylbenzene sulfonate (35.07% active, 10 μL) was instilled directly on the cornea. The eyelids were not held shut and the eyes were not washed. The eyes were examined at 3 hours, and 1, 2, 3, 4, 7, 14, and 35 days. At each examination time, 5 rats were killed, the eyes removed, and examined.

At 3 hours, the irritant score was 34.3 of 110. The score for the cornea was 21.6 of 80, 9.1 of 20 for the conjunctiva, and 3.6 of 10 for the iris. The conjunctiva had erosion/attenuation and denudation, which was no longer evident on day 3 or 7. Regeneration was observed beginning on day 1 and was no longer evident on day 14. Edema of the substantia propria occurred at 3 hours and was no longer evident on day 4 or 7. Inflammation, principally neutrophilic associated with substantia propria, was noted at 3 hours and no longer evident on day 14.

The cornea had epithelial cell loss at 3 hours with erosion/attenuation and denudation.

Regeneration in the form of conjunctivalization was observed beginning day 1. In the stroma, keratinocyte loss was evident at 3 hours but not on day 7. Edema and inflammation, principally neutrophils, were present beginning at 3 hours. Edema was no longer evident on day 4 or 7; inflammation was no longer evident on day 4. Neovascularization associated with the anterior stroma was observed beginning on day 2. Inflammation associated with the iris/ciliary body occurred in 1 rat at day 1. At day 35, 2 rats still had not fully recovered. [46]

Alkylbenzene sulfonate. Hine et al[39] instilled a product containing alkylbenzene sulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 0.1 mL, 5%) into the eyes of rabbits and observed them at 1, 24, and 96 hours. There was a moderate response that disappeared by the final reading. There was no loss of corneal substance as indicated by the fluroescein test for breaks in the continuity of the epithelium.

Dermal Irritation

Sodium dodecylbenzene sulfonate. Sodium dodecylbenzene sulfonate at 15% is severly irritating to rabbit skin.

Alkylbenzene sulfonate. Hine et al[39] performed a Draize test on intact and abraded skin using shaved rabbits. A product containing alkylbenzene sulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 1, 10, or 20 ppm) was applied to occluded skin for 24 hours. The skin was washed and evaluated immediately and at 48 and 96 hours. There were no deaths and no evidence of absorption of the product. There was moderate edema, erythema, and scabbing of the abraded skin that returned to normal. There were no effects on the intact skin.

The authors applied the product (0.5 g) to 4 shaved areas (intact and abraded) on the backs of albino rabbits and the areas were occluded for 24 hours. The covering was removed and the areas read immediately and at 72 hours. There were no readings taken for the intact skin (no explanation given). Abraded skin had slight persistent edema and erythema.[39]

Dermal Sensitization

Alkylbenzene sulfonate. Hine et al[39] injected a product containing alkylbenzene sulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 0.1% in 0.9% saline) intradermally into the backs of albino guinea pigs (n = 3) on alternate days for 10 injections. The first injection was 0.05 mL; all others were 0.01 mL. Readings were taken 24 hours after each injection. Two weeks after the last injection, a test injection (0.05 mL) was made into the flank. There was no erythema or wheal formation 24 hours after the challenge injection. The authors concluded that alkylbenzene sulfonate is nonirritating and nonsensitizing.

Reproductive and Developmental Toxicity

Oral

Sodium alkylbenzene sulfonate. Tusing et al[47] used 10 males and 10 females from each group in the sodium alkylbenzene sulfonate feeding study described earlier for a reproductive and developmental toxicity study. After 14 weeks on the treated feed (0%, 0.05%, or 0.1% sodium alkylbenzene sulfonate), the rats were paired and mated while continuing on the test diet. After 3 days, the males were returned to their original cages; the females were allowed to deliver and nurse for 21 days. They were then returned to their original cages and the pups were fed the parental diet. At approximately 130 days, the F_1 pups were paired and mated. The F_2 pups were continued on the parental diet for 8 weeks. Sodium alkylbenzene sulfonate had no observed effects on fertility, litter size, lactation, or survival of offspring. There were no remarkable findings in the hematologic studies, urinalysis, or blood urea nitrogen tests. Gross and microscopic examinations of the offspring were also unremarkable.

Alkylbenzene sulfonate. Omori et al[48] incorporated alkylbenzene sulfonate (0%, 0.25%, 0.1%, 0.5%, 1.0%, or 2.0%) into the diets of pregnant rats (n = 15 [0%, 0.25%, and 0.5%], 16 [0.1%], 14 [1.0%], 5 [2.0%]; strain not specified). Dams in the 1.0% and 2.0% groups had diarrhea. No clinical signs were noted in the other groups. Feed intake was decreased in the high-dose group. At necropsy, placenta weights were decreased compared with controls in the high-dose group (0.26 ± 0.01 vs 0.36 ± 0.01). The number of pups per litter was reduced in the high-dose group (3.6 ± 2.4 vs 10.4 ± 0.7). The number of dead litters and dead pups were increased and the number of resorptions was reduced in the high-dose group. In the high-dose group, body weight, body length, and tail length of the pups were reduced. There were no differences in organ weights of the pups.

Mice (n = 22-24; strain not specified) were orally administered alkylbenzene sulfonate (0, 24, or 240 mg/kg) on day 7 and 13 of pregnancy. There was a slight decrease in maternal weight gain (80.6, 62.9, 56.3 g, respectively). There were no effects observed on the fetuses from dams in the low-dose group. The number of dead pups increased in the high-dose group. There were no congenital malformations observed in either treatment group.[48]

Linear alkylbenzene sulfonate. Palmer et al[49] tested for teratogenic effects of LAS in CD rats (n = 20), CD-1 mice (n = 20), and New Zealand white rabbits (n = 13). Linear alkylbenzene sulfonate (0, 0.2, 2.0, 300, or 600 mg/kg per d in water) was orally administered from day 6 to day 15 in rats and mice and to day 18 in rabbits. The rats, mice, and rabbits were killed and necropsied on day 20, 17, and 29, respectively.

For the mice, 7 dams died in the 300-mg/kg perd group and 18 died in the 600-mg/kg per d group; all others survived. For the rats, only 1 died in the 600 mg/kg per d group. For the rabbits, 1, 11, and 13 died in the 2-, 300-, and 600-mg/kg per d

groups, respectively. The mice in the 300-mg/kg per d group had retarded weight gains and weight loss was observed in the 600-mg/kg per d group. There were retarded weight gains for the rats in the 600-mg/kg per d group. There was weight loss for rabbits in the 300- and 600-mg/kg per d groups. In all species, toxic effects of the gastrointestinal tract were observed, especially in the rabbits (diarrhea, anorexia, weight loss, and cachexia prior to death). Total litter loss (abortion and/or total resorption) tended to occur as a secondary consequence. The authors concluded that 300 and 600 mg/kg per d caused marked maternal toxicity or undue interference with maternal economy. At maternally toxic dosages, there was increased fetal loss and reduced litter size in rabbits and mice, mostly due to total litter loss. At nontoxic and slight-to-moderately toxic dosages, values for litter size and fetal loss were unaffected (mice and rabbits, 0.2 and 2.0 mg/kg per d; rat, all dosages). Examination of the fetuses revealed no increase in abnormalities.[49]

Sodium alkylbenzene sulfonate mixture. As described earlier, Freeman et al[38] conducted a subchronic toxicity study in which the fertility of the treated rats also was determined. A sodium alkylbenzene sulfonate mixture (0.5 g/100 g feed) was incorporated into the feed of rats (strain not specified; 21 days old; n = 21) for 65 days. Control rats received the basal diet. According to these authors, the sodium alkylbenzene sulfonate mixture had no effect on fertility in rats. Half of the original dose was initially applied and allowed to dry slightly before the application of the second half.

Dermal

Linear alkylbenzene sulfonate. Palmer et al[50] applied LAS (0%, 0.03%, 0.3%, or 3.0% in distilled water; 0.5 or 10 mL) to the shaved backs of CD-1 mice (2 × 3 cm; n = 20), CD rats (4 × 4 cm; n = 20), and New Zealand white rabbits (12 × 20 cm; n = 13) to test for teraterogenic effects. Half of the original dose was initially applied and allowed to dry slightly before application of the remaining dose. The mice were treated on days 2 to 13 of pregnancy, rats were treated on days 2 to 15, and rabbits were treated days on 1 to 16. The applications were not occluded or washed. No other procedural details were provided.

One mouse died in the low-dose group, no rats died during treatment, and 1 rabbit died in the mid-dose group. The mouse and rabbit dams had dermal reactions consisting of erythema and edema with peak response at days 6 to 7. The mice also had dead skin and accumulated test material formed a scabrous layer; the rabbits had cracking and bleeding of the skin. There were minor dermal reactions in the rats. Recovery was evident in rats and rabbits after the peak response was attained. All animals had increasing irritability, with peak hypersensitivity at the same time as the local reactions. There was weight loss or marked weight retardation for mice and rabbits in the high-dose group. There was a decrease in number of litters containing viable young in the high-dose groups. The authors concluded that for the dams, marked toxicity was evident in the high-dose groups of mice and rabbits. Mild toxicity was observed in the mid-dose groups for mice and rabbits and the high-dose group for rats. Litter and mean pup weights were not affected by any dose in any of these species. There were no abnormalities associated with treatment at the low- and mid-dose levels. The high-dose level did not have enough litters for assessment.

Daly et al[51] tested the reproductive and developmental effects of dermally applied LAS to clipped pregnant Wistar rats (n = 20 or 21). The test material was LAS (20.5%), alkylbenzene (0.2%), ash (0.6%), and water (77.7%). The 3 control groups were untreated and unclipped, clipped, or clipped and treated with water. The test groups were treated with the test material (1%, 5%, or 20% in water; 20, 100, or 400 mg/kg per d, respectively) by applying the test material, rubbing it in for 3 minutes, leaving it on for 30 minutes, and then rinsing off with water. The other test groups were treated with test material (0.05%, 0.1%, or 0.5%; 1, 2, or 10 mg/kg per d), which was not removed after application. The dams were treated daily from day 0 to 20 of gestation and then killed and necropsied. The fetuses were examined for deformities.

There were no mortalities during the test period. The mean body weights of the high-dose wash-off group were decreased compared with controls for gestation day 12 to 21. Feed consumption was comparable in all groups. There were no cutaneous manifestations in the 0.05%, 0.1%, or 0.5% leave-on groups. There was a light brown skin discoloration in 3 dams on day 3 to 6 of the 1.0% wash-off group, and 14 of 20 dams in the 5.0% wash-off group had slight erythema and dry skin on day 3 to 6 and slight skin thickening in 7 of 20 animals. After day 6, erythema and fissuring were no longer observed. Brown discoloration continued in 1 or 2 animals throughout treatment. The high-dose wash-off group had slight erythema on most dams on day 2 to 4. After day 6, this reaction was no longer observed. There was slight skin thickening at the application site on 2 dams on day 2 and on all dams by day 5. Moderate skin thickening was noted in 6 dams the first half of gestation. Slight fissuring was noted in 18 dams from day 4. Clear exudate and brown skin discoloration were occasionally noted.

There were no differences between groups with regard to number of corpora lutea, implantations, viable fetuses, or resorptions. No abnormalities were observed at necropsy. There were no differences among groups of offspring for viability or deformities. The authors concluded that LAS applied to the skin of pregnant rats (either left on or washed off) elicits skin reactions and decreases maternal body weight but does not have any teratogenic or embryopathic effects.[51]

Genotoxicity

Linear alkylbenzene sulfonate. In an in vitro transformation assay of LAS, cryopreserved hamster embryo cells (n = 9) were used as the source of target and feeder cells. No

transformations were produced at concentrations up to 50 μg/mL, but LAS was cytotoxic at this concentration.[52]

Linear dodecylbenzenesulfonates/ozone/UV. Murakami et al[25] exposed linear dodecylbenzenesulfonates to ozone and UV for 4 and 8.5 hours or ozone alone for 16 hours (with an antifoaming agent). A mutation frequency assay was performed using the resulting degradation products (0-100 μL/plate) and *Salmonella typhimurium* (TA98, TA100, and TA104) with and without metabolic activation. The LDS decomposition products were lethal at 10^{-4} mol/L. The degradation products from the 4-hour treatment were mutagenic in a concentration-dependent manner for all 3 strains, with and without metabolic activation. The products of the 8.5-hour and ozone-alone treatments were mildly mutagenic. The experiment was repeated with formaldehyde and glyoxal at the same concentrations as that resulting from the 4-hour ozone/UV experiment and various concentrations of linear dodecylbenzenesulfonates and antifoaming agent. There were no interactions or effects observed. The same assay was repeated with just formaldehyde or glyoxal. Formaldehyde was mutagenic for TA104 with and without activation and TA100 with activation. Glyoxal was mutagenic for TA104 and TA100 with and without activation. The authors suggest that the mutagenic activity of decomposed linear dodecylbenzenesulfonates was in part due to formaldehyde and glyoxal, but not entirely.

Murakami et al[26] exposed sodium linear dodecylbenzenesulfonates to UV and ozone for 4 hours. The resulting degradation products (0.1 mL) or linear dodecylbenzenesulfonates (0.1 mL) were used in a mutation assay using *S typhimurium* (TA100 and TA104) with and without metabolic activation. Sodium LDS was not mutagenic.

The decomposition products were mutagenic for both strains with and without activation. Linear dodecylbenzenesulfonates with activation was not lethal to TA104 up to approximately 10^{-2} mol/L or without activation up to approximately 10^{-4} mol/L, but was above these concentrations. Linear dodecylbenzenesulfonates with activation was not lethal to TA100 up to approximately 10^{-3} mol/L or without activation up to approximately 10^{-4} mol/L but was above these concentrations. The authors calculated the total amount of formaldehyde and glyoxal in the decomposed linear dodecylbenzenesulfonates solution accounted for 44.9% of the total mutagenicity of the decomposed linear dodecylbenzenesulfonates solution without metabolic activation and 68.4% with activation for TA104. Formaldehyde and glyoxal accounted for 31.75% and 88.0% of the total mutagenicity for TA100, respectively. However, when linear dodecylbenzenesulfonates, formaldehyde, and glyoxal were assayed in different combinations, the authors concluded that the mixture does not increase the mutagenicity by interaction between formaldehyde and glyoxal.

Clinical Assessment of Safety

Dermal Absorption

Dodecylbenzenesulfonate. Campeau[53] tested the dermal absorption of dodecylbenzenesulfonate in the form of triethanolamine salt of alkyl (kerosene) benzenesulfonic acid (alkyl benzenesulfonate [52%], triethanolamine sulfate [8%], and water [40%]). The test substance was used as a scrub for 2 minutes. The substance was extracted from the skin using acid methanol in a test tube with a known area of the mouth by inverting the test tube over the skin 30 times. The absorption was used to determine the amount of recovered dodecylbenzenesulfonate (n not provided). On the human palm, 570 μg/cm^2 was recovered. On the fingertips and the forearm, 360 and 94 μg/cm^2 dodecylbenzenesulfonate was recovered, respectively. When the pH was adjusted, the amount of dodecylbenzenesulfonate recovered increased as pH decreased. At a low pH of 3, adsorption continues even after prolonged scrub periods, but at pH 7, the rate of adsorption does not increase after 8 minutes. Dodecylbenzenesulfonate is completely removed from the skin with soap. The authors concluded that dodecylbenzenesulfonate adsorbs readily to the skin.

Oral Toxicity

Sodium alkylbenzene sulfonate. Freeman et al[38] orally administered a sodium alkylbenzene sulfonate mixture (100 mg/d) in capsule form to male adults (n = 6) with meals (33.3 mg/meal) for 4 months. Red and white blood cell counts and hemoglobin content were not affected. There was no change in kidney function. There was transient flatulence and loss of appetite in 2 participants. One participant did not take the capsules with a meal and suffered epigastric pain after ingestion, which ceased after following instructions.

In another experiment, feces were collected from male participants (n = 6) in two 5-day periods, one with a consistent diet and the other with the consistent diet plus 33.3 mg sodium alkylbenzene sulfonate mixture in capsules at each of 3 meals/d. In 5 of the participants, there were no effects on the fat and nitrogen content of the feces. The sixth participant had an increase in fecal fat and nitrogen. The authors concluded that the sodium alkylbenzene sulfonate mixture has a low-order toxicity when ingested with food or when taken just before a meal.[38]

Summary

An earlier safety assessment of SDDBS, TEA-DDBS, and sodium decylbenzenesulfonate was expanded to include ammonium dodecylbenzenesulfonate, calcium dodecylbenzene-sulfonate, DEA-dodecylbenzenesulfonate, isopropylamine dodecylbenzenesulfonate, magnesium isodecylbenzenesulfonate, MIPA-dodecylbenzenesulfonate, potassium dodecylbenzenesulfonate, sodium tridecylbenzenesulfonate, and TEA-tridecylbenzenesulfonate.

Sodium dodecylbenzenesulfonate is a LAS. The breakdown products of SDDBS exposed to a combination of ultraviolet irradiation and ozone includes formaldehyde and glyoxal. Sodium dodecylbenzenesulfonate is soluble in water; partially soluble in alcohol. Impurities can include organic fillers, sodium sulfonate, sodium chloride, neutral oil, arsenic, iron,

and lead. Linear alkylbenzene sulfonates impurities include dialkyltetralin, dialkylnaphthalenes, and to a lesser extent, dialkylbenzene.

In data provided to the FDA under the VCRP, SDDBS is currently used in 12 products at 2% to 3%. Triethanolamine-DDBA is currently used in 39 products at 0.002% to 5%. Sodium decylbenzenesulfonate has no uses currently reported to FDA, but a use concentration of 0.02% has been reported by industry. There are no reports of uses or concentrations of use for ammonium dodecylbenzenesulfonate, calcium dodecylbenzenesulfonate, DEA-dodecylbenzenesulfonate, isopropylamine dodecylbenzenesulfonate, magnesium isodecylbenzenesulfonate, MIPA-dodecylbenzenesulfonate, potassium dodecylbenzensulfonate, sodium tridecylbenzenesulfonate, or TEA-tridecylbenzenesulfonate. All of these ingredients function as surfactant-cleansing agents.

Rats orally administered LAS excreted almost all of it in the feces and urine. Orally administered LAS to rhesus monkeys was excreted mostly in the urine in the first 24 hours.

Orally administered LAS to developing rats for 10 weeks affected enzymatic activity in the liver and kidneys.

A mixture of sodium alkylbenzene sulfonates had inhibitory effects on amylase, lipase, trypsin, pepsin, phosphatase, and various enzymes collected from a dog and a human.

The oral LD_{50} of a detergent solution containing 15% SDDBS was 7.5 mL/kg for rats and 12.6 mL/kg for mice. A lethal dosage for dogs was 400 mL/kg; 100 mL/kg had no effect. Alkylbenzene sulfonate administered orally to mice caused death in all 8 mice administered 1.5 g/kg. At 3.5 g/kg, 15 of 20 rats died. At 2.2 g/kg, 3 of 4 rabbits died.

No significant changes were observed in rats fed LAS at approximately 5000 ppm or up to 0.25 g/kg per d for 12 weeks. Alkylbenzene sulfonate was not classified as a toxic compound in rats at concentrations up to 50% for 45 days. Dogs orally administered a sodium alkylbenzene sulfonate up to 4.0 g/d showed anorexia.

There was increased chronic inflammatory cell infiltration at the SC injection sites and injection-associated pseudocysts, hemorrhage, and necrosis in rhesus monkeys injected SC with LAS after oral administration of LAS. There were no treatment-related findings with regard to ophthalmological, laboratory, and other pathological tests.

In a subchronic study with SDDBS at 2.5 mL/kg per d in drinking water, growth rates were decreased in rats, which became rapid weight loss at 5.0 mL/kg per d. Weight increased with discontinuation of treatment. Mild necrosis of intestinal mucosa with hemosiderosis of the spleen, liver, and kidneys was observed at necropsy.

No effects were observed for rats administered feed with 40% or more alkylbenzene sulfonate at 2 ppm except that females had increased kidney weights compared with controls; there was no evidence of kidney damage.

A sodium alkylbenzene sulfonate mixture (1.0 g/d) administered to dogs in capsules for 6 months had no adverse effects. Rats fed 0.5 g/100 g feed also had no adverse effects after 65 days.

Sodium dodecylbenzenesulfonate in the feed of rats at 2000 ppm over 104 weeks caused no behavioral or clinical signs. Several rats had unthrifty appearance, rough coats, alopecia, bloody noses and eyes, dyspnea, and sores on the head or body and had lower growth rates. Beagles fed SDDBS at 0.5% for 104 weeks had weakness, lack of activity, decreased feed consumption, and anemia. Livers had slight degenerative changes. At microscopic examination, dogs given 100 and 1000 mg/kg SDDBS in the diet had hemorrhagic necrosis of the intestine and infiltration of chronic inflammatory cells.

There was no evidence of toxicity by sodium alkylbenzene sulfonate at 0.1% in feed or drinking water to rats for 104 weeks. There were no adverse effect to rats administered feed with 0.5% LAS for 2 years. A decrease in body weight gain, tissue damage in the cecum and liver, and increased severity of renal lesions, specifically glomerular atrophy and necrosis of urinary tubules were observed in rats fed high doses (not specified) of LAS.

Sodium alkylbenzene sulfonate at 1% was a mild ocular irritant in rabbits. Sodium alkylbenzene sulfonate at 35% caused erosion/attenuation and denudation of the conjunctiva, edema of the substantia propria, and inflammation, principally neutrophilic associated with substantia propria. The cornea had epithelial cell loss at 3 hours with erosion/attenuation and denudation. At day 35, 2 of 40 rats still had not fully recovered. Concentrations of 0.1% or less of LAS produced mild to no irritation in rabbits. There was a moderate response that disappeared by 96 hours in the eyes of rabbits treated with alkylbenzene sulfonate at 40%.

Alkylbenzene sulfonate applied to the abraded skin of shaved rabbits caused slight persistent edema and erythema.

Dermal application of LAS at 3.0% produced marked toxicity that was evident in mice and rabbit dams, whereas there were no effects to the pups. Linear alkylbenzene sulfonate, up to 10 mg/kg per d, applied to the skin of pregnant rats elicited skin reactions and decreased maternal body weight but did not have any teratogenic or embryopathic effects.

Orally administered sodium alkylbenzene sulfonate at 1% had no observed effects on fertility, litter size, lactation, or survival of offspring in rats. Orally administered alkylbenzene sulfonate at 1% and 2% caused diarrhea in pregnant rats. The weight of the placenta was reduced, the number of pups per litter was reduced, the number of dead litters and dead pups was increased, and the number of resorptions was reduced in the high-dose group. In the high-dose group, body weight, body length, and tail length of the pups were reduced. Pregnant mice orally administered alkylbenzene sulfonate had decreased maternal weight gain. There were no effects observed on the fetuses from dams at 24 mg/kg per d. The number of dead pups increased at 240 mg/kg per d. There were no congenital malformations observed in either treatment group.

Linear alkylbenzene sulfonate was not mutagenic but was cytotoxic at 50 μg/mL. Linear alkylbenzene sulfonate, treated with ozone and UV, was mutagenic to *S typhimurium*.

Discussion

The irritant properties of SDDBS are similar to those of other detergents, with the severity of irritation dependent on the concentration and pH of the ingredient. Although ocular irritation by SDDBS may be dependent on the test setting, the CIR Expert Panel recognized that SDDBS, at pH 9, may be an ocular irritant. In preparations containing SDDBS designed to remain in contact with the skin, the product should be formulated to ensure that the irritancy potential is minimized.

The Expert Panel further noted that DEA, TEA, and MIPA had been evaluated previously and were found to be safe as used.

Dialkylnaphthalenes and dialkyltetralin are impurities in alkylbenzylsulfonates. Although the concentrations are low, they may absorb through the skin. No evidence of carcinogenic activity was reported in oral studies of SDDBS or LAS. Because of concern about the carcinogenicity of *N*-nitroso compounds, however, these salts of alkylbenzene sulfonates should not be used in products where *N*-nitroso compounds may be formed.

The CIR Expert Panel recognized that there are data gaps regarding use and concentration of this ingredient. However, the overall information available on the types of products in which this ingredient is used and at what concentration indicated a pattern of use, which was considered by the Expert Panel in assessing safety.

Although there were minimal toxicity data available on the other ingredients in this report, the Expert Panel determined that the chemical structures of SDDBS, ammonium dodecylbenzenesulfonate, calcium dodecylbenzenesulfonate, DEA-dodecylbenzenesulfonate, isopropylamine dodecylbenzenesulfonate, magnesium isodecylbenzenesulfonate, MIPA-dodecylbenzenesulfonate, potassium dodecylbenzenesulfonate, sodium decylbenzenesulfonate, sodium dodecylbenzenesulfonate, sodium tridecylbenzenesulfonate, TEA-DDBS, and TEA-tridecylbenzenesulfonate were all sufficiently similar, such that the safety test data available in this report could be extended to support the safety of all of the salts of alkylbenzene sulfonates.

Amended Conclusion

Salts of alkylbenzene sulfonates, including ammonium dodecylbenzenesulfonate, calcium dodecylbenzenesulfonate, DEA-dodecylbenzenesulfonate, isopropylamine dodecylbenzenesulfonate, magnesium isodecylbenzenesulfonate, MIPA-dodecylbenzenesulfonate, potassium dodecylbenzenesulfonate, sodium decylbenzenesulfonate, SDDBS, sodium tridecylbenzenesulfonate, TEA-DDBS, and TEA-tridecylbenzenesulfonate, are safe as cosmetic ingredients in the practices of use given in this safety assessment when formulated to be nonirritating.

Author's note

The 2009 Cosmetic Ingredient Review Expert Panel members are Chairman, Wilma F. Bergfeld, MD, FACP; Donald V. Belsito, MD; Ronald A. Hill, PhD; Curtis D. Klaassen, PhD.; Daniel C. Liebler, PhD; James G. Marks, Jr, MD; Ronald C. Shank, PhD; Thomas J. Slaga, PhD; and Paul W. Snyder, DVM, PhD. The CIR Director is F. Alan Andersen, PhD. The CIR Expert Panel is aware that audits found fabricated and falsified data in many studies conducted by IBT. In the interest of full disclosure of available information IBT studies have been included. The uncertainty regarding the data, however, led the panel not to base any part of its conclusion on IBT data.

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th St., Suite 412, Washington, DC 20036, USA.

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