

Final Report on the Amended Safety Assessment of Sodium Polynaphthalenesulfonate and Sodium Naphthalenesulfonate¹

Sodium Polynaphthalenesulfonate (SPNS) and Sodium Naphthalenesulfonate (SNS) are sodium salts of naphthalene sulfonic acid. SPNS was used as an emulsion stabilizer, surfactant—hydrotrope, and/or surfactant—suspending agent at concentrations between 0.1% and 0.4%, in a wide range of products, including one lipstick. SNS is described as a surfactant—hydrotrope; no current uses were reported, but information was provided indicating that use concentrations would be typically below 2%. SNS is manufactured by reacting naphthalene with sulfuric acid to produce a sulfonic acid, which is then reacted with sodium hydroxide to produce the final product. The polymer form uses the sulfonic acid intermediate in a reaction with formaldehyde and water under conditions of heat and pressure to form the polymer sulfonic acid form, to which sodium hydroxide is added to make the final SPNS. The residue level of formaldehyde was 0.09%. Only around 1% of SNS in a 1-mg/ml solution applied to porcine skin penetrated the skin after 24 h, a similar amount was found noncovalently bound to the skin, and the concentration of material applied to the surface of the skin was largely unchanged. Both chemicals were not toxic in acute oral or dermal studies. In a subchronic oral toxicity study in rats, the effects noted were increases in urinary sugar in females and urine protein concentrations in males. Although undiluted SPNS was not a significant eye irritant in rabbits, undiluted SNS was a moderate eye irritant in rabbits. At 2%, SNS was a minimal eye irritant in rabbits. Undiluted SNS was at most a mild irritant in Guinea pigs, and was nonirritating at 20% and 2%. In a delayed contact hypersensitivity test in Guinea pigs, 30% SNS used in the induction phase and in the challenge phase produced no reactions. In a Guinea pig maximization test, 1% SNS used with Freund's complete adjuvant (FCA) injected in the initial sensitization, 50% SNS applied topically in the second sensitization, and up to 30% SNS applied topically in the challenge phase did not produce any irritation or sensitization. Both ingredients were negative in Ames mutagenesis assays. In clinical studies, SNS was neither an irritant (tested up to 2%), cumulative irritant (tested up to 1%), nor a sensitizer (tested up to 1%). The Panel considered the low penetration in concert with the low concentrations of use of these ingredients and the absence of significant overall toxicity and the limited negative genotoxicity findings sufficient to support a conclusion that SNS and SPNS are safe as used in cosmetic formulations intended to be applied to the skin. Use of SPNS in a

lipstick formulation, was not considered to be different from application to the skin in that the barrier properties of the skin do not apply when these ingredients may contact mucous membranes or may be ingested. Accordingly, the Panel concluded that the available data are insufficient to support the safety of SNS and SPNS in cosmetic formulations that may contact mucous membranes or be ingested. The additional data needed to make a safety assessment for these uses include dermal reproductive and developmental toxicity data and one genotoxicity assay in a mammalian system, and if that study is positive, then a 2-year dermal carcinogenicity study using National Toxicology Program (NTP) methods may be needed.

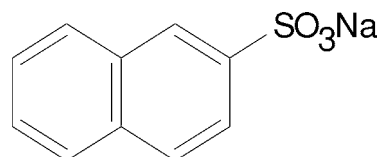
INTRODUCTION

Sodium Polynaphthalenesulfonate (SPNS) and Sodium Naphthalenesulfonate (SNS) are listed as cosmetic ingredients in the *International Cosmetic Ingredient Dictionary and Handbook* (Pepe, Wenninger, and McEwen 2002). The available data relevant to the assessment of the safety of these ingredients in cosmetics is included in this report. Most of the data are on SPNS.

CHEMISTRY

Definition and Structure

SNS (CAS no. 532-02-5) is the sodium salt of naphthalene sulfonic acid that conforms to the formula (Pepe, Wenninger, and McEwen 2002):



Synonyms include 2-naphthalenesulfonic acid, sodium salt; sodium beta-naphthalenesulfonate; and sodium 2-naphthalenesulfonate (Registry of Toxic Effects of Chemical Substances [RTECS] 1997).

SPNS (CAS no. 9084-06-4) is the sodium salt of the product obtained by the condensation polymerization of naphthalene sulfonic acid and formaldehyde. It has the following empirical

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TABLE 1
Chemical and physical properties of Sodium Polynaphthalenesulfonate (Hampshire Chemical Corp. 1995)

Property	Sodium Polynaphthalenesulfonate description		
	Tamol SN ^a	Tamol L ^a	Daxad 11/15 ^a
Color	Tan	Brown	Amber
State	Powdered solid	Liquid	Powder
pH	8.8–10.0 (1% solution)	8.8–10.0	7–10.5 (1% solution)
Specific gravity	0.4–0.7 bulk density	1.25	NA
Water solubility	Completely soluble	Dilutable	Miscible
Percent volatility	3%–7% water	51%–54% water	2%–10% as water
Molecular weight	NA	NA	3000–40000

^aTrade names for Sodium Polynaphthalenesulfonate.

formula (Pepe, Wenninger, and McEwen 2002): (C₁₀H₈O₃S · CH₂O)_x · xNa. No range of values for x was available.

Synonyms include Naphthalenesulfonic Acid, Polymer with Formaldehyde, Sodium Salt; and Sodium Salt of Sulfonated Naphthaleneformaldehyde Condensate (RTECS 1997). In addition, the ingredient is known by trade names such as Atlox, Barra super, Bevaloid 35, Blancol dispersant, Darvan 1, Darvan No. 1, Daxad (11, 15, 18), Dispergator NF, Disperser NF, Dispersing agent NF, Dispersol ACA, Flube, Humifen NBL 85, Leukanol NF, Lissatan AC, Lomar (D, LS, PW), Na-Cemmix, NF, NF (dispersant), Pozzolith 400N, Surfactant NF, Tamol L, and Tamol SN (RTECS 1997).

Physical and Chemical Properties

Table 1 presents a summary of the physical and chemical properties of SPNS. The Cosmetic, Toiletry, and Fragrance Association (CTFA) provided the chemical and physical properties of SNS listed in Table 2 (CTFA 1999a).

Ultraviolet Radiation Absorption

SPNS absorbs ultraviolet (UV) radiation at a maximum of Naphthalenesulfonate.

The Food and Drug Administration (FDA) reported a maximum absorbance for SNS at 273 nm (FDA 1999).

TABLE 2
Chemical and physical properties of Sodium Naphthalenesulfonate (CTFA 1999a)

Property	Description
Color	White to pale yellow
Density/apparent	0.4
Solubility	Soluble in water
pH at 25°C	5–7
Melting point/range	275°C

Method of Manufacture

According to Hampshire Chemical Corp. (1995), SPNS is made by reacting naphthalene with sulfuric acid under conditions of heat and pressure. Formaldehyde and water are then added to produce the acid polymer under the same conditions of heat and pressure. Caustic is added to the acid polymer resulting in the final product.

Kao Corp. (1998) reported that SNS is made by reacting naphthalene with sulfuric acid. The resulting naphthalenesulfonic acid is then reacted with sodium hydroxide. Formaldehyde is not used in the manufacture of this ingredient.

Impurities

Rohm and Haas (1994), a supplier of SPNS, noted that one trade compound contained 41% to 44% SPNS, 2% to 5% sodium sulfate, and 51% to 54% water. Another compound contained 86% to 88% SPNS, 7% to 9% sodium sulfate, and 3% to 7% water. The two trade mixtures each contained 0.09% formaldehyde (maximum). In its safety assessment of Formaldehyde, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that a limit of 0.2% free formaldehyde was necessary to ensure safety (Elder 1984).

Limits for SPNS suggested by Hampshire Chemical Corp. (1995) are as follows: sulfate (as sodium sulfate) not more than 0.5%; heavy metals not more than 20 ppm; and, arsenic not more than 2 ppm.

Kao Corp. (1998) listed the following limits for SNS: not more than 0.5% sulfate (as sodium sulfate); not more than 20 mg/kg of heavy metals; and not more than 2 mg/kg arsenic.

USE

Cosmetic

SPNS is used in cosmetics as an emulsion stabilizer, surfactant—hydrotrope, and/or surfactant—suspending agent (Pepe, Wenninger, and McEwen 2002). As shown in Table 3, 50 uses of SPNS were reported to the FDA (FDA 1998). Hampshire Chemical Corp. (1995) stated that the typical concentration of

TABLE 3

Frequency of use of Sodium Polynaphthalenesulfonate (FDA 1998)

Product category	No. formulations in category	No. containing ingredient
Eye shadow	506	1
Mascara	167	8
Other eye makeup preparations	120	3
Blushers (all types)	238	1
Foundations	287	6
Lipstick	790	1
Makeup bases	132	25
Other makeup preparations	135	4
Moisturizing	769	1
1998 total		50

use to be between 0.1% and 0.4%. Concentrations of use reported to the CTFA are shown in Table 4 (CTFA 1999b).

SNS is described as a surfactant—hydrotrope for use in cosmetics (Pepe, Wenninger, and McEwen 2002). This ingredient, however, was not reported to FDA to be in use in 1998 (FDA 1998), nor were concentration of use data provided to CTFA. Kao Corp. (1998) suggested that use concentrations were “typically below 2%.” Goldwell GmbH (1999) and Kao (1999) reported that SNS was not used in formulations which may contact mucous membranes.

According to the Ministry of Health, Labor and Welfare (MHLW) in Japan, SNS and SPNS are not restricted in any manner in cosmetic formulations (MHLW 2001).

Neither SNS nor SPNS are listed in Annex II (list of substances that must not form part of the composition of cosmetic products) or Annex III (list of substances that cosmetic products must not contain except subject to the restrictions and conditions laid down) of the *Cosmetics Directive of the European Union* (European Commission 2003).

TABLE 4

Concentration of use data of Sodium Polynaphthalenesulfonate (CTFA 1999b)

Product type	Reported maximum concentration (%)
Mascara	0.3
Other eye makeup preparations	0.1
Blushers (all types)	0.2
Foundations	0.3
Makeup bases	0.3

GENERAL BIOLOGY

Dermal Absorption

The absorption of SNS was measured in porcine skin (Cytotest Cell Research GmbH & Co. 1997). Porcine ears obtained from a slaughterhouse on the day of slaughter, before the pig carcasses were steam-cleaned. The ears were washed and cleaned with cold, deionized water and shaved. The skin was removed by dissection (2 to 3 mm skin thickness).

The skin was mounted in each of four glass diffusion chambers with a total surface area exposed of 1.13 cm². Receptor chambers were filled with 7 ml of physiologic saline (0.9% NaCl solution) and 339 μ l of SNS (at a concentration of 1 μ g/ μ l in deionized water) was placed in donor chambers. Each donor chamber was covered with parafilm and the diffusion chambers placed in an incubator at 37°C. Samples (0.5 ml) were drawn from the receptor chamber at regular intervals. After the sample was taken, 0.5 ml of deionized water was added to each receptor chamber to keep volume constant. Samples were analyzed by measuring the amount of UV absorbed at 227 nm. The experiment was replicated once.

The appearance of SNS in the receptor fluid increased with time as shown in Table 5. The concentration of SNS in the receptor chambers was corrected by subtracting the measured values in the receptor chamber at 0 h and then presented in Table 6 as a percentage of the amount of material applied. At 24 h, the portion of the applied material that appeared in the receptor fluid ranged from 0.64% to 1.34%.

After the last sample was taken, the concentration of SNS in the donor chamber was determined by taking a 10- μ l sample and measuring absorbance at 227 nm. Skin patches were removed and eluted with 2 ml of deionized water, centrifuged, and the concentration of SNS in the supernatant was determined; this value was converted to a total quantity of material eluted. The concentration of SNS in the donor chamber and the total amount eluted from the skin patches is shown in Table 7. It was possible to elute only a small quantity of SNS (on the order of 5 μ g) from the skin sample and the donor fluid concentration was almost identical to that at the start of the experiment (1000 μ g/ml).

The authors concluded that only small amounts of SNS were lost from the donor fluid by penetration through or absorption into porcine skin. Of the 339 μ g applied, only around 5 μ g was noncovalently bound to the skin and only approximately 1% of the applied material appeared in the receptor fluid (Cytotest Cell Research GmbH & Co. 1997).

ANIMAL TOXICOLOGY

Acute Oral Toxicity

SPNS has an oral LD₅₀ of 3.8 g/kg in rats (RTECS 1997).

An azo-mixture containing 64.7% SPNS had an oral LD₅₀ of 0.37 g/kg in albino rats. A screening dose of 5.0 g/kg resulted in 90% mortality (MB Research Labs 1981).

TABLE 5

Concentration ($\mu\text{g/ml}$) of Sodium Naphthalenesulfonate appearing in receptor chambers as a function of time (Cytotest Cell Research GmbH & Co. 1997)

Time (hours)	Experiment 1				Experiment 2			
	Chamber 1	Chamber 2	Chamber 3	Chamber 4	Chamber 1	Chamber 2	Chamber 3	Chamber 4
0	0.00	0.08	0.05	0.01	0.09	0.13	0.10	0.10
0.5	0.13	0.14	0.14	0.08	0.14	0.09	0.09	0.14
1.0	0.14	0.17	0.16	0.09	0.17	0.13	0.14	0.19
2.0	0.24	0.25	0.28	0.22	0.22	0.17	0.25	0.25
4.0	0.24	0.28	0.28	0.18	0.31	0.27	0.39	0.33
6.0	0.34	0.42	0.37	0.29	0.38	0.34	0.50	0.36
8.0	0.31	0.49	0.41	0.33	0.38	0.32	0.55	0.35
24.0	0.51	0.53	0.52	0.62	0.49	0.44	0.75	0.58

A 25% suspension of SPNS (as Darvan no. 1) in water was administered intragastrically to albino rats. The oral LD_{50} was 3.25 g/kg (Food and Drug Research Labs 1961).

SNS had an oral LD_{50} of 13.9 g/kg in rats (RTECS 1997).

Subchronic Oral Toxicity

A trade compound containing 86% SPNS was administered in feed at 0, 50, 150, 500, 1000, and 2500 ppm to groups of 10 male and 10 female rats for 90 days. There were no reported clinical signs of toxicity, feed consumption effects, or body weight effects. Also no changes in blood chemistry, blood counts, organ weights, or pathology were observed at any dose level. The no-observed-effect level (NOEL) for this study was reported at 500 ppm due to slight increases in urinary sugars in both males and females and urine protein concentrations in males (Rohm and Haas 1998).

Acute Dermal Toxicity

SPNS powder (as Darvan no. 1) (4, 8, 16 g/kg) was applied to the moistened depilated trunk of rabbits (1 inch of area was

abraded). Two rabbits were tested at each dose. The material was wiped off after 24 h and rabbits observed for 14 days. Transient erythema and edema were observed. Using the Draize scale with a maximum score of 8, scores of 3 were noted in all rabbits on days 1 and 2. The reactions lessened during the 2-week observation period; on day 14, rabbits dosed with 4 and 8 g/kg had 0 scores and rabbits dosed with 16 g/kg had scores of 1. The approximate dermal LD_{50} > 16.0 g/kg (Food and Drug Research Labs 1961).

Acute Ocular Toxicity

SPNS powder (as Darvan no. 1) (10 mg) was instilled into one conjunctival sac of three rabbits. Eyes were scored according to the Draize scale (maximum score of 110). Slight, transient irritation of conjunctiva was observed; the cornea and iris were not affected. Individual scores were 14, 10, and 14 at the 4-h observation; 4, 4, 4 on day 1; 4, 4, 2 on day 2; and 0 on days 4 and 7 (Food and Drug Research Labs 1961).

The ocular irritation potential of undiluted SNS was tested in three New Zealand white rabbits by Safepharm Laboratories Ltd. (1997). One drop of local anesthetic was instilled into both

TABLE 6

Percentage of applied Sodium Naphthalenesulfonate appearing in receptor chamber as a function of time (Cytotest Cell Research GmbH & Co. 1997)

Time (hours)	Experiment 1				Experiment 2			
	Chamber 1	Chamber 2	Chamber 3	Chamber 4	Chamber 1	Chamber 2	Chamber 3	Chamber 4
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.27	0.11	0.17	0.14	0.09	0.00	0.00	0.09
1.0	0.28	0.17	0.22	0.15	0.15	0.00	0.07	0.20
2.0	0.49	0.34	0.47	0.44	0.26	0.07	0.30	0.31
4.0	0.50	0.41	0.48	0.35	0.44	0.29	0.59	0.48
6.0	0.70	0.70	0.66	0.58	0.58	0.42	0.81	0.55
8.0	0.63	0.84	0.74	0.66	0.59	0.38	0.93	0.53
24.0	1.05	0.92	0.97	1.26	0.81	0.64	1.34	1.00

TABLE 7

Sodium Naphthalenesulfonate concentration in donor fluid ($\mu\text{g}/\text{ml}$) and the amount (μg) eluted from skin patches at the end of the experiment (Cytotest Cell Research GmbH & Co. 1997)

Chamber	Experiment 1		Experiment 2	
	Concentration in donor fluid*	Amount eluted from skin	Concentration in donor fluid*	Amount eluted from skin
1	947.13	4.74	996.51	5.99
2	985.04	5.59	1003.49	5.69
3	995.51	5.19	1000.00	4.99
4	929.18	5.39	992.02	4.89

*Sodium Naphthalenesulfonate was applied at a concentration of $1 \mu\text{g}/\mu\text{l}$ in a $339\text{-}\mu\text{l}$ aliquot.

eyes at 3-min intervals over a period of 15-min before treatment. A volume of 0.1 ml (approximately 64 mg) of SNS was placed into the conjunctival sac of the right eye. For the conjunctivae, redness, chemosis, and discharge were determined and for the cornea, degree of opacity and area of opacity were determined. Any damage to the iris was noted. Assessments were made at 1, 24, 48, and 72 h. Additional observations were made on days 5 and 7 to assess the reversibility of any ocular effects.

Areas of diffuse corneal opacity were noted in all treated eyes at 1 and 24 h, which lessened at 48 and 72 h. Areas of translucent corneal opacity persisted in one treated eye at the day 5 observation. Sloughing of the cornea was noted in one treated eye at day 5, but the other two animals' eyes returned to normal at day 7. The authors concluded that SNS was at least a moderate irritant to the rabbit eye. Because one rabbit showed irreversible ocular damage, the test material was viewed as corrosive to the eye (Safepharm Laboratories Ltd. 1997).

A similar study was conducted by Safepharm Laboratories Ltd. (1998) using 2% SNS in polyethylene glycol 400. A single instillation of a 2% (*w/v*) dilution to the conjunctival sac nonanesthetized, nonirrigated right eye of three rabbits. The damage measures described above were used. Observations were made at 1, 24, 48, and 72 h after exposure. Minimal conjunctival irritation was observed at 1 h, but did not persist, and treated eyes appeared normal at 24 h. The authors concluded that 2% SNS was a minimal irritant to the rabbit eye.

Dermal Irritation

The Drug Safety Testing Center Co., Ltd. (1992a) tested SNS using three female Japanese albino rabbits. The test material (0.5 g) was applied to abraded and intact skin at clipped sites on the animals' backs and a closed patch applied. After 24 h, the closed patch was removed, and the skin reactions were scored at 3, 24, and 48 h thereafter.

Three abraded and three intact sites received SNS at a concentration of 100%, 20%, and 2% (these latter concentrations were diluted with petroleum jelly). One abraded and one intact site received petroleum jelly. Reactions were scored for erythema and eschar formation on a scale of 0 to 4, and for edema on

the same scale. A total score in the range of ≥ 5 to 8 was considered severely irritating; ≥ 2 to < 5 was moderately irritating; > 0 to < 2 was mildly irritating; and a score of 0 was considered not irritating. In only one animal, at the 3-h reading, was a grade 1 erythema seen with the undiluted material. No positive erythema or edema scores were seen with the other animals exposed to undiluted SNS, or with any animal exposed to the 2% or 20% dilution in petroleum jelly, and to the petroleum jelly alone. The authors concluded that SNS may be considered a mild irritant when applied undiluted, but that the 2% and 20% dilutions are not irritating (Drug Safety Testing Center Co., Ltd. 1992a).

Dermal Sensitization

The Drug Safety Testing Center Co., Ltd. (1992b) evaluated delayed contact hypersensitivity in Guinea pigs exposed to SNS. Ten animals were in the treatment group and 10 in the control group. The test site on the flank was clipped and shaved and 0.5 g of SNS at a concentration of 30% (*w/w*) (diluted in petroleum jelly) was applied for 6 h under a closed patch, once a week, for 3 weeks. A control site received only the petroleum jelly. Two weeks after the last application, 0.1 g each of 30%, 10%, 3%, or the petroleum jelly were applied to the shaved skin and left for 24 h under a closed patch. Skin reactions were scored on a —, \pm , +, ++, +++ scale at 24 and 48 h. In no case was there a positive response, leading the authors to conclude that SNS has no potential to induce delayed contact hypersensitivity.

A Guinea pig maximization test was conducted by the Gifu Research Laboratory (1999). Ten animals were treated and 5 animals served as controls. A day before initial sensitization, hair was clipped and the skin shaved in the dorsal neck area. Materials used in initial sensitization were a 1:1 emulsion of Freund's complete adjuvant (FCA) with distilled water; a 1:1 emulsion of FCA with SNS (2% *w/w* in physiologic saline); a 1% SNS solution in distilled water; and distilled water alone. In each of the 10 test animals, a volume of 0.1 ml each of the FCA/distilled water emulsion was injected into each of two sites. That procedure was repeated for the FCA/SNS emulsion and the 1% SNS solution. Each of five control animals received 0.1 ml

injections of distilled water at two sites and FCA/distilled water emulsion at four sites. On day 7, the same shaved area as in the initial sensitization of each animal in the treatment group received 0.2 ml of 50% SNS solution on a lint pad, with a closed patch over the pad for 48 h. Control animals were treated in a similar manner, except with distilled water. On day 21 after the initial sensitization, remote induction sites on treated and control animals were exposed to 0.1 ml/site (on a lint pad) of 30%, 10%, or 5% SNS solution or distilled water and a closed patch applied for 24 h. Skin reactions were observed and graded for erythema and eschar formation (scale of 0 to 4) and edema (scale of 0 to 4) at 24, 48, and 72 h.

No skin irritation was seen at any site during the initial or the second sensitization treatments. No reactions were seen to any of the induction concentrations of SNS in either the treatment or the control animals (Gifu Research Laboratory 1999).

GENOTOXICITY

SPNS (tan granules identified under the trade name Tamol SN) was tested in the Ames assay using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 at 5000 $\mu\text{g}/\text{plate}$. It was negative both with and without metabolic activation at a dose range of 0.1 to 500 $\mu\text{g}/\text{plate}$ (Litton Bionetics, Inc. 1977).

Safepharm Laboratories Ltd. (1996) stated that SNS was negative in an Ames assay using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538. Five dose levels (50, 150, 500, 1500, and 5000 $\mu\text{g}/\text{plate}$) were studied, in triplicate, with and without addition of S9 liver homogenate metabolic activation. Positive controls included *N*-ethyl-*N'*-nitro-*N*-nitroguanidine for TA100 and TA1535; 9-aminoacridine for TA1537; 4-nitro-*o*-phenylenediamine for TA1538, and 4-nitroquinoline-1-oxide for TA98. A vehicle control was used, as well as a positive control with 2-aminoanthracene, which is mutagenic only with metabolic activation.

SNS was not toxic to any of the strains tested at any of the concentrations tested. SNS produced no significant increase in the mutation frequency in any of the strains tested at any of the concentrations tested. All of the positive controls produced marked increases in the mutation frequency, and the S9 liver homogenate metabolic activation was confirmed active with the additional positive control. The authors concluded that SNS is not mutagenic under the conditions of the test (Safepharm Laboratories Ltd. 1996).

CLINICAL ASSESSMENT OF SAFETY

Kao Corporation (1992) applied SNS at concentrations of 2% and 0.2% (*w/w* in distilled water) with a Finn chamber and an occlusive patch to 40 healthy subjects. Distilled water was the control. The 25 male subjects ranged in age between 20 and 25 years and the 15 female subjects were between 21 and 28 years of age. The Finn chamber was removed 48 h after application and the site graded 3, 24, and 48 h thereafter. Grading

was done on a $-$, \pm , $+$, $++$, $+++$ scale. Apparent erythema ($+$) was observed in one subject and slight erythema (\pm) in 3 to 4 subjects exposed to 2% SNS. Erythema with edema ($++$) was observed in 1 subject, apparent erythema in 2 others, and slight erythema in 5 to 9 subjects exposed to 0.2% SNS. Distilled water produced apparent erythema in 1 to 2 subjects, and slight erythema in 6 to 11 subjects. The authors concluded that the reactions to both concentrations of SNS was not substantially different from distilled water and that the skin irritation potential of SNS is considered to be weak.

ConTox Limited (1997) conducted a 21-day cumulative irritation and sensitization study using 50 subjects. There were initially 52 subjects, but 2 dropped out of the study for personal reasons. Occlusive patches containing 0.2 ml of a 1% SNS solution (*w/v* in distilled water) were applied to the back. The patch locations were randomized from subject to subject. Each patch was removed after 24 h. The skin was graded 30 min later and a fresh patch of the test material applied to the same site. This procedure was repeated for 21 consecutive applications as the induction phase. After approximately 2 weeks, the subjects were challenged at the same site and at a remote, previously untreated site under occlusive patches for 24 h. All sites were graded 24, 48, and 72 h after removal of the challenge patch. A 0.5% solution (*w/v* in distilled water) of sodium lauryl sulfate was used as a positive control and a commercial baby oil product was the negative control in both the induction and challenge phase. The authors reported slight erythema in one individual on 3 successive early induction days, but no reactions on any other induction days. No positive findings were seen in the other 49 subjects at any time during the induction phase, leading the authors to conclude that 1% SNS is not a primary or cumulative skin irritant. One individual had a slight erythema at the remote, previously untreated site at the 24-h reading, but not at 48 or 72 h. No other subjects had a positive reaction at either the original site or the remote site. The authors concluded that 1% SNS is not a dermal sensitizing agent under the study conditions.

SUMMARY

SPNS and SNS are sodium salts of naphthalene sulfonic acid. Formaldehyde is used in the production of SPNS and remains in the final product.

In 1998, the cosmetics industry reported to FDA that SPNS was used in 50 formulations. Industry data indicate concentration of use ranged from 0.1% to 0.4%. SPNS functions as an emulsion stabilizer, surfactant—hydrotrope, and/or surfactant—suspending agent. SNS functions as a surfactant—hydrotrope, but was not reported to be used.

Neither ingredient absorbs in the UVA or UVB region of the spectrum. SNS is manufactured by reacting naphthalene with sulfuric acid to produce a sulfonic acid, which is then reacted with sodium hydroxide to produce the final product. The polymer form uses the sulfonic acid intermediate in a reaction with formaldehyde and water under conditions of heat and pressure to

form the polymer sulfonic acid form, to which sodium hydroxide is added to make the final SPNS. The residue level of formaldehyde was 0.09%, below the 0.2% limit for free formaldehyde established earlier by the Cosmetic Ingredient Review (CIR) Expert Panel for formaldehyde.

Only around 1% of SNS in a 1-mg/ml solution applied to porcine skin penetrated the skin after 24 h, only a little over 1% was found noncovalently bound to the skin, and the concentration of material applied to the surface of the skin was largely unchanged.

SPNS had an oral LD₅₀ of 3.8 g/kg and SNS had an oral LD₅₀ of 13.9 g/kg in rats. SPNS had a dermal LD₅₀ >16.0 g/kg in rabbits. A NOEL of 500 ppm was reported in a subchronic oral toxicity study in rats based on increases in urinary sugar in females and urine protein concentrations in males.

Although undiluted SPNS was not a significant eye irritant in rabbits, undiluted SNS was a moderate eye irritant in rabbits. At 2%, SNS was a minimal eye irritant in rabbits.

Undiluted SNS was at most a mild irritant in Guinea pigs, and was nonirritating at 20% and 2%. In a delayed contact hypersensitivity test in Guinea pigs, 30% SNS used in the induction phase and in the challenge phase produced no reactions. In a Guinea pig maximization test, 1% SNS used with FCA injected in the initial sensitization, 50% SNS applied topically in the second sensitization, and up to 30% SNS applied topically in the challenge phase did not produce any irritation or sensitization.

Both ingredients were negative in Ames mutagenesis assays.

In clinical studies, SNS was neither an irritant (tested up to 2%), cumulative irritant (tested up to 1%), nor a sensitizer (tested up to 1%).

DISCUSSION

When these ingredients were considered by the CIR Expert Panel in March, 1999, a final conclusion was reached that the available data were insufficient to support the safety of these ingredients in cosmetic formulations. The Panel based this decision on a lack of information on either direct determination of dermal penetration or on an octanol/water partition coefficient value that could predict potential penetration. If such data did indicate significant skin penetration, or if these ingredients would be used in formulations that may contact mucous membranes or be ingested, the Panel further indicated that dermal developmental and reproductive toxicity data, genotoxicity data, and possibly carcinogenicity data may be needed.

Under the CIR Procedures, Section 46, Amendment of a Final Report, a petition to amend a Final Report may be submitted after the further data and information requested by the Expert Panel has been obtained. The Panel has since received several pieces of data on SNS, including new skin penetration data, and complete study reports on ocular toxicity and dermal irritation and sensitization in animals, mutagenesis studies, and clinical tests.

In assessing this new information, the Panel considered the relatively low penetration of the monomer, SNS, and the small amount of the monomer that appeared to be bound to the skin, even after 24 h, to be a worst-case scenario. The likely penetration of SPNS would be even lower. The Panel also considered that a 24-h dermal absorption study was acceptable because formulations containing these ingredients would be washed off at least once every day. Although 1% penetration through the skin is not so low as to preclude any concern regarding possible systemic toxicity, the Panel considered the low penetration in concert with the low concentrations of use of these ingredients and the absence of significant overall toxicity and the limited negative genotoxicity findings sufficient to support a tentative amended conclusion that SNS and SPNS are safe as used in cosmetic formulations intended to be applied to the skin.

The Panel did receive information from two companies that SPNS is not used in products intended to contact mucous membranes. Such uses by other companies is unclear, however. Also, use of SPNS in formulations that may contact mucous membranes or be ingested seems likely given the types of cosmetic products in which they are used. The Panel remains concerned that the barrier properties of the skin do not apply when these ingredients may contact mucous membranes or may be ingested. Accordingly, the Panel has reaffirmed the initial conclusion that the available data are insufficient to support the safety of SNS and SPNS in cosmetic formulations that may contact mucous membranes or be ingested. The additional data needed to make a safety assessment for these uses are:

1. Dermal reproductive and developmental toxicity data.
2. One genotoxicity assay in a mammalian system, and if that study is positive, then a 2-year dermal carcinogenicity study using National Toxicology Program (NTP) methods may be needed.

CONCLUSION

On the basis of the available data, the CIR Panel concludes that SPNS and SNS are safe as used in cosmetic formulations intended to be applied to the skin. The available data, however, are insufficient to support the safety for use in cosmetic products which may contact mucous membranes or be ingested.

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