Amended Safety Assessment of Isethionate Salts as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review Expert Panel reviewed the safety of twelve isethionate salts, which function as surfactants in cosmetic products. Although there are data gaps, the similar chemical structures, physicochemical properties, functions and concentrations in cosmetics, and the expected bio-handling enabled grouping these ingredients and reading across the available toxicological data to support the safety assessment of each individual compound in the entire group. The Panel concluded that isethionate salts were safe as cosmetic ingredients in the present practices of use and concentration, when formulated to be non-irritating.

INTRODUCTION

In 1993, the Cosmetic Ingredient Review (CIR) published the safety assessment of sodium cocoyl isethionate with the conclusion "safe for use in cosmetic formulations at 50% in rinse-off products and at 17% in leave-on products".[1] These concentration limits were based on the maximum concentrations reported in safety test data at the time. Sodium cocoyl isethionate functions primarily as a surfactant-cleansing agent and the majority of the uses reported are in coloring and non-coloring hair products.[2,3]

Since the original review, a few new studies were published relating to general toxicokinetics and clinical assessment of safety. These new data have been incorporated in this amended safety assessment.

The information from the original safety assessment is summarized in italics at the beginning of each section.

In addition to the original ingredient, sodium cocoyl isethionate, the ingredients ammonium cocoyl isethionate, sodium hydrogenated cocoyl methyl isethionate, sodium isethionate, sodium lauroyl isethionate, sodium lauroyl methyl isethionate, sodium methyl isethionate, sodium myristoyl isethionate, sodium oleoyl isethionate, sodium oleyl methyl isethionate, sodium palm kerneloyl isethionate, and sodium stearoyl methyl isethionate have been added to this safety assessment.

The similar chemical structures, physicochemical properties, functions and concentrations in cosmetics, and the expected bio-handling enabled grouping these ingredients and reading across the available toxicological data to support the safety assessment of each individual compound in the entire group. These cosmetic ingredients include components that have been previously reviewed and concluded to be safe for use by the CIR Expert Panel. The ingredients, their conclusions, a summary of the findings, and published citations are found in Table 1.

CHEMISTRY

Definition and Structure

The definitions and structures of the ingredients presented in this report are found in Table 2. The ingredients in this report are related by a common 2-hydroxyethanesulfonic acid structural core (Figure 1), which has an alcohol moiety at one end of a two carbon alkyl chain, and a sulfonic acid at the other end (that is in an acid salt form in these ingredients). Sodium isethionate is the cosmetic ingredient name for the sodium salt of 2-hydroxyethanesulfonic acid, while the rest of the ingredients in this report are simple alkyl esters (or mixtures of simple alkyl esters) of 2-hydroxyethanesulfonic acid. These chemicals have the classical structural components of surfactants, with a hydrophobic alkyl tail and a hydrophilic sulfonate anion at the opposite end.

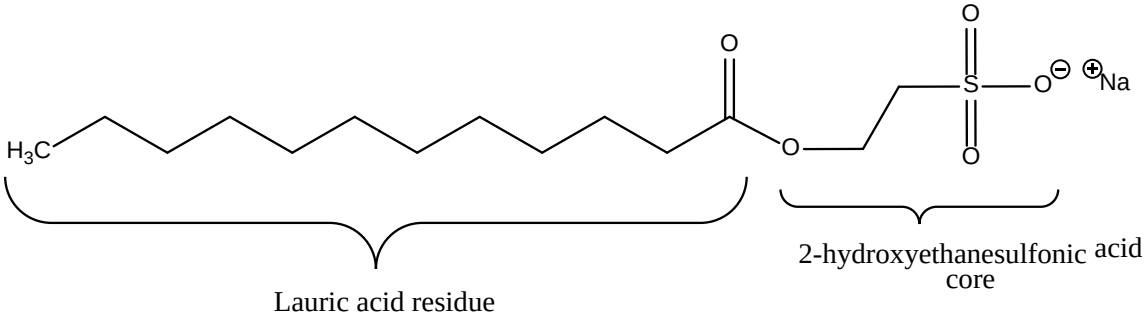


Figure 1. Sodium Lauroyl Isethionate

Physical and Chemical Properties

Physical and chemical properties of sodium cocoyl isethionate and sodium isethionate can be found in Table 3.

Sodium cocoyl isethionate has limited solubility in water (0.01% by weight at 25ºC). Zwitterionic detergents (betaines), alkylamphoacetates, and nonionic sugar surfactants of alkyl glucose esters, aldobionamides, gluconamides, glyceramides, glyceroglycolipids, polyhydroxy fatty acid amides, and alkyl polyglycosides have been used in liquid detergents to increase the solubility of sodium cocoyl isethionate.[4]

Impurities

As reported in the original safety assessment, sodium cocoyl isethionate may contain the following impurities: arsenic (3 ppm max.), iron (25 ppm max.), lead (20 ppm max.), sodium chloride (0.8% max.), free fatty matter (10% max.), sodium isethionate (5%), free fatty acid (18%), and sodium soap (3%).[1]

USE

Sodium cocoyl isethionate is reported to be a surfactant ingredient in mild synthetic detergent (syndet) cleansing bars.[5]

Table 4a presents the available product formulation data for the sodium cocoyl isethionate ingredients. According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Reporting Program (VCRP), sodium cocoyl isethionate was used in a total of 52 cosmetic products at the time of the original safety assessment. Use concentrations ranged from 10 to 50%.[1] Current VCRP data indicate that sodium cocoyl isethionate is now used in at least 490 cosmetic products, with almost half of the uses reported to be in hair dyes and colors.[2] A survey of use concentrations conducted by the Personal Care Products Council in 2008 reported a range from 0.1 to 53%.[6]

Table 4b presents the 2013 VCRP data and the 2008 use concentration data for the cosmetic ingredients that were added to the sodium cocoyl isethionate safety assessment. Currently, the VCRP database indicates that, of the additional ingredients, sodium isethionate has the most uses (77) with the majority in bath soaps and detergents.[2] The maximum use concentration range for sodium isethionate was 0.1% to 5%, with the 5% reported in bath soaps and detergents.[6]

Those ingredients with no reported uses or use concentrations are listed in Table 3c.

Sodium cocoyl isethionate was reported to be used in indoor tanning preparations that may be in aerosol form and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.[7-10] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[8,9]

The isethionate salts are not restricted from use in any way under the rules governing cosmetic products in the European Union.[11]

TOXICOKINETICS

Sodium Cocoyl Isethionate

Female Yorkshire pig skin was used in an in vitro study of the effects of the size of sodium cocoyl isethionate micelles relative to the aqueous pores in the stratum corneum through mannitol skin permeability and average skin electrical resistivity measurements.[12] A sodium cocoyl isethionate contacting solution (0.2-200 mM) was applied to the skin in vertical Franz diffusion cells for 5 h. The exposure was in the context of a hindered-transport aqueous pore pathway model of the stratum corneum.

Sodium cocoyl isethionate micelles and the aqueous pores of the stratum corneum had average radii of 33.5 $\pm$ 1 Angstroms and 29 $\pm$ 5 Angstroms, respectively, as determined with dynamic light-scattering measurements. The size of the sodium cocoyl isethionate micelles relative to the pore size prevented penetration into the stratum corneum. The authors concluded that sodium cocoyl isethionate micelles cannot contribute to sodium cocoyl isethionate skin penetration and associated skin barrier perturbation, which allows sodium cocoyl isethionate to be mild to the skin.

The authors also performed an in vitro quantitative skin radioactivity assay using radiolabeled sodium cocoyl isethionate and pig full-thickness skin. Skin penetration of sodium cocoyl isethionate was concentration-dependent in a manner consistent with the effects of micelle formation. This finding further supported the authors' conclusion that sodium cocoyl isethionate micelles cannot penetrate through the smaller aqueous pores of the stratum corneum, and thus cannot induce skin barrier perturbation.[12]

The ability of sodium cocoyl isethionate to affect the skin barrier was studied using two-photon fluorescence microscopy (TPM).[5] In addition to the isethionate, sodium dodecyl sulfate (SDS), with and without glycerol, glycerol, and the control, phosphate buffered saline (PBS), were also studied. Sodium cocoyl isethionate was prepared for visualization as a 1% by weight solution with sulforhodamine B (SRB) and applied to harvested female Yorkshire pig

skin in Franz diffusion cells for 5 h. After the application period, the skin samples were rinsed four times with PBS, exposed to an aqueous SRB fluorescent probe solution in the diffusion cells for an additional 24 h, and then rinsed again four times with PBS and blotted to remove excess SRB. The skin samples then underwent TPM imaging.

When compared to SDS, sodium cocoyl isethionate had a weaker skin barrier interaction, especially in the corneocyte envelopes and the corneocyte keratins. The authors found that sodium cocoyl isethionate does not induce the formation of localized transport regions in the skin barrier. The authors also found that sodium cocoyl isethionate promoted SRB penetration into the intercellular lipid bilayers of the stratum corneum, although this effect is also lower than that observed in SDS. Sodium cocoyl isethionate did not induce significantly deeper penetration of SRB and had significantly smaller SRB-skin partition coefficients and SRB-skin penetration depths, all when compared to SDS. This study indicates that sodium cocoyl isethionate is a mild surfactant relative to SDS because it reduces skin penetration of an irritant by reduced porosity-to-tortuosity ratio without reduced average pore radius.[5]

ANIMAL TOXICOLOGY

Sodium cocoyl isethionate is slightly to practically nontoxic, with an oral LD_{50} of $\geq$ 4.33 g/kg for rats. Dermal application of 1.0% -36.0% w/w aqueous sodium cocoyl isethionate to rats for 28 days did not result in significant toxic effects. Erythema was observed at times during the study.[1]

Acute Toxicity

Oral – Non-Human

Sodium Isethionate

In an acute oral toxicity study, 5 male and 5 female Wistar rats received 5000 mg/kg bodyweight sodium isethionate in water (50% w/v).[13] One female rat died after administration of the test substance. The death was determined to not be treatment-related. No clinical signs of toxicity were observed in any of the rats. Decreased body weight was observed in 1 female rat. There were no macroscopic findings at necropsy. The LD_{50} value was greater than 5000 mg/kg bodyweight.

Repeated Dose Toxicity

Oral – Non-Human

Sodium Isethioante

In a repeated oral dose toxicity study, male and female Wistar rats received sodium isethionate at doses of 50, 200 or 1000 mg/kg body weight/day in bi-distilled water (10 ml/kg body weight) daily for 91/92 days via gavage.[13] The study was performed according to OECD guideline 408. Test groups were comprised of 10 animals of each sex, except for the control group and the high dose group, which consisted of 15 animals of each sex. All animals were killed at study end and gross pathology and histopathology exams were performed.

All rats survived until study end. No clinical signs of toxicity were observed during daily or weekly observations. There were also no toxicologically relevant ophthalmoscopic changes, no differences in the mean feed consumption, no changes in hematology parameters at 50 mg/kg/day or 200 mg/kg/day, and no changes in urinalysis parameters at 50 mg/kg/day. Statistically significant differences were noted in the mean hindlimb grip strength values of males treated with 1000 mg/kg/day, but these were considered to be secondary effects to decreased body weights. Slightly decreased mean absolute and relative body weights were observed in 1000 mg/kg/day males. Changes in the hematology parameters of 1000 mg/kg/day group included decreased mean corpuscular hemoglobin concentration values, increased mean absolute and relative reticulocyte counts, and a 'left-shift' in the reticulocyte maturity indices indicative of increased reticulocyte turnover, and decreased hemoglobin distribution width in females only. In 1000 mg/kg/day rats, the clinical biochemistry parameters included decreased glucose levels, increased total bilirubin levels, increased cholesterol and phospholipid levels, and increased aspartate or alanine aminotransferase activities. Increased sodium levels in all 3 dose groups, decreased potassium levels in all 3 dose groups, increased calcium levels at 1000 mg/kg/day, increased phosphorus in females at 1000 mg/kg/day, and increased chloride levels in males at 200 mg/kg/day were also observed. Gross pathology and histopathology findings included increased spleen weights in rats at 1000 mg/kg/day, macroscopic changes in the liver (an increased incidence of tan foci reported in the liver of males and females treated with 1000 mg/kg/day) after the treatment period only, microscopic changes in the liver (presence of degeneration) necrosis (focal or of single hepatocytes), bile ducts hyperplasia, focal hepatocytic hyperplasia, peribiliary fibrosis and an increased incidence and severity of mixed inflammatory cells infiltration in the parenchyma) and spleen (increased hemopoiesis) with complete post-recovery reversibility. In this repeated oral dose toxicity study, it was concluded that the no-observed-adverse-effect-level (NOAEL) for sodium isethionate was 200 mg/kg body weight/day.[13]

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Sodium Isethionate

The teratogenic potential of sodium isethionate was studied in Wistar rats.[13] Groups of 4 females received once daily oral treatments of 0, 50, 200, or 1000 mg/kg body weight sodium isethionate in highly purified water (dose volume = 10 ml/kg) from day 0 to day 20 post coitum. During the treatment period, the dams were observed for clinical signs of toxicity, and feed consumption and body weights were measured. All dams were killed on day 21 post coitum for necropsy and the fetuses were removed by Caesarean section for examination. All dams survived until the scheduled necropsy and no clinical signs of toxicity were observed. Feed consumption was marginally decreased when compared to the controls in the high dose group, but the body weight gains were within normal parameters and this observation was not considered toxicologically relevant. Feed consumption and body weight gains were within normal parameters in the remaining dose groups. Pre- and post-implantation loss and the mean number of fetuses per dam were not affected by treatment with sodium isethionate at any dose level. No macroscopic findings were noted during necropsy. In the fetuses, no test material-related effects on fetal sex ratios or fetal body weights were observed. Also, no test material-related abnormalities were noted during the visceral examination or during the examination of fetal skeletons and cartilages. It was concluded that sodium isethionate was not teratogenic in the doses tested in this study and the NOAEL for maternal and fetal organisms was considered to be 1000 mg/kg body weight/day.

GENOTOXICITY

Sodium cocoyl isethionate was negative for genotoxicity in an Ames test at concentrations up to 1000 µg/ml with metabolic activation and up to 100 µg/ml without metabolic activation. Sodium cocoyl isethionate was also negative for genotoxic potential in a Chinese hamster ovary cytogenetics assay with and without metabolic activation at concentrations up to 300 µg/ml.[1]

In Vitro

Sodium Isethionate

In an Ames test, sodium isethionate was tested for mutagenicity with *Salmonella typhimurium* strains TA 98, TA100, TA 1535, TA 1537, and TA 1538 and *E. coli* WP2uvrA. The test was conducted with and without metabolic activation with concentrations up to 10,000 µg/plate.[13] Sodium isethionate was not toxic to the bacterial strains. No dose-dependent increase in the number of revertants was observed in any of the bacterial strains with and without metabolic activation. Sodium isethionate was not mutagenic in this Ames test.

The potential of sodium isethionate to induce mutations was studied using the mouse lymphoma thymidine kinase locus L5178Y assay according to OECD guideline 476.[13] Two parallel experiments were performed: the first had a 4 h treatment period with and without metabolic activation, and the second had a 24 h treatment period without metabolic activation and a 4h treatment period with metabolic activation. A range-finding experiment preceded the main testing. Sodium isethionate in deionized water was tested at concentrations up to 1500 µg/mL. Positive controls were methyl methane sulfonate and cyclophosphamide. No substantial and reproducible dose dependent increase in mutant colony numbers was observed in both main experiments. No relevant shift of the ratio of small versus large colonies was observed up to 1500 µg/mL. The positive controls yielded expected results. In this mouse lymphoma thymidine kinase locus L5178Y assay, sodium isethionate did not induce mutations with or without metabolic activation.

The potential for sodium isethionate up to 1500 µg/ml to induce micronuclei in human lymphocytes was assessed according to OECD guideline 487.[13] Two parallel experiments were performed: in the first, the exposure period to sodium isethionate in deionized water was 4 h with and without metabolic activation, and in the second, the exposure period to the test material was 24 h without metabolic activation mix and 4 h with metabolic activation. The chromosomes were prepared 32 h (experiment 1) and 52 h (experiment 2) after start of treatment with the test material. No visible precipitation of the test item in the culture medium was observed. No relevant cytotoxicity, indicated by reduced cytochalasin blocked proliferation index (CBPI) and described as cytostasis could be observed in this study up to 1500 µg/ml. In both experiments, with and without metabolic activation, no biologically relevant increase in the number of cells carrying micronuclei was observed.

CARCINOGENICITY

No relevant published carcinogenicity studies on isethionate salts were discovered and no unpublished data were submitted.

IRRITATION AND SENSITIZATION

In ocular irritation studies in rabbits, 2.5% -49% sodium cocoyl isethionate was a mild to a primary ocular irritant; sodium cocoyl isethionate was defined as an ocular irritant at concentrations ≥ 15%. In a dermal study, sodium cocoyl isethionate at a concentration of 15.0% and pH of 7.0 was moderately irritating to the intact and abraded skin of rabbits. In 2 dermal irritation studies of 5% sodium cocoyl isethionate solutions using rabbits, the test article was not a primary dermal irritant in one study (but had potential for mild irritation) and it was a moderate primary dermal irritant in the other study. A 2% solution of a formulation containing 47.5% sodium cocoyl isethionate was not phototoxic, but it was mildly irritating to the skin of rabbits. In 2 studies in which a modified Buehler test was performed using guinea pigs, sodium cocoyl isethionate did not produce a sensitization reaction.[1]

In human irritation studies, an 8% aqueous solution of sodium cocoyl isethionate produced minimal irritation in 5 modified soap chamber tests while testing was discontinued in a sixth study due to the resulting irritation. A 4% aqueous solution of a formulation containing 15% sodium cocoyl isethionate was non-irritating. Solutions containing 0.10%-1.0% sodium cocoyl isethionate were mildly irritating, where as a 4%-6% solution of a formulation containing 15% sodium cocoyl isethionate was a moderate to severe irritant. An RIPT was performed using a formulation containing 49.87% sodium cocoyl isethionate at 0.1%-0.5% under a closed patch and at 4.0%-8.0% under open conditions. The test article did not produce a sensitization reaction. In 2 RIPTs, one using a formulation containing 17% sodium cocoyl isethionate and the other using a 2% solution of a formulation containing 47.5% sodium cocoyl isethionate, the test article was not clinically irritating and did not induce allergic contact dermatitis. In a human study using a modified Draize procedure, a formulation containing 15% sodium cocoyl isethionate did not produce an allergic reaction.[1]

Irritation

Dermal – Non-Human

Sodium Isethionate

The skin irritation potential of sodium isethionate was tested according to OECD guideline 404 in 3 New Zealand White rabbits.[13] Approximately 500 mg of sodium isethionate in 0.1 ml of isotonic saline was applied to shaved skin and semi-occluded for 4 h before being rinsed off. The skin did not show any sign of erythema or edema up to 3 days after application. Mean scores on all observation time points after application were 0 for the 3 animals. The test substance was classified as not irritating.

Ocular – Non-Human

Sodium Isethionate

The eye irritation potential of sodium isethionate was tested according to OECD guideline 405 in 3 New Zealand White rabbits.[13] Approximately 100 mg of the test substance (undiluted) was instilled for 24 h. Swelling of the lids and redness of the conjunctiva and iris one hour after application was observed in the eyes. The mean scores for the 3 animals on day 1, 2 and 3 for chemosis and redness of the conjunctiva were 0.2 and 0.7, respectively. These symptoms were fully reversible by 48 hours. The test substance was not considered irritating.

Sensitization

Dermal – Non-Human

Sodium Isethionate

The sensitization potential of sodium isethionate was investigated by a LLNA test according to OECD guideline 429.[13] Female CBA mice (5 animals/dose) received the test materials at concentrations of 10%, 25% or 50% in ethanol:deionized water (30:70) according to study protocol. No deaths were observed during the study period. No symptoms of local toxicity on the ears of the mice and no signs of systemic toxicity were observed during the study. The body weights were within normal ranges. The positive control, hexyl cinnamic aldehyde, yielded expected results. The stimulation indices (SI) were determined to be 0.46, 0.48, and 0.56 for sodium isethionate at 10%, 25%, and 50%, respectively. An EC_3 value could not be calculated. It was concluded that sodium isethionate was not a skin sensitizer in this LLNA test.

CLINICAL ASSESSMENT OF SAFETY

Sodium Cocoyl Isethionate

Sodium cocoyl isethionate (2.9%) as well as sodium lauryl sulfate (SLS), disodium lauryl 3-ethoxysulfosuccinate (SUC), and a sodium soap of fatty acids derived from palm oil and coconut oil (SOAP) were used to evaluate the outcome of different irritancy testing methods in 25 volunteers.[14] In visual scoring of one-time occlusive tests, the irritancy rank order for the anionic detergents was SOAP $\geq$ SLS $\geq$ sodium cocoyl isethionate > SUC, while in visual scoring of repeated occlusive and open tests, the order was SLS > sodium cocoyl isethionate $\geq$ SOAP >SUC. Evaluation of the irritancy testing methods using trans-epidermal water loss (TEWL) measurements yielded similar rank orders for all the testing methods.

The different aspects of irritant reactions and skin barrier recovery was studied in 8 surfactants, including 5% sodium cocoyl isethionate.[15] The substances were diluted in a citrate buffer and then applied with Finn chambers to the forearms of 12 volunteers for 48 h. Irritancy was evaluated by clinical assessment, an evaporimeter, a laser Doppler flowmeter, and a corneometer on the day the patches were removed (day 1), and again on days 2, 5, 9, and 14. Sodium cocoyl isethionate produced visual erythema in 42%, 31%, 23%, 13%, and 10% of total on days 1, 2, 5, 9, and 14, respectively. Scaling was observed on day 2 in 3% of total and increased to 22% by day 14. TEWL was elevated on days 1 and 2 with median values at approximately 37 and 31 $g/m^2/h$, respectively. Cutaneous blood flow was elevated on day 2. Among the 8 surfactants tested, SLS was the most irritating, with sodium cocoyl isethionate the next most irritating.

SUMMARY

Note that the Summary only includes information available since the original safety assessment was published. The original safety assessment should be consulted for details on the studies that support the original conclusion.

Sodium cocoyl isethionate functions primarily as a surfactant-cleansing agent and the majority of the uses reported are in coloring and non-coloring hair products. In 1993, CIR published a safety assessment on this ingredient with the conclusion “safe for use in cosmetic formulations at 50% in rinse off products and at 17% in leave on products”. Because of similar chemical structures, physicochemical properties, and functions , the cosmetic ingredients ammonium cocoyl isethionate, sodium hydrogenated cocoyl methyl isethionate, sodium isethionate, sodium lauroyl isethionate, sodium lauroyl methyl isethionate, sodium methyl isethionate, sodium myristoyl isethionate, sodium oleoyl isethionate, sodium oleyl methyl isethionate, sodium palm kerneloyl isethionate, and sodium stearoyl methyl isethionate have been added to this safety assessment.

Sodium cocoyl isethionate was reported to be used in a total of 52 cosmetic products at the time of the original safety assessment. Use concentrations ranged from 10 to 50%. Current VCRP data indicate that sodium cocoyl isethionate is used in 490 cosmetic products, with almost half of the uses reported to be in hair dyes and colors. A survey of use concentrations conducted by the Personal Care Products Council in 2008 reported a range from 0.1 to 53%. Amongst the ingredients added to this amended safety assessment, sodium isethionate has the most uses (77) with the majority in bath soaps and detergents. The maximum use concentration range for sodium isethionate was 0.1% to 5%, with the 5% reported in bath soaps and detergents.

Toxicokinetics studies have found that sodium cocoyl isethionate micelles cannot contribute to sodium cocoyl isethionate skin penetration and associated skin barrier perturbation.

The LD_{50} value was greater than 5000 mg/kg bodyweight in an acute oral toxicity study in Wistar rats that received 5000 mg/kg bodyweight sodium isethionate in water (50% w/v). In a repeated oral dose toxicity study in Wistar rats that received sodium isethionate at doses of 50, 200 or 1000 mg/kg body weight/day in bidistilled, the NOAEL was 200 mg/kg/day.

Sodium isethionate was not teratogenic in Wistar rat dams that received daily oral treatments of 0, 50, 200, or 1000 mg/kg sodium isethionate in highly purified water on days 0 through 20 of gestation. The maternal and fetal NOAEL were considered to be 1000 mg/kg body weight/day.

Sodium isethionate was not mutagenic in an Ames test at concentrations up to 10,000 µg/plate. This ingredient at concentrations up to 1500 µg/ml also did not induce mutations in a mouse lymphoma thymidine kinase locus L5178Y assay, nor did it induce micronuclei in a human lymphocyte assay

In New Zealand White rabbits, sodium isethionate was not a dermal irritant nor was it an ocular irritant.

When tested at concentrations up to 50% in ethanol: deionized water, sodium isethionate was not a skin sensitizer in a LLNA test.

Clinical testing of sodium cocoyl isethionate (2.9%) to compare irritancy potential to other surfactants found that sodium cocoyl isethionate was irritating, but less irritating than SLS.

DISCUSSION

A safety assessment for sodium cocoyl isethionate was published by CIR in 1993 with the conclusion of safe for use in cosmetic formulations at 50% in rinse off products and at 17% in leave on products. These concentration limits were based on the maximum concentrations reported in safety test data at the time. The CIR Expert Panel reopened the final report on sodium cocoyl isethionate based on new data and determined that the report should also address the safety of 11 additional isethionate salts.

The Panel considered that the available single dose and repeated dose animal studies, including reproductive and developmental toxicity studies, supported the safety of sodium cocoyl isethionate and sodium isethionate. The Panel noted the absence of carcinogenicity data, but considered the data demonstrating that sodium cocoyl isethionate and sodium isethionate were not mutagenic or clastogenic in in vitro genotoxicity studies adequate to support the safety of these ingredients.

Although there are data gaps, the similar chemical structures, physicochemical properties, functions and concentrations in cosmetics, and the expected bio-handling enabled grouping these ingredients and reading across the available toxicological data to support the safety assessment of each individual compound in the entire group.

The Panel looked at changes in the pattern of use and concentration of use since the original safety assessment of sodium cocoyl isethionate and noted that the earlier safety assessment had specified use concentrations of up to 50% in rinse-off products and up to 17% in leave-on products as safe. The most recently reported concentration of use of sodium cocoyl isethionate in rinse-off products is 53%. The Panel noted that most surfactants exhibit some irritancy, as was the case with sodium cocoyl isethionate at 2.9%. Products using these ingredients should be formulated to be non-irritating.

The Panel discussed the issue of incidental inhalation exposure from indoor tanning preparations. There were no inhalation toxicity data available. The Panel considered pertinent data indicating that incidental inhalation exposures to some of these ingredients in such aerosolized cosmetic products would not cause adverse health effects, including dermal irritation and sensitization.

The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs; in principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the twelve isethionate salts listed below are safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating. This conclusion supersedes the earlier conclusion issued by the Expert Panel in 1993.

Sodium Cocoyl Isethionate
Ammonium Cocoyl Isethionate
Sodium Hydrogenated Cocoyl Methyl Isethionate*
Sodium Isethionate
Sodium Lauroyl Isethionate
Sodium Lauroyl Methyl Isethionate
Sodium Methyl Isethionate
Sodium Myristoyl Isethionate*
Sodium Oleoyl Isethionate*
Sodium Oleyl Methyl Isethionate*
Sodium Palm Kerneloyl Isethionate*
Sodium Stearoyl Methyl Isethionate*

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

TABLES AND FIGURES

Table 1. Constituent acids with CIR conclusions

Constituent	Conclusion (year issued; maximum use concentration reported)	Summary of Findings	Reference
Coconut Acid and Palm Kernel Acid	safe as used (2011; coconut and palm kernel acid not reported in leave-ons; coconut acid14% and palm kernel acid 12% in rinse-offs)	The safety focus of use of the plant-derived fatty acid oils was on the potential for irritation and sensitization since the cosmetic ingredients reviewed were also found in the foods that are consumed daily. 5% aq. solutions of a bar soap containing 13% sodium cocoate had irritation scores of 1.6-4.0/8 in animal studies. However, the remaining animal and clinical irritation and/or sensitization studies conducted on a large number of the oils included in this report, primarily in formulation, did not report any significant irritation or sensitization reactions, indicating that refined oils derived from plants are not dermal irritants or sensitizers.	16-18
Lauric Acid, Oleic Acid, and Stearic Acid	safe as used (1987; reaffirmed in 2006; lauric acid 10%, oleic acid 25% and stearic acid > 50% in leave-ons; lauric acid 25% and oleic and stearic acid 50% in rinse-offs)	Oleic, lauric, palmitic, and stearic acids are fatty acids with hydrocarbon chains ranging in length from 12 to 18 carbons with a terminal carboxyl group. These fatty acids are absorbed, digested, and transported in animals and humans. Little acute toxicity was observed when oleic, lauric, palmitic, or stearic acid or cosmetic formulations containing these fatty acids were given to rats orally at doses of 15-19 g/kg body weight. Feeding of 15% dietary oleic acid to rats in a chronic study resulted in normal growth and health, but reproductive capacity of female rats was impaired. Results from topical application of oleic, palmitic, and stearic acid to the skin of mice, rabbits, and guinea pigs produced little or no apparent toxicity. Studies using product formulations containing oleic and stearic acids indicate that neither is a sensitizer or photosensitizing agent. Animal studies also indicate that these fatty acids are not eye irritants. Lauric, stearic, and oleic acids were noncarcinogenic in separate animal tests. In primary and cumulative irritation clinical studies, oleic and stearic acids at high concentrations were nonirritating. Cosmetic product formulations containing oleic, lauric, palmitic, and stearic acids at concentrations ranging up to 13% were not primary or cumulative irritants, nor sensitizers.	19,20
Myristic Acid	safe as used (2010; 15% in leave-ons; 50% in rinse-offs)	Myristic acid is approved as a food reagent and additive. Myristic acid enhanced the dermal penetration of several drugs. The acute oral LD_{50} and acute dermal LD_{50} of salts of myristic acid were >8 g/kg and >16 mL/kg, respectively, in rats. Acute dermal application of butyl myristate (2 g/kg) was nontoxic and nonirritating to rabbits. When 10 rabbits were treated with a single dermal dose of ethyl myristate (5 g/kg) resulted in the death of 2 over 7 days. The intraperitoneal and subcutaneous LD_{50} for isopropyl myristate exceeded 79.5 mL/kg in rats and the intraperitoneal LD_{50} was >50.2 mL/kg in mice. No death occurred, and no evidence of systemic toxicity was found at necropsy when the rats were exposed to aerosolized isopropyl myristate. Myristic acid, isopropyl myristate, and myristyl myristate were minimally irritating to the eyes of rabbits. Butyl myristate was nonirritating to the rabbit eye. Myristic acid was nonirritating in a single insult occlusive patch test and slightly irritating in a repeat open patch test on rabbits. Butyl myristate was a moderate skin irritant in rabbits and guinea pigs. Isopropyl myristate and myristyl myristate were minimally irritating in several formulations in rabbits and mice. Isopropyl myristate was nonirritating when injected parenterally in albino rabbits. Butyl myristate and myristyl myristate were nonsensitizing to guinea pigs. Isopropyl myristate and myristyl myristate were comedogenic to rabbit ears. Isopropyl myristate tested negative in the Salmonella/microsome test, with and without activation. In clinical primary and cumulative irritation studies, myristic acid was nonirritating. Isopropyl myristate can produce slight irritation but is not a human sensitizer at up to 50%.	20,21

Table 2. Definitions, structures, and functions of isethionate salts.[3] (The italicized text and larger structures below were generated by CIR staff.)

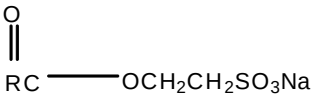
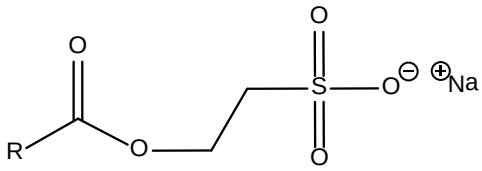
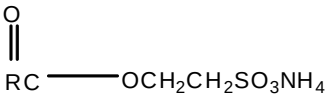
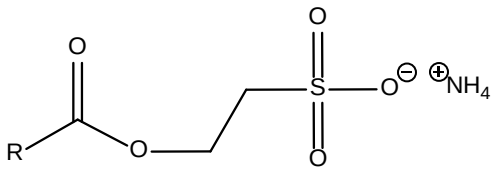
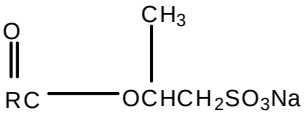
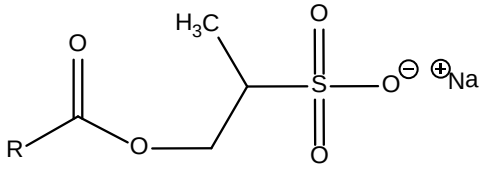
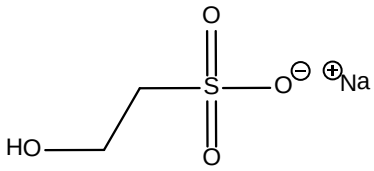
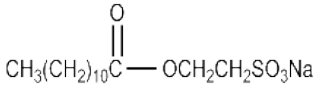
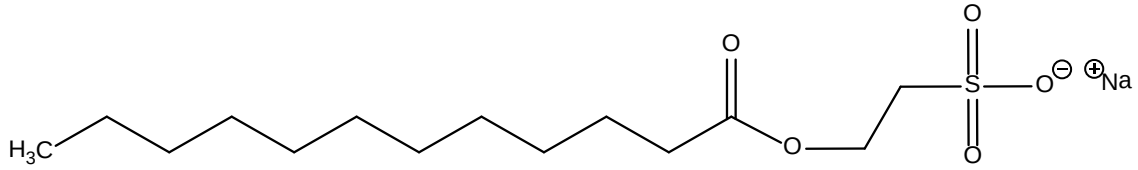
Ingredient	Definition	Structure*	Function
Sodium Cocoyl Isethionate (CAS Nos. 58969-27-0; 61789-32-0)	The sodium salt of the coconut fatty acid ester of isethionic acid.	  RCO- represents the fatty acids derived from coconut oil.	Surfactants - Cleansing Agents
Ammonium Cocoyl Isethionate (CAS No. 223705-57-5)	The ammonium salts of the coconut fatty acid ester of isethionic acid.	  RCO- represents the fatty acids derived from coconut oil.	Surfactants - Cleansing Agents
Sodium Hydrogenated Cocoyl Methyl Isethionate	The organic compound with fatty acids derived from Hydrogenated Coconut Oil. *The sodium salt of 1-(hydrogenated cocoyl oxy)propane-2-sulfonic acid.*	  RCO- represents the fatty acids derived from coconut oil.	Surfactants - Cleansing Agents; Surfactants - Foam Boosters
Sodium Isethionate (CAS No. 1562-00-1)	The organic salt of isethionic acid. *The sodium salt of 2-hydroxyethanesulfonic acid.*	$HOCH_2CH_2SO_3Na$ 	NA
Sodium Lauroyl Isethionate (CAS No. 7381-01-3)	The sodium salt of the lauric acid ester of isethionic acid.	 	Surfactants - Cleansing Agents

Table 2. Definitions, structures, and functions of isethionate salts.[3] (The italicized text and larger structures below were generated by CIR staff.)

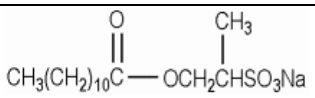
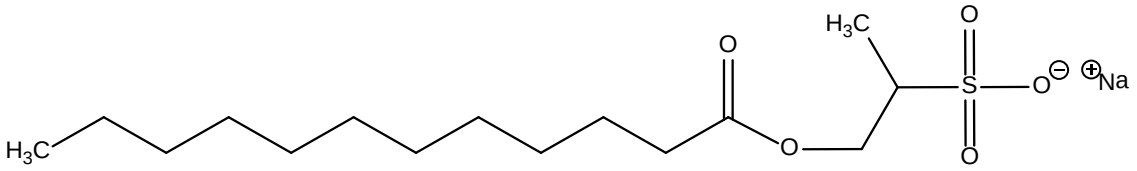
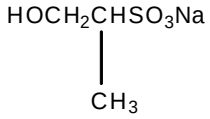
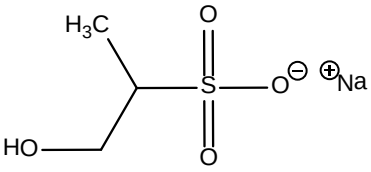
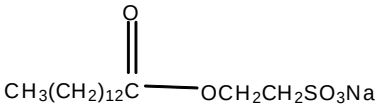
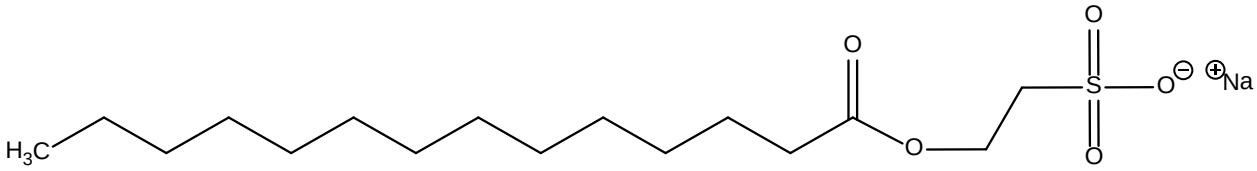
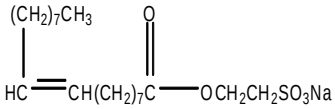
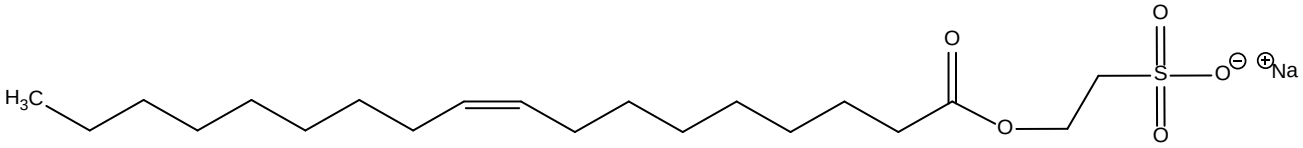
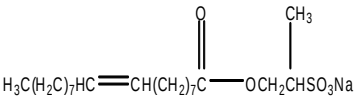
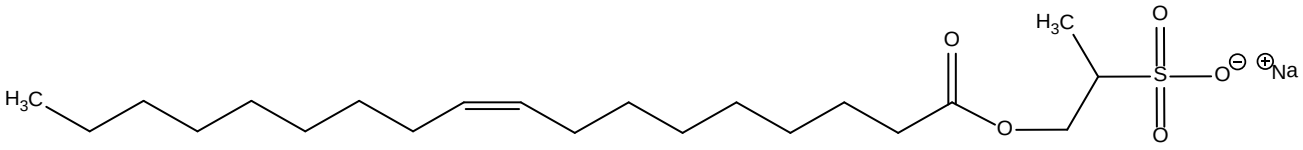
Ingredient	Definition	Structure*	Function
Sodium Lauroyl Methyl Isethionate	The sodium salt of methyl lauric acid ester of isethionic acid. *The sodium salt of 1-lauroyloxypropane-2-sulfonic acid.*	 	Surfactants - Cleansing Agents
Sodium Methyl Isethionate (CAS No. 869737-84-8)	The sodium salt of methyl ester of isethionic acid. *The sodium salt of 1-hydroxypropane-2-sulfonic acid*	 	Surfactants - Emulsifying Agents
Sodium Myristoyl Isethionate (CAS No. 37747-10-7)	The sodium salt of the myristic acid ester of isethionic acid.	 	Hair Conditioning Agents; Surfactants - Cleansing Agents
Sodium Oleoyl Isethionate (CAS No. 142-15-4)	The sodium salt of the oleic acid ester of isethionic acid.	 	Hair Conditioning Agents; Surfactants - Cleansing Agents
Sodium Oleyl Methyl Isethionate (CAS No. 880353-25-3)	The sodium salt of the oleic acid ester of methyl isethionic acid. *The sodium salt of 1-oleoyloxypropane-2-sulfonic acid.*	 	Surfactants - Cleansing Agents; Surfactants - Foam Boosters

Table 2. Definitions, structures, and functions of isethionate salts.[3] (The italicized text and larger structures below were generated by CIR staff.)

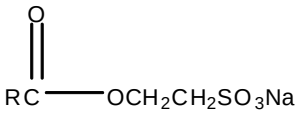
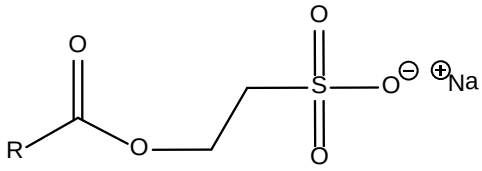
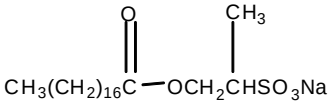
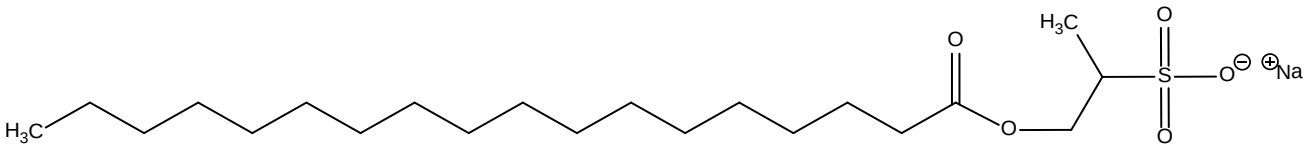
Ingredient	Definition	Structure*	Function
Sodium Palm Kerneloyl Isethionate (CAS No. 93572-04-4)	The sodium salt of the palm kernel fatty acids (mixed) esters of isethionic acid	  RCO- represents the fatty acids derived from palm kernel oil.	Surfactants - Cleansing Agents
Sodium Stearoyl Methyl Isethionate	The sodium salt of the stearic acid ester of α-methyl isethionic acid. *The sodium salt of 1-stearoylpropane-2-sulfonic acid.*	 	Surfactants - Cleansing Agents; Surfactants - Foam Boosters

Table 3. Physical and chemical properties.

	Property	Reference
Sodium Cocoyl Isethionate		
Physical Form	Fine powder	[1]
Color	White	[1]
Odor	Mild	[1]
UV absorbance – molar extinction coefficient ϵ		[1]
210 nm	0.277-99	[1]
290 nm	0.009-2	[1]
320 nm	0.005-0.7	[1]
400 nm	0.004-0.3	[1]
500 nm	0.003-baseline	[1]
Water Solubility g/100 ml @ 25 ºC	0.01	[1]
Water Solubility g/100 ml @ 70 ºC	> 50	[1]
Stability	Stable at pH 6-8, hydrolyzes outside of range	[1]
Assay	82% -83% minimum	[1]
Surface Tension dynes/cm @ 25 ºC	33 in 0.01% soln., 27 in 0.1% soln.	[1]
Sodium Isethionate		
Physical Form	Solid crystaline	[13]
Color	White	[13]
Odor	Odorless	[13]
Density/Specific Gravity g/cm^3 @ 20 ºC	1.76	[13]
Melting Point ºC	190.6-191.6	[13]
Boiling Point ºC	280 (decomp.)	[13]
Water Solubility g/L @ 20 ºC & pH 7.5	534	[13]
Other Solubility mg/L @ 20 ºC	11.7	[13]
Disassociation constants @ 25 ºC	pKa1=15.1, pKa2=1.39	[13]

Table 4a. Historical and current use and concentration of use data for Sodium Cocoyl Isethionate.[1,2,6]

	# of Uses		*Max Conc of Use (%)*	
	Sodium Cocoyl Isethionate			
Data Year	**1993**	**2013**	**1993**	**2008**
Totals*	**52**	**490**	**10-50**	**0.04-53**
Duration of Use				
Leave-On	7	43	NR	0.04-3
Rinse-Off	45	435	10-50	0.1-53[a]
Diluted for (Bath) Use	NR	12	NR	1-22
Exposure Type				
Eye Area	NR	1	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	8	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	38	206	50	0.1-53[a]
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	14	78	10-25	0.04-10
Hair-Coloring	NR	205	NR	0.5
Nail	NR	1	NR	NR
Mucous Membrane	30	99	50	0.7-50[a]
Baby Products	NR	1	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

NR = Not reported.

[a] 3% in a shower gel; 9% in a body exfoliator; 16% in a body wash.

Table 4b. Frequency(2013) and concentration of use (2008) according to duration and type of exposure for expanded Isethionate Salts group.[2,6]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Ammonium Cocoyl Isethionate		**Sodium Isethionate**		**Sodium Lauroyl Isethionate**	
Totals*	**3**	**0.8-5**	**77**	**0.1-5**	**50**	**12-50**
Duration of Use						
Leave-On	NR	NR	1	NR	NR	NR
Rinse-Off	3	0.8	76	0.1-5	50	12-50
Diluted for (Bath) Use	NR	5	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	2	0.8-5	66	0.1-5	44	12-50
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	5	11	NR	6	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	5	61	0.6-5	44	50
Baby Products	NR	5	NR	NR	NR	NR

	Sodium Lauroyl Methyl Isethionate		**Sodium Methyl Isethionate**	
Totals*	**33**	**NR**	**1**	**NR**
Duration of Use				
Leave-On	NR	NR	NR	NR
Rinse Off	33	NR	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	15	NR	1	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	18	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	12	NR	NR	NR
Baby Products	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
NR = Not reported

Table 4c. Not reported in use.
Sodium hydrogenated cocoyl methyl isethionate
Sodium myristoyl isethionate
Sodium oleoyl isethionate
Sodium oleyl methyl isethionate
Sodium palm kerneloyl isethionate
Sodium stearoyl methyl isethionate

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