PINK

Safety Assessment of Isethionate Salts as Used in Cosmetics

CIR EXPERT PANEL MEETING

JUNE 10-11, 2013

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett
Scientific Writer/Analyst
Date: May, 2013
Subject: Draft Tentative Report on Isethionate Salts

Way back in December 2008, the CIR Expert Panel re-reviewed Sodium Cocoyl Isethionate and determined to re-open the report to allow for the development and incorporation of new reproductive and developmental data from Industry. The data at the time were not ready and the Panel agreed to table the report until the data were ready. The data were supposed to be available by the end of 2009. Meanwhile, at the March 2009 meeting with the newest Panel members seated, the Panel agreed to expand the ingredient report to include additional isethionate salts to bring the total number of ingredients reviewed in this safety assessment to 12.

Nearly 5 years have passed and we never received the promised data directly from Industry. We have been recently informed that the data were submitted for REACH and can be accessed through the European Chemicals Agency (ECHA) website (http://echa.europa.eu/en/information-on-chemicals). While we are waiting on legal clarification in general on how we can proceed with utilizing copyrighted material from the ECHA site for unknown third party data, we have been given permission to use the data on sodium isethionate (CAS # 1562-00-1) from all involved parties. These data have been incorporated into the report.

In the time that has passed, the reported uses to the FDA VCRP database have doubled for sodium cocoyl isethionate. In 2008, the reported number of uses was 216. The total number of uses from the most recent query of the VCRP database indicates that there are a total of 490 uses, with almost half of the uses reported to be in hair dyes and colors. We have not received updated concentration of use data, but the 2008 maximum use concentration range was 0.04% to 53%. The Council is currently performing a new concentration of use survey.

Updated searches for sodium cocoyl isethionate as well as the additional salts have been performed. The little relevant data that were available have been incorporated into this safety assessment.

Please note that the minutes from the team and full Panel meeting were taken before CIR began using the transcriptionists.

As noted in the report's introduction, the Panel previously has reviewed the safety of several related fatty acid constituents. These supporting materials have not been included in this report's package; however, if they are needed during the course of your review of the materials, please contact me and I will gladly provide them to you.

The Panel should review the materials in the Isethionate Salts package as well as the draft abstract, discussion, and conclusion of safety assessment and issue a Tentative Amended Safety Assessment.

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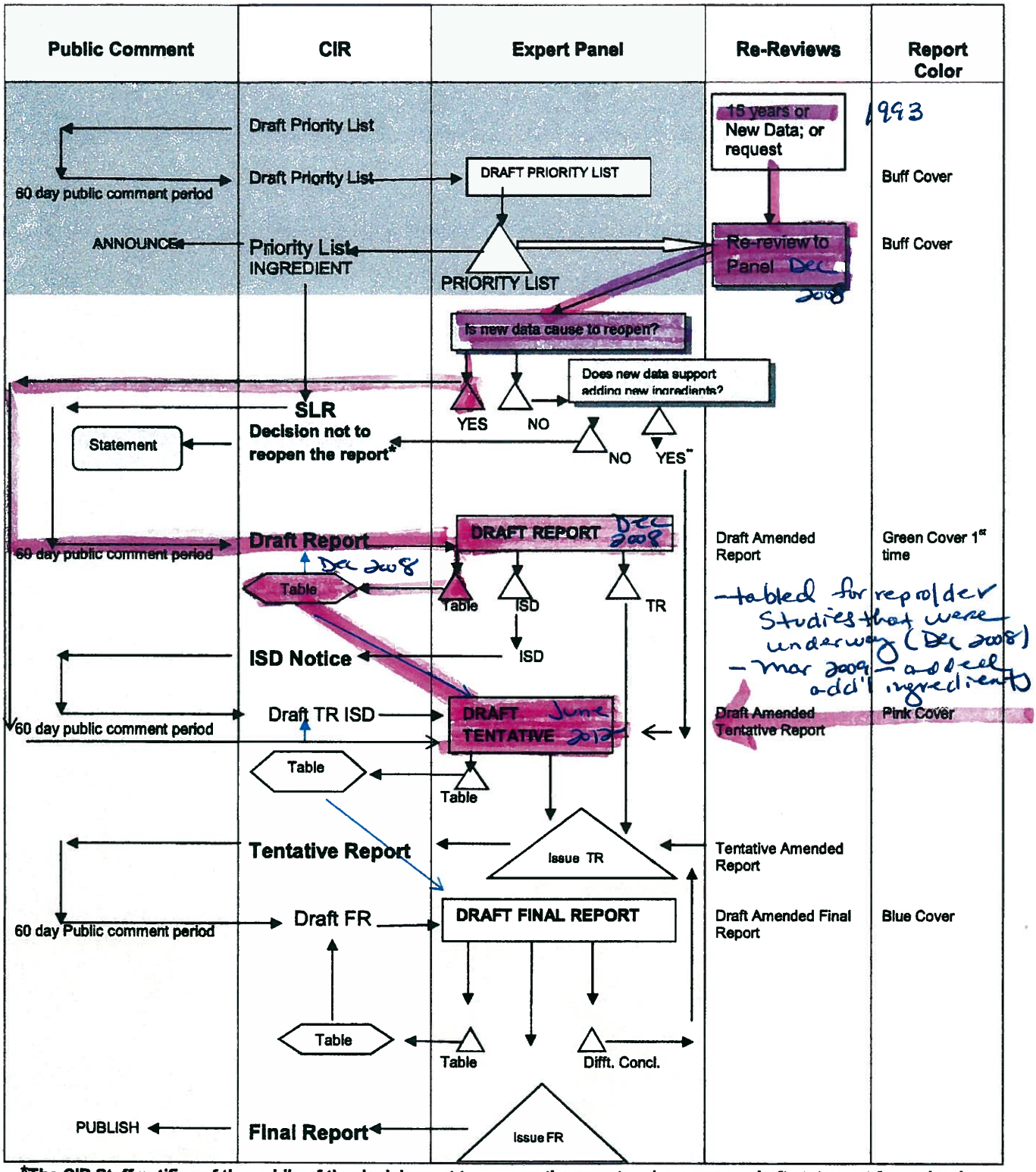
ISethionate Salts

June 2013

SAFETY ASSESSMENT FLOW CHART



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision

Isethionate Salts History

1993 - CIR published the safety assessment on 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".

December 2008 – The Panel re-reviewed Sodium Cocoyl Isethionate and determined to re-open the report to allow for the development and incorporation of new reproductive and developmental data from Industry. The data at the time were not ready and the Panel agreed to table the report until the data were ready. The data were supposed to be available by the end of 2009.

March 2009 – The Panel agreed to expand the ingredient report to include additional isethionate salts to bring the total number of ingredients reviewed in this safety assessment to 12.

Pre-June 2013 - Nearly 5 years have passed and we never received the promised data directly from Industry. We have been recently informed that the data were submitted for REACH and can be accessed through the European Chemicals Agency (ECHA) website (http://echa.europa.eu/en/information-on-chemicals). CIR has been given permission to use the data on sodium isethionate (CAS # 1562-00-1) from all involved parties. These data have been incorporated into the report and the draft amended tentative safety assessment will be reviewed by the Panel.

Minutes from Team and Full Panel Meetings on Sodium Cocoyl Isethionate

DECEMBER 2008

Belsito Team

Dr. Belsito reviewed the history of Sodium Cocoyl Isethionate with the team. He asked if the team felt the report should be reopened to add new data and/or ingredients.

Dr. Mallon from Unilever advised the team that new studies on reproductive toxicity are being developed by industry in order to fulfill EPA's HPV requirements.

Dr. Belsito said that the report should be reopened due to the availability of new data.

Dr. Bailey noted that if the report is tabled, it may be 6 months to a year before the new data is available.

Dr. Snyder noted that the conclusion may need to be amended due to changes in the concentration of use.

Dr. Belsito said that the report could be reopened to add new ingredients. The writer would not need to bring the report back before the Panel right away in order to wait for the new data.

Dr. Andersen agreed that the report could be reopened to add the new ingredients and that the writer could take her time in preparing the draft in order to wait for the new data.

The team reviewed the Barany paper with Ms. Burnett.

Marks Team

The team reviewed the Barany paper with Ms. Burnett.

Representatives from industry alerted the team that reproductive toxicity studies are currently in progress and asked the team to consider tabling the report for a year or so until the new data is ready.

Dr. Shank asked if the proper procedure is to reopen the report first and then table it. The team mulled over their options.

Dr. Mallon from Unilever advised the team that new studies on reproductive toxicity are being developed by industry in order to fulfill EPA's HPV requirements.

Dr. Marks noted that the original report did not flag any missing data needs.

Dr. Mallon explained that the EPA now has more rigorous standards.

Dr. Shank felt that the report could be reopened to add new related ingredients. He said it seems funny to reopen the report to immediately table it for 1 year.

Dr. Marks started reviewing the potential additional ingredients. Dr. Mallon suggested that the new CIR Panel and staff members could assist in determining which ingredients should be incorporated into the reopened report.

Dr. Eisenmann noted that a bulk of the data is on the parent chemical, sodium isethionate.

Dr. Shank asked if free acid is removed during manufacture. Industry replied that almost all free acid is removed.

The team asked Dr. Andersen if it would be appropriate to table discussion of the additional ingredients until the new CIR Panel and staff members were onboard. Dr. Andersen felt tabling the report until the new members arrived was fine.

The team decided to table the report until industry can provide new data and until new CIR members can review the proposed additional ingredients.

Full Panel

Dr. Marks stated that a CIR Final Report with the following conclusion was published in 1993: Based on the products and concentrations tested in studies documented in this report, the CIR Expert Panel concludes that Sodium Cocoyl Isethionate is safe for use in cosmetic formulations at 50% in rinse-off products and at 17% in leave-on products.

Dr. Marks said that his Team was informed that genotoxicity and reproductive toxicity data are expected from industry. He added that the Panel needs to determine which similar ingredients listed in the International Cosmetic Ingredient Dictionary and Handbook should be added to the safety assessment, and that the 2 chemists who will be joining the Panel will contribute greatly to this process. Thus, Dr. Marks' Team agreed that the re-review document should be tabled for the preceding reasons.

Dr. Belsito said that the Panel could proceed to reopen the Final Report and signal its intent to potentially add ingredients.

The Expert Panel voted unanimously in favor of reopening the Final Report on Sodium Cocoyl Isethionate.

March 2009

Belsito Team

Dr. Belsito reviewed the history of Sodium Cocoyl Isethionate with the team. The Panel decided to reopen the report in December in order to incorporate additional related ingredients and to incorporate genotoxicity and reproductive toxicity data that are being developed by industry.

The team noted that the nomenclature needs to reflect the structure of the compounds. In Table 1, sodium methyl isethionate actually should be named to demonstrate that it is a propyl compound.

The team felt that all of the ingredients could be added to the report. The proposed title by the team is "Salts and Ester of Isethonic Acid and Methyl Isethionic Acids as used in cosmetics".

An industry member suggested that the title use the term "acyl esters". Another industry member suggested the title "Fatty Acyl Isethionates and Methyl Isethionate Salts".

The team noted that one use of Sodium Cocoyl Isethionate exceeded the Panel's original limit of 50%.

Industry reported that the new genotoxicity and reproductive toxicity data should be available by the end of the year.

The team noted that a literature search should be performed on the new additions to the report. The report will be tabled until data is available from industry. The team felt that Sodium Cocoyl Isethionate is OK for use at 53% in rinse-off products even though data only on used up to 49% in rinse-off products.

The report is reopened to allow the addition of new data that is being developed and to add related ingredients. Both public and industry data submissions will be incorporated into the report. Studies are in progress.
The Panel received information on the EPA HPV submission that morning. The team expects that it will be added to the report.

The team felt that the likely conclusion of this ingredient group's safety assessment will be "safe in rinse-off products when formulated to be non-irritating". The current limits on the use are based on test data available during the initial review.

Marks Team

Ms. Burnett reviewed the handout that was provided that morning to the team and made the team aware that the report was the same as the one reviewed in December. The Panel is only making a decision on which ingredients to add to the report at this meeting.

Dr. Marks reviewed the history of the ingredient with the team. The report was reopened in December to allow industry to provide new genotoxicity and reproductive toxicity data and to add related ingredients. The toxicity data is still being developed.

Dr. Hill thought that all of the suggested ingredients should be added to the report. Dr. Shank agreed.

Dr. Marks said that the team will suggest adding all of the proposed ingredients in Table 1 at the full panel session the next day.

Ms. Burnett asked the team what they felt the report should be titled.

Dr. Marks replied that the report should be titled "Salts of Isethionic Acid".

Dr. Andersen responded that Isethionic Acid is not a cosmetic ingredient and can't be used in the title of the report.

The title "Fatty Acyl Isethionate Salts" was suggested during the team session.

An audience member found that this title would agree with the REACH nomenclature.

Dr. Hill noted edits for Table 1. There is an issue with the INCI naming of Sodium Methyl Isethionate.

Dr. Shank voiced a concern over including Sodium Hydrogenated Cocoyl Methyl Isethionate in the report.

Dr. Marks asked the team if they felt that all of the proposed ingredients should be added.

Dr. Hill saw no reason not to add all of the ingredients.

Full Panel

At the December 8-9, 2008 Expert Panel meeting, the Panel voted unanimously in favor of reopening the Final Safety Assessment on Sodium Cocoyl Isethionate. At the present meeting, the Expert Panel agreed that the following ingredients should be added to this safety assessment: 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.

Isethionate Salts Data Profile* – June 2013 – Writer, Christina Burnett																								
	In-Use	Composition	Method of Mfg	Toxicokinetics	Acute Tox - Derm	Acute Tox - Oral	Acute Tox - Inhalation	Acute Tox - IV	Acute Tox - Other	Repeated Dose - Dermal	Repeated Dose - Oral	Repeated Dose - Inhalation	Repeated Dose -IV	Repeated Dose - Other	Repro/Dev Tox	Genotoxicity	Carcinogenicity/ Tumor Promoton	Dermal Irritation – Non-Human	Dermal Irritation-Human	Dermal Sens – Non-Human	Dermal Sens – Human	Ocular Irritation	Case Studies	Phototoxicity/ Photosensitization
Sodium Cocoyl Isethionate	X	X	X	X		X				X						X		X	X	X	X	X		X
Ammonium Cocoyl Isethionate	X																							
Sodium Hydrogenated Cocoyl Methyl Isethionate																								
Sodium Isethionate	X					X					X				X	X		X				X		
Sodium Lauroyl Isethionate	X																							
Sodium Lauroyl Methyl Isethionate	X																							
Sodium Methyl Isethionate	X																							
Sodium Myristoyl Isethionate																								
Sodium Oleoyl Isethionate																								
Sodium Oleyl Methyl Isethionate																								
Sodium Palm Kerneloyl Isethionate																								
Sodium Stearoyl Methyl Isethionate																								

"X" indicates that data were available in the category for that ingredient.

Profile takes in account data from original report.

Search Strategy for Isethionate Salts

Search performed in 2008/2009 yielded 5 usable references pertaining to Sodium Cocoyl Isehtionate.

April 2013: SCIFINDER search for Isethionate Salts Using INCI name and CAS #

- For Sodium Cocoyl Isethionate, limited search for time period since 1993.
- Limited for adverse effects, including toxicity - 9 references came back.

	TOXLINE, minus PUBMED	PUBMED
Isethionate	167	795
Isethionate, limit since 1993	137	319
Sodium Cocoyl Isethionate, limit since 1993 + CAS #	11	5
Ammonium Cocoyl Isethionate + CAS #	0	0
Sodium Hydrogenated Cocoyl Methyl Isethionate + CAS #	0	0
Sodium Isethionate + CAS #	1	33
Sodium Lauroyl Isethionate + CAS #	12	2
Sodium Lauroyl Methyl Isethionate + CAS #	0	0
Sodium Methyl Isethionate + CAS #	1	0
Sodium Myristoyl Isethionate + CAS #	0	0
Sodium Oleoyl Isethionate + CAS #	0	0
Sodium Oleyl Methyl Isethioante + CAS #	0	0
Sodium Palm Kerneloyl Isethionate + CAS #	0	0
Sodium Stearoyl Methyl Isethionate + CAS #	0	0

Total references ordered: 7

Amended Safety Assessment of Isethionate Salts as Used in Cosmetics

Status: Draft Tentative Report for CIR Panel Review
Release Date: May 17, 2013
Panel Meeting Date: June 10-11, 2013

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Christina Burnett, Scientific Analyst/Writer, and Bart Heldreth, Ph.D., Chemist CIR.

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DRAFT ABSTRACT

The Cosmetic Ingredient Review Expert Panel reviewed the safety of isethionate salts, which function as surfactants in cosmetic products. The Panel reviewed relevant animal and human data provided in this safety assessment, and 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 on 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] 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 at the beginning of each section in italics.

The cosmetic ingredients 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, and functions and concentrations in cosmetics enable grouping these ingredients and reading across the available toxicological data to support the safety assessment of 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 functional group 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 and the opposite end.

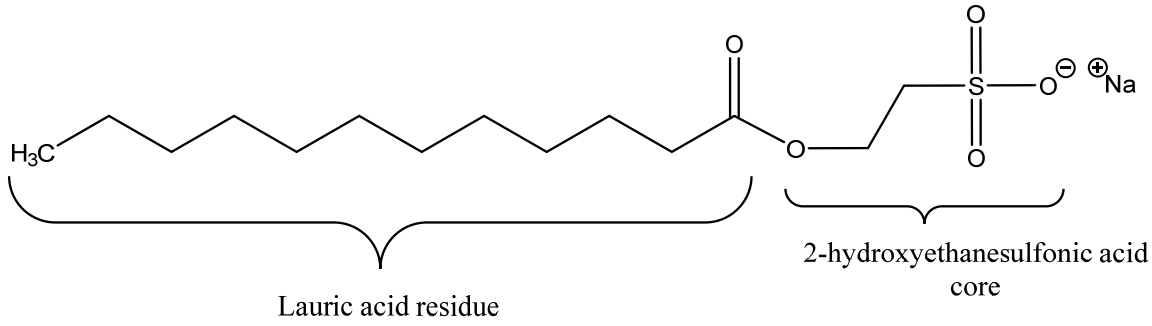


Figure 1. Sodium Lauroyl Isethionate

Physical and Chemical Properties

Physical and chemical properties of sodium cocoyl isethionate can be found in the original safety assessment.[1] Physical and chemical properties of 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, glycerogycolipids, polyhydroxy fatty acid amides, and alkyl polyglycosides have been used in detergents to increase the solubility of sodium cocoyl isethionate in liquid detergents.[4]

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 used in 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 current product formulation 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 a study of the size of sodium cocoyl isethionate micelles relative to the aqueous pores in the stratum corneum through in vitro mannitol skin permeability and average skin electrical resistivity measurements.[12] A sodium cocoyl isethionate contacting solution was applied to the skin in vertical Franz diffusion cells. The exposure was in the context of a hindered-transport aqueous porous 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. Sodium cocoyl isethionate had significant steric hindrance which 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.

This study 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 dose-dependent. This finding 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 with 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 were comprised 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 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 solucions 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

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 dams that received daily treatments of 0, 50, 200, or 1000 mg/kg sodium isethionate in highly purified water. The NOAEL for maternal and fetal organisms was 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 less irritating than SLS.

DRAFT 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. 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, were supportive of 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, and functions and concentrations in cosmetics allow grouping these ingredients together and interpolating the available toxicological data to support the safety of 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 determined that concentration limits need no longer be specified. 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 and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. 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.

DRAFT CONCLUSION

The CIR Expert Panel concluded that the isethionate salt ingredients 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.)

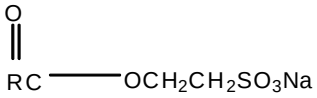
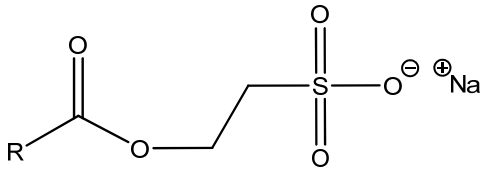
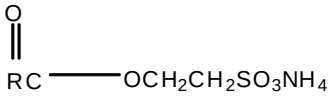
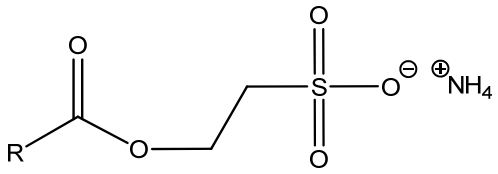
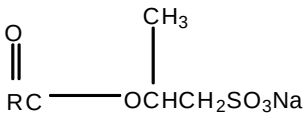
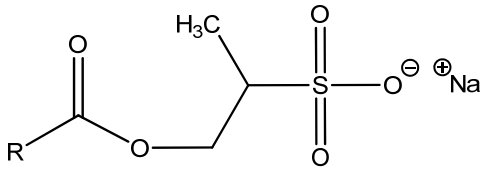
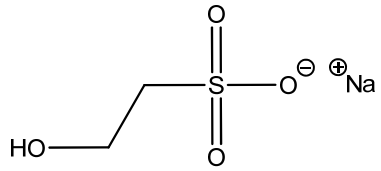
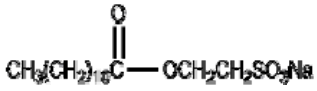
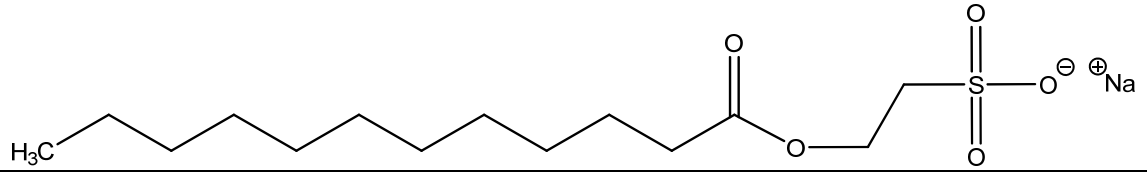
Ingredient	Definition	Structure*	Function
Sodium Cocoyl Isethionate (CAS Nos. 58969-27-0; 61789-32-0)	The sodium salt of the coconut fatty acid ester of isethionic acid.	  RCO- represents the fatty acids derived from coconut oil.	Surfactants - Cleansing Agents
Ammonium Cocoyl Isethionate (CAS No. 223705-57-5)	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)propane-2-sulfoninc 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.)

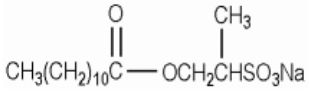
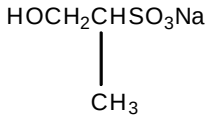
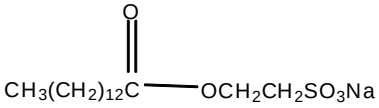
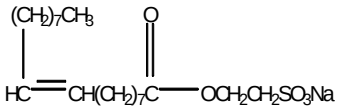
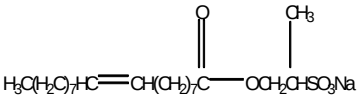
Ingredient	Definition	Structure*	Function
Sodium Lauroyl Methyl Isethionate	The sodium salt of methyl lauric acid ester of isethionic acid. *The sodium salt of 1-lauroylpropane-2-sulfonic acid.*		Surfactants - Cleansing Agents
Sodium Methyl Isethionate (CAS No. 869737-84-8)	The sodium salt of methyl 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 myristic acid ester of isethionic acid.		Hair Conditioning Agents; Surfactants - Cleansing Agents
Sodium Oleoyl Isethionate (CAS No. 142-15-4)	The sodium salt of 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 methyl oleic acid ester of isethionic acid. *The sodium salt of 1-oleoylpropane-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.)

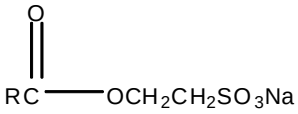
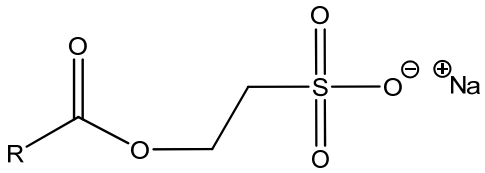
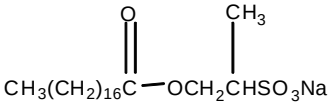
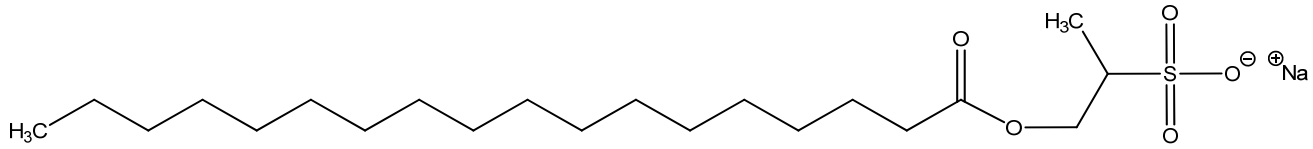
Ingredient	Definition	Structure*	Function
Sodium Palm Kerneloyl Isethionate (CAS No. 93572-04-4)	The sodium salt of the palm kernel fatty acid ester of isethionic acid	  RCO- represents the fatty acids derived from palm kernel oil.	Surfactants - Cleansing Agents
Sodium Stearoyl Methyl Isethionate	The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

Table 3. Physical and chemical properties of sodium isethionate

	Property	Reference
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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2013 FDA Raw Data

05F - Shampoos (non-coloring)	999002038	AMMONIUM COCOYL ISETHIONATE	1
12A - Cleansing	999002038	AMMONIUM COCOYL ISETHIONATE	2
01C - Other Baby Products	61789320	SODIUM COCOYL ISETHIONATE	1
02A - Bath Oils, Tablets, and Salts	61789320	SODIUM COCOYL ISETHIONATE	3
02B - Bubble Baths	61789320	SODIUM COCOYL ISETHIONATE	7
02D - Other Bath Preparations	61789320	SODIUM COCOYL ISETHIONATE	2
03D - Eye Lotion	61789320	SODIUM COCOYL ISETHIONATE	1
05A - Hair Conditioner	61789320	SODIUM COCOYL ISETHIONATE	2
05F - Shampoos (non-coloring)	61789320	SODIUM COCOYL ISETHIONATE	73
05G - Tonics, Dressings, and Other Hair Grooming Aids	61789320	SODIUM COCOYL ISETHIONATE	3
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	61789320	SODIUM COCOYL ISETHIONATE	202
06F - Hair Lighteners with Color	61789320	SODIUM COCOYL ISETHIONATE	2
06H - Other Hair Coloring Preparation	61789320	SODIUM COCOYL ISETHIONATE	1
08G - Other Manicuring Preparations	61789320	SODIUM COCOYL ISETHIONATE	1
10A - Bath Soaps and Detergents	61789320	SODIUM COCOYL ISETHIONATE	69
10E - Other Personal Cleanliness Products	61789320	SODIUM COCOYL ISETHIONATE	18
11E - Shaving Cream	61789320	SODIUM COCOYL ISETHIONATE	3
11F - Shaving Soap	61789320	SODIUM COCOYL ISETHIONATE	1
11G - Other Shaving Preparation Products	61789320	SODIUM COCOYL ISETHIONATE	1
12A - Cleansing	61789320	SODIUM COCOYL ISETHIONATE	60
12C - Face and Neck (exc shave)	61789320	SODIUM COCOYL ISETHIONATE	9
12D - Body and Hand (exc shave)	61789320	SODIUM COCOYL ISETHIONATE	9
12F - Moisturizing	61789320	SODIUM COCOYL ISETHIONATE	9
12H - Paste Masks (mud packs)	61789320	SODIUM COCOYL ISETHIONATE	3
12J - Other Skin Care Preps	61789320	SODIUM COCOYL ISETHIONATE	2
13B - Indoor Tanning Preparations	61789320	SODIUM COCOYL ISETHIONATE	8
05F - Shampoos (non-coloring)	1562001	SODIUM ISETHIONATE	11
10A - Bath Soaps and Detergents	1562001	SODIUM ISETHIONATE	45
10E - Other Personal Cleanliness Products	1562001	SODIUM ISETHIONATE	16
12A - Cleansing	1562001	SODIUM ISETHIONATE	4
12D - Body and Hand (exc shave)	1562001	SODIUM ISETHIONATE	1
05F - Shampoos (non-coloring)	7381013	SODIUM LAUROYL ISETHIONATE	6
10A - Bath Soaps and Detergents	7381013	SODIUM LAUROYL ISETHIONATE	25
10E - Other Personal Cleanliness Products	7381013	SODIUM LAUROYL ISETHIONATE	19
05F - Shampoos (non-coloring)	999003023	SODIUM LAUROYL METHYL ISETHIONATE	18
10A - Bath Soaps and Detergents	999003023	SODIUM LAUROYL METHYL ISETHIONATE	12
12A - Cleansing	999003023	SODIUM LAUROYL METHYL ISETHIONATE	3
12A - Cleansing	869737848	SODIUM METHYL ISETHIONATE	1

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Final Report on the Safety Assessment of Sodium Cocoyl Isethionate

ABSTRACT

Sodium Cocoyl Isethionate is used as a surfactant–cleansing agent in cosmetic formulations. Sodium Cocoyl Isethionate is slightly to practically nontoxic, with an oral LD_{50} of ≥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 produce any significant toxic effects.

The ocular irritation produced by Sodium Cocoyl Isethionate was concentration dependent, ranging from a mild reaction at a test concentration of 2.5% to a primary ocular irritant at test concentrations of 49%. Sodium Cocoyl Isethionate is neither a sensitizer nor phototoxic compound.

Sodium Cocoyl Isethionate was nonmutagenic in an *in vitro* chromosomal aberration assay and did not produce a positive response in an *S. typhimurium* reverse mutation assay.

Based on the concentration of test cited in this report, it is concluded that Sodium Cocoyl Isethionate is safe for use in cosmetic formulations at 50% in rinse-off products and at 17% in leave-on products.

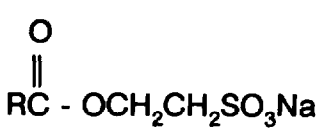
INTRODUCTION

SODIUM COCOYL ISETHIONATE IS THE SODIUM salt of the coconut fatty acid ester of isethionic acid which functions as a surfactant–cleansing agent (Nikitakis, 1988).

CHEMISTRY

Definition and Structure

Sodium Cocoyl Isethionate (CAS No. 61789-32-0) generally conforms to the formula (Estrin et al., 1982a):



where RCO- represents the coconut acid moiety.

Sodium Cocoyl Isethionate is also known as Coconut Fatty Acid, 2-Sulfoethyl Ester, Sodium Salt (Hunting, 1983); Fatty Acids, Coconut Oil, Sulfoethyl Esters, Sodium Salts; Igepon AC-78 (Estrin et al., 1982a); and Jordapon CI (CTFA, 1990a).

Physical and Chemical Properties

Sodium Cocoyl Isethionate is in the form of a fine white powder that consists of active ingredient plus minor impurities and has a mild odor (Estrin et al., 1982b). Sodium Cocoyl Isethionate is stable at a pH of 6–8 and hydrolyzes outside of this pH range (Hunting, 1983). Physical and chemical properties are summarized in Table 1.

Manufacture and Production

Sodium Cocoyl Isethionate is prepared via the following reaction: sodium isethionate is reacted with either the fatty acid mixture from coconut oil (Hoffmann, 1990) or the corresponding chlorides to form Sodium Cocoyl Isethionate (Hunting, 1983). The sodium isethionate was first prepared by adding 1 mole of ethylene oxide to sodium bisulfite.

TABLE 1. CHEMICAL AND PHYSICAL PROPERTIES OF SODIUM COCOYL ISETHIONATE

		References
Physical appearance	Fine white powder	Estrin et al., 1982b
Odor	Mild	Estrin et al., 1982b
UV absorbance—molar extinction coefficient ϵ		CTFA, 1991
210 nm	0.277–99	
290 nm	0.009–2	
320 nm	0.005–0.7	
400 nm	0.004–0.3	
500 nm	0.003–baseline	
Solubility	Soluble in warm water	Hunting, 1983
	Soluble in water	Estrin et al., 1982b
	In water:	CTFA, 1990a
	at 25°C-0.01 g/100 ml	
	at 70°C->50 g/100 ml	
Stability	Stable in pH range of 6–8; hydrolyzes outside this pH range	Hunting, 1983
Assay	83% minimum	Hunting, 1983
	82% minimum	Estrin et al., 1982b
Surface tension	At 25°C:	CTFA, 1990a
	0.01% solution-33 dynes/cm	
	0.1% solution-27 dynes/cm	
Impurities		Estrin et al., 1982b
Arsenic (As)	3 ppm maximum	
Iron (Fe)	25 ppm maximum	
Lead (Pb)	20 ppm maximum	
Sodium chloride	0.8% maximum	
Free fatty matter	10.0% maximum	
Sodium Isethionate	5%	CTFA, 1991
Free fatty acid	18%	
Sodium soap	3%	

Analytical Methods

Sodium Cocoyl Isethionate was identified via infrared spectroscopy; there was no indication of foreign materials (Estrin et al., 1982b).

Ultraviolet Absorbance

Sodium Cocoyl Isethionate was dissolved in high-performance liquid chromatography (HPLC) grade methanol at 1002 mg/L and the ultraviolet (UV) absorbance of the solution was determined using a Perkin Elmer Lambda 4B UV/VIS spectrophotometer (CTFA, 1991). The UV spectrum was scanned from 210 to 500 nm. Sodium Cocoyl Isethionate did not absorb in the UVA or UVB range.

Impurities

The impurities that may be found in Sodium Cocoyl Isethionate are listed in Table 1 (Estrin et al., 1982b; Hunting, 1983). Other impurities and by-products include soap, fatty acid, and unreacted sodium isethionate.

USE

Cosmetic

The product formulation data submitted to the Food and Drug Administration (FDA) in 1992 stated that Sodium Cocoyl Isethionate was contained in a total of 52 cosmetic product formulations (Table 2). Sodium Cocoyl Isethionate was used in the preparation of bath soaps and detergents, noncoloring shampoos, tonics, dressings, and other hair grooming aids, and skin cleansing preparations. The greatest reported use of Sodium Cocoyl Isethionate was in the preparation of bath soaps and detergents, 30 formulations.

Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, the product formulation data submitted to the FDA in 1984 stated that Sodium Cocoyl Isethionate was used at a concentration of ≤50% in bath soaps and detergents and at 10–25% in noncoloring shampoo formulations (FDA, 1984). In 1984, Sodium Cocoyl Isethionate was not reported to be used in tonics, dressings, and other hair grooming aids or skin cleansing preparations.

TABLE 2. PRODUCT FORMULATION DATA FOR SODIUM COCOYL ISETHIONATE (FDA, 1992)[a]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*
Bath soaps/detergents	148	30
Hair shampoos (noncoloring)	909	7
Tonics, dressings, and other hair grooming aids	290	7
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	8
1992 Totals		52

[a]CIR requests that the cosmetic industry provide current formulation data on each product category.

Sodium Cocoyl Isethionate is used as a mild foaming and cleansing agent (Hunting, 1983). It is manufactured primarily for use in synthetic detergent (syndet) bars.

Noncosmetic

As stated in the section on cosmetic use, Sodium Cocoyl Isethionate is used as an ingredient in syndet bars (Hunting, 1983). It is not stated whether this use is only cosmetic or if it has noncosmetic applications.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

An acute oral toxicity test of a syndet bar containing 47.5% Sodium Cocoyl Isethionate was performed on five male and five female albino Sprague-Dawley rats (Hazleton Laboratories America, Inc., 1986a). A uniform suspension of test material in distilled water, at a concentration of 0.25 g/ml, was used. A single dose of 5 g/kg at a volume of 20 ml/kg was given orally by gavage. Animals were fasted for a period of approximately 16–22 h prior to dosing; individual doses were calculated using the fasted weight. Animals were observed for clinical signs and mortality 1, 2.5, and 4 h after dosing, and for 14 days thereafter. Feed and water were available *ad libitum* following dosing. The animals were weighed before fasting, prior to dosing, and at the termination of the study.

Clinical observations for the males included: red-stained faces, diarrhea, and possible respiratory congestion. Three of the males were normal following dosing and through day 14; the other two males were normal by day 1. Observations made for the females included excessive salivation, red-stained faces, diarrhea, hypoactivity, and yellow-staining of the genital area. Two of the females appeared normal by day 1 and the remaining three appeared normal by day 2. An average weight gain was observed for both males and females over the 14 day period. All animals were killed at study termination; necropsy was not performed. The estimated oral LD_{50} was >5.0 g/kg for both male and female Sprague-Dawley rats.

An acute oral toxicity test of a gel cleanser containing 15% Sodium Cocoyl Isethionate was performed using five male and five female Sprague-Dawley CD^R rats (Bio/dynamics, Inc., 1985a). A single dose of 5 g/kg at a volume of 5 ml/kg was administered by oral intubation. Animals were fasted for approximately 18 h prior to dosing; individual doses were calculated using the fasted weight. Animals were observed for clinical signs 1, 2, and 4 h after dosing, and for 14 days thereafter; a viability check was made twice daily. Feed and water were available *ad libitum* following dosing. The animals were weighed before fasting, prior to dosing, and at study termination.

All animals were normal following dosing and for the remainder of the study except for one female with diarrhea on day 3. A weight gain was observed for all animals over the 14-day period. All animals were killed at study termination; necropsy was not performed. The estimated oral LD_{50} was >5.0 g/kg for both male and female Sprague-Dawley rats.

In a paper submitted to CTFA (1990a), the rat oral LD_{50} of pure Sodium Cocoyl Isethionate was 4.33 g/kg.

Short-Term Toxicity

Dermal

A 10-day dose-range-finding study was conducted using Charles River COBS CD^R rats (Unilever Research U.S., Inc., 1991). A daily application of 10.0, 20.0, 40.0, or 60.0% w/w aqueous Sodium Cocoyl Isethionate was applied to the shaved dorsal surface of rats (number of males and females per group not specified) and the test sites were covered by an occlusive patch for 6 h. (These concentrations resulted in dermal dosages of approximately 0.75, 1.52, 2.22, and 4.35 g/kg/day, respectively.)

Dermal irritation was observed at the test site by day 6 for all rats in the 40 and 60% Sodium Cocoyl Isethionate groups. The occurrence and severity of irritation decreased during the remainder of the study. Signs of systemic toxicity were not observed.

A 28-day dermal study was conducted using Charles River COBS CD^R rats to determine the potential systemic effects and target organ toxicity of Sodium Cocoyl Isethionate (Unilever Research U.S., Inc., 1991). Three groups of rats, 10 males and 10 females per group, were dosed with 1.0, 14.0, or 36.0% w/w aqueous suspensions of Sodium Cocoyl Isethionate. (The suspensions for the low- and mid-dose groups were dosed at a volume of 10.0 ml/kg, whereas the suspension for the high-dose group was dosed at a volume of 11.5 ml/kg due to the physical nature of the suspension.) The control group, which was also comprised of 10 males and 10 females, received dermal applications of vehicle.

The hair on the dorsal surface of the rat was shaved the day prior to study initiation. The test article was applied to a surface area of 32 cm^2 for rats <350 g, 36 cm^2 for rats 350–400 g, and 40 cm^2 for rats >400 g. The hair on an area of the hind quarters was also clipped to provide normal skin for comparison. Each animal was dosed once daily for 28 days. An occlusive covering was applied for 6 h after dosing and upon removal of the covering the test site was rinsed.

Prior to dosing, the test site was examined for irritation according to the methods of Draize (Draize, 1959). Toxicologic observations were made twice daily. Body weight and feed consumption were recorded weekly.

Very slight erythema was observed at the application sites of two male rats of the high-dose group during wks 3 and 4 of the study. However, a significant difference in dermal irritation was not observed between the males of the control and high-dose groups. Dermal irritation was not observed for males of the low- and mid-dose groups.

Very slight erythema was observed at the application sites of four of 10 female rats of both the low- and mid-dose groups during wk 1 of the study only. Very slight and well-defined erythema, which was significantly different from controls, was observed at application sites of female rats of the high-dose group on days 4, 5, 6, and 7 of the study only. Very slight edema, which was not significantly different from the controls, was also observed at application sites of females of the high dose group at times throughout the study.

During wks 2 and 3, significant differences in weight gain were observed for males as compared to the controls. A significant effect was not observed for male rats during wk 4 or over the duration of the study. A significant difference in weight gain was not observed for female rats in the test groups as compared to controls. A significant increase in feed consumption was observed for male rats of the mid-dose group during wks 1 and 4 of the study; a significant increase was also observed in cumulative feed consumption data. No other significant differences in feed consumption were observed for male or female rats in the test groups as compared to the controls.

No differences attributable to Sodium Cocoyl Isethionate administration were found in hematologic and clinical chemistry parameters.

A significant increase was observed in the relative organ to body weight ratio for the relative heart weight of males of the high-dose group and for the relative adrenal gland weight for females of the high-dose group. A significant difference in absolute weight was not observed for any of the examined organs in any of the test groups.

One male in the mid-dose group was found dead on day 19. Death was attributed to mechanical trauma and not the application of Sodium Cocoyl Isethionate. Gross and microscopic examination of all animals at study termination did not produce any observations related to dosing with Sodium Cocoyl Isethionate. Dermal application of Sodium Cocoyl Isethionate to rats for 28 days did not result in significant toxic effects.

Ocular Irritation

Ocular irritation studies for Sodium Cocoyl Isethionate are summarized in Table 3.

Three New Zealand White (NZW) rabbits, gender not specified, were used to determine the ocular irritation potential of a cosmetic formulation containing 49% Sodium Cocoyl Isethionate (Lever Research, 1988). The test article was prepared as a 50% aqueous solution and 0.1 ml was applied into the conjunctival sac of each rabbit for 5 min. After 24 h, corneal opacity was observed for all animals and positive conjunctival effects for two of three animals. These effects were not seen after 48 h. The average weighted Draize scores were 14.3/110 after 24 h, 8.0/110 after 48 h, 4.7/110 after 72 h, 2.3/110 after 7 days, and 0.0/110 after 14 days.

An ocular irritation study of a syndet bar containing 47.5% Sodium Cocoyl Isethionate was performed using three male and three female albino NZW rabbits (Hazleton Laboratories America, Inc., 1986b). The eyes of each animal were examined the day before dosing using fluorescein dye and prior to test article application without dye. Test animals were chosen on the basis of an absence of ocular injury or irritation and a body weight >1.5 kg. A dose of 100 mg of test material was placed in the conjunctival sac of one eye of each animal. The eye was held shut for 1 sec following application to prevent loss of material and it was not rinsed following test article application. The other eye of each animal was untreated and served as a control. Body weights were determined prior to test material administration and at weekly intervals throughout the study. Clinical observations were made daily. Eyes were checked for irritation on days 1, 2, 3, 4, and 7. Sodium fluorescein was used to check for corneal injury and the eyes were scored for irritation according to the methods of Draize (Draize, 1975).

The primary ocular irritation score is the total ocular irritation score for all the animals divided by the number of animals observed. The maximum average score (MAS), which is the highest primary eye irritation score, occurred on day 1 and was 34.2. Blanching of the conjunctivae and corneal epithelial peeling were observed in all six animals. On day 7, the primary eye irritation score was 20.3. At this time, the blanching of the conjunctivae and corneal epithelial peeling were still observed in four animals, pannus and corneal neovascularization were seen in three animals, and necrotic areas of the conjunctivae were observed in two animals. No clinical signs were observed throughout the study. The test article was a "primary eye irritant."

An ocular irritation study of a gel cleanser containing 15% Sodium Cocoyl Isethionate was performed using two male and four female albino NZW rabbits (Bio/dynamics, Inc., 1985b). The eyes of each animal were examined the day before

TABLE 3. OCULAR IRRITATION STUDIES FOR SODIUM COCOYL ISETHIONATE

Number, sex, strain	*Dose*	*Methods*	*Results*	*References*
3 NZW rabbits (sex not specified)	49% in formulation	The test article was prepared as a 50% aqueous solution and 0.1 ml was placed in the conjunctival sac of the eye of each animal for 5 min.	At 24 but not 48 h, corneal opacity was observed for all animals and positive conjunctival effects for 2 animals. The average weighted Draize scores were: 14.3/110-24 h; 8.0/110-48 h; 4.7/110-72 h; 2.3/110-7 days; 0.0/110-14 days	Lever Research 1988
6 albino NZW rabbits (3/sex)	47.5% in formulation	A dose of 100 mg was placed in the conjunctival sac of one eye; the eye was not rinsed. The other eye served as a control. Sodium fluorescein was used to evaluate corneal injury.	On day 1, the MAS was 34.2; all animals had blanching of the conjunctivae and corneal epithelial peeling. On day 7, the primary eye irritation score was 20.3; 4 animals had blanching of the conjunctivae and corneal epithelial peeling; 3 animals had pannus and corneal neovascularization; 2 animals had necrotic areas of the conjunctivae. The test article was a "primary eye irritant."	Hazleton Labs. Inc., 1986b
6 albino NZW rabbits (2 males and 4 females)	15% in formulation	A volume of 0.1 ml was placed in the conjunctival sac of the right eye; it was not stated whether the eye was rinsed. The left eye served as a control. Sodium fluorescein was used to evaluate corneal injury.	On day 1, the MAS was 23.3; on day 7, the average score was 1.7. Moderate conjunctival irritation, iridial changes and corneal opacities, ulceration, and stippling was observed for most animals. By day 7, 5 animals had slight conjunctival irritation, while 1 animal had no ocular irritation; none of the animals had corneal irritation. The test article produced "mild and transient ocular irritation" and was an ocular irritant.	Bio/dynamics, Inc., 1985b

TABLE 3. OCULAR IRRITATION STUDIES FOR SODIUM COCOYL ISETHIONATE (*CONTINUED*)

Number, sex, strain	*Dose*	*Methods*	*Results*	*References*
6 albino NZW rabbits (2 males and 4 females)	15% in formulation	A volume of 10 µl was placed on the cornea of one eye; it was not stated whether the eye was rinsed.	On day 1, the MAS was 3.0; on day 3, the average score was 0.0. Slight conjunctival irritation was observed on days 1 and 2 for 5 animals. The test article was "very mildly irritating to the eye" and was not considered an ocular irritant.	Bio/dynamics, Inc., 1985c
9 New Zealand albino rabbits (sex not specified)	5% solution	A volume of 0.1 ml was placed in the conjunctival sac of the eye. The eyes of 3 rabbits were rinsed after 30 sec and the eyes of 6 rabbits were not rinsed. The other eye served as a control.	Rinsed eyes: the solution was minimally irritating, with a maximum mean total score of 8.33/110. Unrinsed eyes: the solution was mildly irritating, with a maximum mean total score of 15.33/110.	Product Safety Labs, 1984a
3 NZW rabbits (sex not specified)	as supplied	A dose of 55 mg was applied to the eye for 5 min.	Corneal opacity and transient iritis was observed in 1 animal 72 h after dosing; opacity was present on day 7 and the eye was completely healed by day 14. Slight iridial and conjunctival irritation was observed in the other 2 animals; these irritations were not observed on day 7. The average weighted Draize scores were: 12.3/110-24 h; 9.0/110-48 h; 9.1/110-72 h; 1.7/110-7 days; 0.0/110-14 days Sodium Cocoyl Isethionate "has the potential to cause sufficient ocular injury as to be considered an eye irritant."	CTFA, 1983
6 NZW rabbits (sex not specified)	2.5% gravimetric aqueous solution	A volume of 0.1 ml was placed in the conjunctival sac of the eye; the eyes were rinsed after 24 h. The other eye served as a control.	The average (Draize) irritation scores were: 3.0-24 h; 1.0-72 h; 0.0-4 days The test article was a "mild ocular irritant."	Consumer Product Testing Co., Inc., 1982

dosing using fluorescein dye and prior to test article application without using dye. A volume of 0.1 ml of test article was placed in the conjunctival sac of the right eye of each animal; the eye was held shut for 1 sec following application to prevent loss of material. (It is not stated whether or not the eye was rinsed.) The left eye of each animal served as a control.

Eyes were checked for irritation on days 1, 2, 3, and 7. On day 1, sodium fluorescein was used to determine corneal ulceration; if stain retention was observed, observation using fluorescein dye was continued until either no dye retention was seen in two observations or the study was terminated (day 7). The eyes were evaluated for irritation according to the methods of Draize (Draize, 1959). A viability check was made twice daily.

The MAS occurred on day 1 and was 23.3. On day 7, the average score was 1.7. Moderate conjunctival irritation characterized by redness, chemosis, and discharge, iridial changes and corneal opacities, ulceration, and stippling was observed for most test animals. By day 7, five animals had slight conjunctival irritation while no ocular irritation was observed for one animal; none of the animals had corneal irritation. The test article produced "moderate and transient ocular irritation" and was an ocular irritant as defined in Title 16 part 1500.3(c) of the Code of Federal Regulations (1985).

An ocular irritation study of a gel cleanser containing 15% Sodium Cocoyl Isethionate was performed using two male and four female albino NZW rabbits (Bio/dynamics, Inc., 1985c). The eyes of each animal were examined as is stated in the previous study. A volume of 10 µl of test article was placed directly on the cornea of one eye of each animal; the eyelid was released immediately after application. (It is not stated whether or not the eye was rinsed.)

Eyes were checked for irritation on days 1, 2, and 3 or until no signs of irritation were present. Irritation was determined as is stated in the previous study. A viability check was made twice daily.

The MAS occurred on day 1 and was 3.0. On day 3, the average score was 0.0. Slight conjunctival irritation characterized by redness and chemosis, was observed in five of the six animals on days 1 and 2. The test article was "very mildly irritating to the eye" and was not considered to be an eye irritant as defined in Title 16 part 1500.3(c) of the Code of Federal Regulations (1985).

Nine New Zealand albino rabbits, sex not specified, were used in a Draize (Draize et al., 1944) primary ocular irritation study of a 5% Sodium Cocoyl Isethionate solution (Product Safety Labs, 1984a). A volume of 0.1 ml of test solution was placed in the conjunctival sac of the eye of each rabbit; the other eye was untreated and served as a control. The treated eyes of three rabbits were rinsed 30 sec after test article administration; the eyes of the remaining six rabbits were not rinsed. The eyes were evaluated for irritation 24, 48, and 72 h following test article application. A 5% Sodium Cocoyl Isethionate solution was minimally irritating to rinsed eyes (classified according to Kay and Callandra, 1962), with a maximum mean total score of 8.33/110, and mildly irritating to unrinsed eyes, with a maximum mean total score of 15.33/110.

Three NZW rabbits were used to determine the ocular irritation potential of Sodium Cocoyl Isethionate (CTFA, 1983). The test article, 55 mg, was applied as supplied to the eye of each rabbit for 5 min. Corneal opacity and transient iritis were observed in one animal for 72 h after dosing. Opacity was present on day 7; the eye was completely healed by day 14. Slight iridal and conjunctival irritation was observed in the other two animals; these irritations were not observed on day 7. The average weighted Draize score was 12.3/110 after 24 h, 9.0/110 after 48 h, 9.1/110 after 72 h, 1.7/110 after 7

days, and 0.0/110 after 14 days. Sodium Cocoyl Isethionate "has the potential to cause sufficient ocular injury as to be considered an eye irritant."

Study of the primary ocular irritation of a 2.5% gravimetric aqueous solution of Sodium Cocoyl Isethionate was performed using six NZW rabbits, sex not specified (Consumer Product Testing Company, Inc., 1982). A volume of 0.1 ml was placed in the conjunctival sac of one eye, which was free from visible ocular defects, of each rabbit. The eye was held shut for 1 sec following test article application. After 24 h, the eye was rinsed. The other eye was untreated and served as a control. The eyes were scored for irritation 24, 48, and 72 h following test article application according to the methods of Draize (1975). If irritation persisted, additional observations were made on days 4 and 7. If two or more animals had a positive reaction the test article was considered an ocular irritant (unless the test was repeated with another six animals without positive reactions).

After 24 h, the average irritation score was 3.0. After 72 h, the average score was 1.0, and on day 4 it was 0.0. The test article, a 2.5% aqueous suspension of Sodium Cocoyl Isethionate, was a "mild ocular irritant."

Dermal Irritation

Three male albino rabbits were used to determine the degree of dermal irritation produced by Sodium Cocoyl Isethionate according to the methods of Draize (Schoenberg, 1985). Sodium Cocoyl Isethionate was adjusted to a total of 15.0% active and pH 7.0. The rabbits' abdomens were shaved and four areas, approximately 10 cm apart, were selected as application sites. The application sites were 1 sq. in.; two sites were abraded and two were left intact.

A volume of 0.5 ml of solution was applied to the skin under gauze that was held in place for 24 h. After 24 h, the patches were removed and the skin was evaluated for irritation. The sites were re-examined after 72 h. The primary irritation score was determined by adding the average values of erythema for intact and abraded skin at 24 and 72 h (four values) and the average values for edema at 24 and 72 h (four values), and dividing the total of the eight values by four. Sodium Cocoyl Isethionate was moderately irritating to the skin of rabbits, with a primary irritation score of 4.2/8.0.

A modified Draize test (Draize, 1975) to determine the irritation potential of a 5% Sodium Cocoyl Isethionate solution was performed using six NZW rabbits, sex unspecified (Consumer Product Testing Company, Inc., 1984). The skin of the mid-dorsal area of the trunk, between the scapulae and the pelvis, was clipped 24 h prior to dose application. Two 2.5 cm^2 areas on opposite sides of the vertebral column were chosen as test sites; the right side was abraded while the left side remained intact. A volume of 0.5 ml of test article was applied once to each site under occlusive wrap for 24 h. After wrap removal, residual test article was removed and the sites were scored for irritation using the Draize scale. The sites were scored again 72 h following dosing. The mean scores from the 24 and 72 h readings were averaged to determine the primary irritation index (PII).

The PII for the 5% Sodium Cocoyl Isethionate solution was 1.38/8.0. This score was interpreted as having potential for mild irritation and the test article may possibly be irritating to some people under occlusive wrap conditions. A 5% Sodium Cocoyl Isethionate solution was not a primary dermal irritant to rabbit skin.

Six New Zealand albino rabbits, sex not specified, were used in a primary dermal irritation study of a 5% Sodium Cocoyl Isethionate solution (Product Safety Labs, 1984b). The trunk of each animal was clipped free of hair. Two 2.5 cm^2 gauze patches

were placed over intact and abraded skin on each animal. A volume of 0.5 ml of test article was applied to intact and abraded skin under two gauze patches; the entire trunk of the animal was wrapped. The patches were removed after 24 h and remaining test article was wiped off. The test sites were evaluated for irritation 24 and 72 h after test article administration. A 5% Sodium Cocoyl Isethionate solution was a moderate primary dermal irritant to rabbits, with a primary irritation score of 2.24/5.1+.

Phototoxicity

A primary dermal irritation and phototoxicity study of a syndet bar containing 47.5% Sodium Cocoyl Isethionate was performed using three male and three female NZW rabbits (Bio/dynamics, Inc., 1987). The day before dosing, the hair on the back of each rabbit was clipped and two test sites, one on each side of the spinal column, were chosen. A Hill Top Chamber was placed on each test site and 0.4 ml of test article, 2% w/v Sodium Cocoyl Isethionate in distilled water, was applied beneath the chamber. The sites were covered by occlusive patches and collars were placed on the animals to prevent disruption of the wrapping and ingestion of test article.

Approximately 2 h after dosing, the occlusive wraps and the patch covering the test site of the right were removed. The patch covering the test site on the left was covered with aluminum foil. The right test site of each animal was subjected to light emitted from a bank of four General Electric F-40BLB UV lights positioned approximately 6 in above the site for 30 min. (The minimal erythemal dose [MED] was not given.) Following exposure, the patches were replaced on the right side of each animal and the aluminum foil was removed from the left side. The test sites were again covered by occlusive patches until 24 h after dosing. Upon patch removal, the test sites were wiped with damp gauze.

One female NZW rabbit served as the positive control and was dosed with 1% Oxsoralen, a known phototoxic agent. The positive control was then treated in the same manner as the test animals.

All sites were scored 1 h after patch removal (the 24 h reading), and 48 and 72 h following dosing according to the Draize scale (Draize, 1975). A modified primary irritation value was calculated for both irradiated and nonirradiated sites by adding the average erythema and edema scores from each reading (six values) and dividing by three.

All six test animals had very slight erythema without edema, both with and without irradiation, after 24 h. After 48 and/or 72 h, only two animals had very slight erythema. The responses of the irradiated and nonirradiated sites were comparable. The positive control had a minimal response at the nonirradiated site, but mild to moderate erythema and edema were observed at the irradiated site. The modified primary irritation values for the test article were 0.4/8 and 0.5/8 for the non-irradiated and irradiated sites, respectively. For the positive control, the primary irritation values were 0.3/8 and 5.3/8 for the non-irradiated and irradiated sites, respectively. The test article was mildly irritating to skin of rabbits, but it did not appear to be phototoxic.

The preceding results are consistent with more recent data indicating that Sodium Cocoyl Isethionate does not absorb in the UVB or UVA range.

Sensitization

The sensitization potential of a syndet bar containing 47.5% Sodium Cocoyl Isethionate was evaluated by performing a modified Buehler test using guinea pigs

(Buehler, 1965; Ritz and Buehler, 1980; Hill Top Research, Inc., 1986). The test was performed using a total of 34 Hartley albino guinea pigs (17 males and 17 females) in three phases.

The appropriate concentration for use in the primary challenge was determined during the primary irritation screen. Four guinea pigs, two males and two females, were used during this phase. The day prior to dosing, the backs of the animals were clipped to provide enough space to test four concentrations. On the day of dosing, occlusive patches incorporating a 25 mm Hill Top Chamber were moistened with 0.3 ml of 0.5%, 1.0%, 1.5%, or 2.0% w/v test article in distilled water. The patches remained in place for 6 h. The next day, a depilatory was applied to the test sites for 8 min and the sites were scored at 24 and 48 h. A concentration of 2.0% w/v in distilled water was chosen for use at induction and at primary challenge.

On the day before induction, the backs of 20 guinea pigs (10 male and 10 females) were clipped free of hair. On the day of dosing, chambers moistened with 0.3 ml of 2.0% w/v test material in distilled water were applied under occlusive patches for 6 h; the sites were scored 24 h after induction. The chambers were reapplied to the same sites, following the same method, during the next 2 wks for a total of three applications.

A primary challenge was performed approximately 2 wks after the last induction. The lower left quadrant of the back of the 20 test animals and of 10 untreated control animals (five males and five females) was clipped. On the following day, a challenge patch moistened with 0.3 ml of 2.0% w/v test article in distilled water was applied to the test and control animals for 6 h. The day after application, a depilatory was applied for 8–11 min. Two and one-half h later, the 24 h observation was made. A 48 h reading was taken the next day.

A plus/minus response, indicating slight patchy erythema, was observed for nine of 20 test animals and seven of 10 untreated controls during the challenge. The incidence and severity of the responses were comparable among the test and control groups. This indicated that sensitization was not induced.

A modified Buehler test using Hartley albino guinea pigs was performed to evaluate the sensitization potential of a gel cleanser containing 15% Sodium Cocoyl Isethionate (Springborn Institute for Bioresearch, Inc., 1985). During the irritation screen, four guinea pigs, two males and two females, were used and concentrations of 10%, 30%, 50%, and 70% test article in distilled water, 0.3 ml/site, were tested. A 70% solution of test article in distilled water was chosen for the induction and 50% test article in distilled water was chosen for the challenge; the volume of test article used in dosing was 0.3 ml for both phases.

During the induction phase, the animals, 10 males and 10 females, were inadvertently dosed with 100% test article as the first application; the following two doses were correct at 70% in distilled water. During the primary challenge, five male and five female guinea pigs were used as the untreated control group.

No responders, scores ≥ 1, were observed in either group following the challenge. Two animals had plus/minus reactions in the test group and six animals had plus/minus reactions in the control group following the primary challenge.

MUTAGENICITY

An *in vitro* chromosomal aberration assay was performed to evaluate the potential of Sodium Cocoyl Isethionate to induce chromosomal aberrations in Chinese hamster

ovary (CHO) cells (Microbiological Associates, Inc., 1991a). The test was performed with and without metabolic activation. Distilled, deionized water (vehicle) was used as the negative control. The positive controls were triethylenemelamine and cyclophosphamide with and without metabolic activation, respectively.

A toxicity test was performed using 0.5–5100 μg/ml Sodium Cocoyl Isethionate. Based on the results of the toxicity test, concentrations of 19, 38, 75, 150, and 300 μg/ml Sodium Cocoyl Isethionate (adjusted for purity of the test article, 72.45%) were used in the study. Metaphase cells were collected for microscopic evaluation 10 h after treatment initiation. At the 150 and 300 μg/ml concentrations, metaphase cells were collected 16 h and 19 h after treatment initiation with and without metabolic activation, respectively, due to a delay in cell cycle kinetics at these concentrations.

Due to excessive toxicity at a concentration of 300 μg/ml, no metaphase cells were obtained at either harvest with or without metabolic activation. Toxicity, as measured by a reduction in mitotic index, was approximately 57 and 71% at the 10 and 16 h harvest, respectively, for 150 μg/ml Sodium Cocoyl Isethionate without metabolic activation. With metabolic activation, toxicity was 94 and 74% at the 10 and 19 h harvest, respectively, for 150 μg/ml. A significant increase in chromosomal aberrations was not observed. Sodium Cocoyl Isethionate was negative in the CHO cytogenetics assay both with and without metabolic activation.

A *Salmonella typhimurium* preincubation reverse mutation assay was performed according to the methods of Ames et al. (1975) and Maron and Ames (1983) to evaluate the mutagenic potential of Sodium Cocoyl Isethionate (Microbiological Associates, Inc., 1991b). *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were used and the study was performed with and without microsomal activation. Sterile, deionized, distilled water (vehicle) was used as the negative control. With metabolic activation, 2-aminoanthracene was used as the positive control. Without metabolic activation, the positive controls were 2-nitrofluorene for TA98 and TA1538, sodium azide for TA100 and TA1535, and ICR-191 for TA1537.

Based on the results of a dose-range-finding study using 10-10,000 μg/ml Sodium Cocoyl Isethionate, concentrations of 10-1000 μg/ml and 1.0-100 μg/ml Sodium Cocoyl Isethionate (adjusted for purity of the test article, 72.45%) were tested with and without metabolic activation, respectively. An initial and a confirmatory assay was performed. In each run, all concentrations of Sodium Cocoyl Isethionate and the positive and negative controls were plated in triplicate.

In the initial assay, a positive response was not observed with or without metabolic activation. Because observed toxicity at 100 μg/ml was marginal, the maximum dose concentration with and without metabolic activation used in the confirmatory assay was increased to 333 μg/ml.

In the confirmatory assay, a 2.0-fold non-dose responsive increase was observed using TA1537 without metabolic activation. However, this was not considered a positive response. Therefore, as in the initial assay, no positive responses were observed with or without metabolic activation.

CLINICAL ASSESSMENT OF SAFETY

Irritation

Five modified soap chamber tests (Frosch and Kligman, 1979) were performed using 8% solutions of Sodium Cocoyl Isethionate (CTFA, 1985a, 1986a, 1986b, 1988a,

1988b). The Webril discs were moistened with approximately 0.2 ml of the test solution in three studies (CTFA, 1985a, 1986a, 1986b) and with 0.1 ml of test article in two studies (CTFA, 1988a, 1988b). The initial patches were applied for 24 h in all the studies, while the patches applied on the remaining 4 days were applied for 6 h periods in all studies except one; in CTFA (1988b), the patches were applied for 5 h periods. Two studies (CTFA, 1985a, 1986a) scored erythema using a scale of 0–5. Three studies (CTFA, 1986b, 1988a, 1988b) scored erythema on a scale of 0–4 and edema and vesicles on a scale of 0–3, with the total irritation score being the sum of these three scores. It was required that all subjects used did not have any skin disorders.

Fifteen subjects completed the first study (CTFA, 1985a). The mean erythema score was 1.9733/5, with individual minimum and maximum mean scores of 0.0 and 4.4, respectively. (A score of 2 was described as moderate, uniform redness.)

The Sodium Cocoyl Isethionate used in the second study, which 14 subjects completed, was 81% active with 15% coco fatty acid (CTFA, 1986a). The test solution was applied to three sites on the right forearm and one site on the left forearm of each subject. The mean erythema scores for the sites on the right forearm were 0.529, 0.486, and 0.686 and the mean erythema score for the site on the left forearm was 1.014, with individual minimum and maximum mean scores for any site of 0.0 and 4.0, respectively. The total average mean erythema score for all four sites was 0.679/5. (A score of 1 was described as slight redness, spotty–follicular or diffuse).

The Sodium Cocoyl Isethionate used in the third study, which 15 subjects completed, was also 81% active with 15% coco fatty acid (CTFA, 1986b). The mean erythema score was 1.36/4, the mean edema score was 0.147/3, and the mean vesicle score was 0.12/3. The total mean irritation score was 1.627. The individual minimum and maximum mean scores were 0.2 and 2.6 for erythema, 0.0 and 0.6 for edema, 0.0 and 0.8 for vesicles, and 0.2 and 3.6 for total irritation score, respectively. (An erythema score of 1 was described as spotty, skin discoloration but not redness–follicular or diffuse, an edema score of 1 corresponded to slight edema, and a vesicle score of 1 corresponded to slight vesicles—one or two.)

In addition to clinical observations for irritation, transepidermal water loss (TEWL) was measured using a Servomed Evaporimeter in the fourth modified soap chamber test, which 19 subjects completed (CTFA, 1988a). TEWL values were measured on day 1 prior to the first application and 30 min after patch removal on days 2 and 5. The TEWL mean readings were 9.6 and 8.9 on days 2 and 5, respectively. The mean erythema score was 1.667/4, the mean edema score was 0.344/3, and the mean vesicle score was 0.258/3. The total mean irritation score was 2.269 (an erythema score of 2 was described as slight redness).

In the fifth study, for which there were 21 subjects at study initiation, it was necessary to discontinue testing on many subjects due to high irritation scores (CTFA, 1988b). (It was noted that irritation scores may have been aggravated by cold, dry weather conditions.) Only the data from the first two days of the study were analyzed. Using these data, an 8% aqueous solution of Sodium Cocoyl Isethionate had a mean irritation score of 2.5 ± 1.5. Sodium Cocoyl Isethionate was numerically much more irritating than the synthetic detergent tauranol, which had a mean score of 2.0.

A modified soap chamber test (Frosch and Kligman, 1979) was performed using an 8% aqueous solution of Sodium Cocoyl Isethionate (CTFA, 1990b). The Webril discs were moistened with 0.1 ml of the test solution and applied to the forearm of subjects for 28 h. Erythema was scored on a scale of 0–4 and edema and vesicles on a scale of 0–3, with the total irritation score being the sum of these three scores. Seventeen subjects,

which were free of any skin disorders, completed the study. According to the protocol, TEWL was to be measured; however, no values for TEWL were reported. The mean erythema, edema, and vesicle scores were 1.235/4, 0.294/3, and 0.0/3, respectively. The total mean irritation score was 1.529.

The primary irritation potential of a gel cleanser containing 15% Sodium Cocoyl Isethionate was evaluated using 12 subjects, seven males and five females (CTFA, 1989). Approximately 20 μl of test material, a 4% aqueous solution, was applied with an occlusive patch to the subscapular region of the back for 48 h. At the end of this 48 h period, the patch was removed and the site was scored 6, 24, and 48 h after removal. In this study, three gel cleansers were tested and it was not made clear if they all contained Sodium Cocoyl Isethionate; however, all three were non-irritating.

A 21-day cumulative irritation patch test was conducted using 0.10% w/v aqueous Sodium Cocoyl Isethionate (Hill Top Research, Inc., 1985). A commercial baby oil was used as a low-irritation control and a concentrate from a purchased deodorant was used as a high-irritation control. Of the initial test group of 40, 35 subjects, 26 females and 9 males, completed the study. A modification of the human skin test of cumulative irritation procedure by Phillips et al. (1972) was used. (The Phillips et al. procedure was a modification of a procedure described by Lanman [1968].)

A volume of 0.3 ml of 0.10% Sodium Cocoyl Isethionate in distilled water, and the same amount of each control, was pipetted onto Webril pads that were applied to the right and left paraspinal regions of the back of each subject. The assignment of test areas for each sample varied among the subjects, but each individual received the same compound on the same site for the duration of the study. Any site scored at the maximum allowable limits was not repatched for the remainder of the study. Each patch was applied for 23 h, after which it was removed and discarded by the subject. The subjects were instructed to bathe after patch removal and report to the laboratory for a 24 h scoring and new patch application. This procedure was carried out for 21 consecutive days.

The group mean score of the 35 subjects who completed 21 days of testing was 0.093/4. The highest individual mean score was 1.143. One subject developed a skin eruption adjacent to the tape area on the lowest site; the lesion was a 2 cm inflamed sebaceous cyst related to the patching procedure and not the material under test. Based on these results, Sodium Cocoyl Isethionate was considered a "very mild" irritant.

A repeat application patch test was conducted using Sodium Cocoyl Isethionate (CTFA, 1984a). Ten of 12 subjects completed the study. Sodium Cocoyl Isethionate was tested as 0.2%, 0.4%, and 1.0% w/v aqueous solutions. A test material on which historical data were known was used as a control. A volume of 0.3 ml of test and control solutions was applied to occlusive clinical patches; the patches were applied to each subject's arm in a vertical row. The assignment of test area for each sample varied among the subjects, but each individual received the same compound on the same site for the duration of the study. A site that was scored a grade of 2+/4 was not repatched for the remainder of the study.

A dot of Gentian Violet dye was applied to the skin at the center of both vertical sides of each patch so that the patch site was identifiable after patch removal. The subjects removed the patches and rinsed the site 24 h after the initial patch application. At 72 h, the subjects reported to the laboratory for scoring of the test areas and to have new patches applied. The patches were removed 24 h after the second application and the area was rinsed. At 120 h, the test areas were scored and patches were applied a third time. After 24 h, the final patches were removed and the area was rinsed. The test areas were scored 24 h following patch removal.

At study termination, the average skin grades for the 0.2%, 0.4%, and 1.0% w/v aqueous solutions of Sodium Cocoyl Isethionate were 0.30/4, 0.20/4, and 0.26/4, respectively. Sodium Cocoyl Isethionate was "very mild" at the three concentrations tested.

A 14-day irritation study of a gel cleanser containing 15% Sodium Cocoyl Isethionate was conducted using 19 subjects (CTFA, 1984b). The subjects were initially treated with 1.3 ml of a 4.0% solution. However, this volume was too large for the patches and spreading reactions resulted. On the second day of treatment, 0.1 ml of a 6.0% solution was used. After 5 days of testing, it was determined that this concentration was too irritating. A 4% solution, 0.1 ml, was used throughout the remainder of the study. The test article produced moderate to severe irritation.

Irritation/Sensitization

Four human repeated insult patch tests (HRIPTs), which consisted of nine induction patches and a challenge were performed using washing bars that contained 49.87% Sodium Cocoyl Isethionate (CTFA, 1990c). In each study, four bars were used simultaneously in a closed patch test on the back of each subject, giving a total dose of four times the patch test concentration to areas served by the same draining lymph node. In three of the four studies, the solutions were openly applied to the arms of the subjects each time patches were applied to the back. For 199 and 197 subjects, a 0.1% solution was used in the closed patch test and an 8.0% solution was used in the open test. For 191 subjects, the solutions were 0.1% and 4.0% for the closed patch and open tests, respectively. In the study using only a closed patch test, a solution of 0.5% was used on 192 subjects. The test materials did not produce a sensitization reaction.

A 9 RIPT was performed to determine the irritation and/or sensitization potential of a skin cleanser containing 17% Sodium Cocoyl Isethionate (Essex Testing Clinic, Inc., 1989). Ninety-six of the initial 106 subjects, 17 males and 89 females, completed the study. (One subject, gender unspecified, discontinued because of an intolerance to the test procedure; an autoeczematous eruption, not considered to be induced by the test article, developed.) Approximately 0.2 g of test article was applied to the back of each subject, between the scapulae and the waist and adjacent to the spinal midline, using a semi-occlusive patch that was removed 24 h after application. A 24 h nontreatment period followed the first two applications of each week and a 48 h nontreatment period followed the third application of each week; testing continued until nine applications were made. If a subject developed a reaction score of 2 (pink–red erythema, uniform in the entire contact site) or greater, the test site was moved to a previously unpatched site. If a ≥ 2 score was observed at the new site, no further applications were made but the challenge was performed.

After the ninth application, there was a non-treatment period of 10–21 days. At the end of this period, a challenge patch, dose not given, was applied to a previously unpatched site. This site was scored 24 and 48 h after test article application.

During the induction and/or challenge phases, 12 of 96 subjects had scattered, transient, barely perceptible to mild nonspecific patch test responses; none of these responses were considered to be irritant or allergenic. Two of the 96 subjects had delayed mild to moderate erythematous reactions during the challenge. The skin cleanser containing 17% Sodium Cocoyl Isethionate "did not induce clinically meaningful irritation potential in human subjects." Follow-up testing of the two panelists who had responses during the challenge was performed.

The two subjects who had a response during the challenge of the previous study were retested to determine the nature of the responses (Essex Testing Clinic, Inc., 1989). Test article, 0.2 ml, was applied under a semi-occlusive patch to previously unpatched sites on the back cleansed with 70% isopropyl alcohol. The patch remained in contact with the skin for 24 h. Concurrently, under open patch test conditions, test article was applied to the left ventral forearm near the antecubital region. The open applications were made three times daily for 3 days, for a total of nine open applications. Both patch-type sites were scored at 24, 48, and 72 h after application of the semiocclusive patch.

One subject had no reaction to either the semi-occlusive or open patch applications. The other subject developed a transient, barely perceptible to mild erythematous reaction to the semiocclusive patch application; this response was of less severity than the response to the original challenge. Very tiny papules, with no erythema, developed after nine open applications.

After five additional days of open applications, for a total of 21 open applications, slight drying with no erythema was observed. Although the subject appeared to be " 'sensitive' in an irritant manner," the response to the open testing was not considered significant. The 9 RIPT and rechallenge of the skin cleanser containing 17% Sodium Cocoyl Isethionate "did not induce allergic contact dermatitis or clinically relevant irritation in human subjects."

An RIPT was performed to determine the irritation and/or sensitization potential of a syndet soap containing 47.5% Sodium Cocoyl Isethionate using modified methods of Marzulli and Maibach (1974) (Concordia Research Laboratories, Inc., 1987). The material was tested as a 2% w/v solution. Of the initial 206 subjects, 203 completed the study. Occlusive patches were applied to the upper back, which was cleansed with 70% isopropyl alcohol, in a paraspinal position for 48 h. Upon patch removal, the site was scored for reaction to the test article. The test material was reapplied to the same site for a total of nine applications. However, if a test grade of 3 (erythema and induration) was observed, the patch was moved to an adjacent site for the remaining applications.

A 14-day nontreatment period followed the ninth application, after which a challenge patch with 2% w/v test solution was applied to an adjacent area of the back for 48 h. The site was scored upon patch removal and 72 h after the challenge was applied. The irritation and sensitization potential of the test article was "very low if existent at all."

The irritation and sensitization potential of a gel cleanser containing 15% Sodium Cocoyl Isethionate was evaluated using the Jordan-King modification (Jordan and King, 1977; Jordan, 1980) of the Draize-Shelanski procedure (CTFA, 1985b). Of the initial 158 subjects, 148 completed the study, 19 male and 129 female. The test material was applied to the scapular region of the back under occlusive patches. (It is not stated whether the test material was diluted prior to application.) The patches were applied three times a week and remained in contact with the skin for 48 h during the week and for 72 h on the weekend. Nine applications, resulting in 10 readings, were made to the same site.

There was a nontreatment period of 14 days following the ninth application, after which two consecutive challenge patches with 48 h readings were applied to a different site than previously used on the scapular region of the back. If a score of ≥ 2 (moderately intense erythema, with or without infiltration and involving at least 25% of the test area) was observed, the patch was moved to another site until it was possible to return it to the original site. The gel cleanser containing 15% Sodium Cocoyl Isethionate produced "no allergic responses."

SUMMARY

Sodium Cocoyl Isethionate is used as a surfactant–cleansing agent in cosmetic formulations. It is in the form of a fine white powder, is soluble in water, and does not absorb in the UVA or UVB range. In 1984, it was reported to the FDA that Sodium Cocoyl Isethionate was used in 35 cosmetic formulations at 0.1–50%. In 1992, Sodium Cocoyl Isethionate was reported to be used in 52 cosmetic formulations.

According to the terminology of Hodge and Sterner (1949), Sodium Cocoyl Isethionate is slightly to practically nontoxic, with an oral LD_{50} of ≥4.33 g/kg for rats. Dermal application of 1.0–36.0% w/w aqueous Sodium Cocoyl Isethionate to Charles River COBS^{R} rats for 28 days did not result in significant toxic effects. Erythema was observed at times during the study.

In ocular irritation studies using 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, 15.0% active and pH 7.0, was moderately irritating to the intact and abraded skin of rabbits. In two dermal irritation studies of 5% Sodium Cocoyl Isethionate solutions using rabbits, the test article was not a primary dermal irritant in one study (but it did have 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 two studies in which a modified Buehler test was performed using guinea pigs, Sodium Cocoyl Isethionate did not produce a sensitization reaction.

Sodium Cocoyl Isethionate was negative in an *in vitro* chromosomal aberration assay at a concentration of 19–300 μg/ml in the presence and absence of metabolic activation. Sodium Cocoyl Isethionate did not produce a positive response in an *S. typhimurium* preincubation reverse mutation assay at concentrations of 10–1000 μg/ml and 1.0–100 μg/ml with and without metabolic activation, respectively.

In human irritation studies, an 8% aqueous solution of Sodium Cocoyl Isethionate produced minimal irritation in five 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 two 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 the Jordan-King modification of the Draize-Shelanski procedure, a formulation containing 15% Sodium Cocoyl Isethionate did not produce an allergic reaction.

DISCUSSION

The CIR Expert Panel recognizes that concentration of use data are no longer submitted to the FDA by the cosmetics industry. Due to this fact, it will be difficult for

the Expert Panel to make the conclusion "Safe as used," as was previously done. The Panel must now consider making a conclusion based on the product and test concentrations used in the report.

The greatest concentration of Sodium Cocoyl Isethionate tested as a rinse-off product was 49.87%. The greatest concentration of Sodium Cocoyl Isethionate tested as a leave-on product was 17%. Therefore, the CIR Expert Panel used these concentrations in making a conclusion of safety.

The Expert Panel realizes that Sodium Cocoyl Isethionate may produce ocular irritation. The irritant effects produced by Sodium Cocoyl Isethionate are similar to those produced by other surfactants, with the severity of irritation increasing with increasing concentration.

CONCLUSION

Based on the products and concentrations tested in studies documented in this report, the CIR Expert Panel concludes that Sodium Cocoyl Isethionate is safe for use in cosmetic formulations at 50% in rinse-off products and at 17% in leave-on products.

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