Safety Assessment of Amphoacetates as Used in Cosmetics

Status:	Scientific Literature Review for Public Comment
Release Date:	March 30, 2023
Panel Meeting Date:	June 12-13, 2023

All interested persons are provided 60 days from the above release date (i.e., May 29, 2023) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651
cirinfo@cir-safety.org

ABBREVIATIONS

AEEA	aminoethylethanolamine
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
CLP	Classification, Labeling, and Packaging
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
DI	denaturation index
ECHA	European Chemicals Agency
European Chemicals Agency	ECHA
ET_{50}	effective time of exposure to reduce tissue viability to 50%
EU	European Union
FDA	Food and Drug Administration
H_{50}	half-maximal effective concentration for hemolysis
HET-CAM	hen's egg test-chorioallantoic membrane
K_{ow}	n-octanol/water partition coefficient
HRIPT	human repeated-insult patch test
LD_{50}	median lethal dose
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NR	not reported
NOAEL	no-observed-adverse-effect-level
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
SIDS	screening information dataset
SLS	sodium lauryl sulfate
TG	test guideline
TUNEL	TdT-dUTP terminal nick-end labeling
US	United States
VCRP	Voluntary Cosmetic Registration Program
wINCI; *Dictionary*	web-based *International Cosmetic Ingredient Dictionary and Handbook*

INTRODUCTION

This assessment reviews the safety of the following 11 amphoacetates as used in cosmetic formulations:

Disodium Cocoamphodiacetate*
Disodium Cocoamphodipropionate*
Disodium Lauroamphodiacetate
Disodium Wheatgermamphodiacetate
Sodium Arganamphoacetate
Sodium Cocoamphoacetate*
Sodium Cocoamphopropionate*
Sodium Cottonseedamphoacetate
Sodium Lauroamphoacetate
Sodium Olivamphoacetate
Sodium Sweetalmondamphoacetate

** previously reviewed by the Expert Panel for Cosmetic Ingredient Safety (Panel)*

Sodium Lauroamphoacetate was included on the Cosmetic Ingredient Review (CIR) 2021 Priority List due to high reported frequencies of use in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP). Four structurally-similar ingredients (i.e., Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate) have previously been reviewed by the Panel in a safety assessment that was published in 1990,[1] and a re-review published in 2008.[2] Accordingly, in that these ingredients would soon be considered for another re-review, it was deemed appropriate to include the 4 previously-reviewed ingredients in this safety assessment. Additionally, 6 other amphoacetate ingredients are included in this grouping. Hence, all ingredients reviewed in this report are structurally similar as they are alkylamido alkylamines.

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients are reported to function in cosmetics as various types of surfactants (cleansing agents, foam boosters, hydrotropes).[3] The majority of these ingredients are also reported to function as hair-conditioning agents (Table 1).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[4] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

In its original 1990 review of Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate, the Panel concluded that these ingredients are safe in the present practices of use and concentration, as described in that assessment.[1] This conclusion was re-affirmed in a re-review published in 2008.[2] Excerpts of summarized data from the original 1990 safety assessment are included throughout the text of this document, as appropriate, and are identified as italicized text. (This information is not included in the tables or Summary section.) For complete and detailed information, the original report can be accessed on the CIR website (https://www.cir-safety.org/ingredients). Accordingly, for these 4 ingredients, an extensive search of the world's literature was performed for studies dated 1985 forward, and relevant new data were included.

Based on the research that was performed on this ingredient group, these ingredients are typically provided as solutions (usually 40-50% of the ingredient itself (represented as percent solids)) instead of standalone ingredients, and commonly include other salts (e.g., sodium chloride and sodium glycolate). When this information is provided, the percent solids and the specific constituents of these solutions are provided herein (e.g., Sodium Lauroamphoacetate (50% solids; water and sodium chloride)); however, it should be noted that these constituents are not provided for all studies included in this report. Clarification is needed regarding the compositions of these ingredients/percentages of these ingredients in finished solutions as used in cosmetics. It should be noted that sodium glycolate has previously been reviewed by the Panel (published in 1998), and it was concluded that this ingredient is safe for use in cosmetic products at concentrations $\leq 10\%$, at final formulation pH ≥ 3.5, when formulated to avoid increasing sun sensitivity, or when directions for use include the daily use of sun protection.[5] This conclusion was re-affirmed in a 2017 published re-review summary.[6]

In addition, it should be noted that these ingredients may contain amidopropyl dimethylamine (a.k.a. amidoamine) impurities, which is a known sensitizer.[7,8] Cocamidopropyl betaine, a surfactant that has been previously reviewed by the Panel (published in 2012) has similar issues of impurities (e.g., amidoamine) and mechanisms of toxicity to the ingredients reviewed in this report.[8] The Panel concluded that the ingredients in the cocamidopropyl betaine report were safe for use as cosmetic ingredients in the practices of use and concentration as stated in that safety assessment, when formulated to be non-sensitizing (which may be based on a quantitative risk assessment).

CHEMISTRY

Definition and Structure

The ingredients reviewed in this report (e.g., Sodium Lauroamphoacetate; CAS No. 68608-66-2; 156028-14-7; 66161-62-4; formula weight = 349.5 g/mol; log K_{ow} = -1) are compounds with both anionic and cationic structures.[9,10] According to the *Dictionary*, Sodium Lauroamphoacetate is an amphoteric organic compound that generally conforms to the structure:

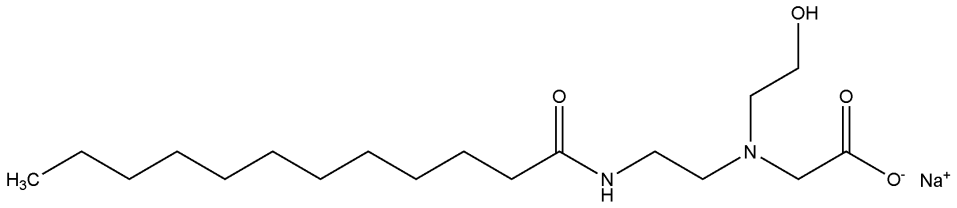


Figure 1. Sodium Lauroamphoacetate

The definitions and structures of all the amphoacetates included in this review are provided in Table 1.

Chemical Properties

Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate are supplied as amber liquids, usually containing 40-50% solids.[1] These ingredients are soluble in water and insoluble in nonpolar organic solvents.

Sodium Lauroamphoacetate is a highly water-soluble, light yellow powder that is typically available as an aqueous solution.[4] Chemical properties of the ingredients in this grouping (some of which may be properties of the ingredient as a solution) are provided in Table 2.

Method of Manufacture

According to the *Dictionary* and published literature, these ingredients are prepared by reacting fatty acid derivatives (e.g., coco fatty acid for Sodium Cocoamphoacetate) with hydroxyethyl ethylenediamine or aminoethylethanolamine (AEEA).[3,11] This reaction produces a substituted imidazoline which is subsequently split via a reaction with an acid (e.g., chloroacetic acid) to yield an amphoteric compound. Compositions of relevant fatty acids (e.g., coconut fatty acid, cottonseed fatty acid) used in the synthesis of these amphoacetates are provided in Table 3.

Composition and Impurities

The compositions of these ingredients as used in cosmetics were not found in the published literature, or provided via unpublished data; however, chemical safety data sheets on trade name products corresponding to several of the ingredients reviewed in this report have been found. These compositions can be found in Table 4. The majority of these ingredients consist of mixtures containing 30 - 60% of the active ingredient, water, dichloroacetic acid, and salts.

AEEA, a potential allergen, may be present in coco-and lauroamphoacetates, amphopropionates, amphodiacetates, and amphodipropionates as an impurity, as it is used as a reagent in the synthesis of these ingredients.[11] The concentration of AEEA in several amphoteric trade name ingredients (corresponding to Disodium Cocoamphodiacetate, Sodium Cocoamphoacetate, and Sodium Lauroamphoacetate) ranged from 4.9 ± 0.2 to 1130 ± 50 ppm. In addition, it should be noted that amidoamine (fatty acid esters of amidopropyl dimethylamine) may be present as an impurity in these ingredients (e.g., a trade name corresponding to Sodium Lauroamphoacetate was reported to contain up to 5% amidoamine).[7,8]

According to a report published by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Disodium Wheatgermamphodiacetate contains 15% saturated fatty acids (e.g., stearic acid), 30% oleic acid, 44% linoleic acid, and 11% linolenic acid.[12] This report states that Disodium Wheatgermamphodiacetate has a purity level of > 99.9%, and may contain chloroacetic acid as an impurity in amounts of < 100 ppm.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the FDA and the cosmetics industry on the expected use of these ingredients in cosmetics and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's VCRP (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council; maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer

habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 FDA VCRP data, Sodium Lauroamphoacetate is reported to be used in 202 total formulations (183 rinse-off formulations; 17 rinse-off formulations; and 2 formulations diluted for bath use; Table 5).[13] Disodium Cocoamphodiacetate has the highest frequency of use (220 total formulations; 40 leave-on formulations, 179 rinse-off formulations, and 1 formulation diluted for bath use; Table 6). The number of uses for this ingredient has increased since it was last reviewed; it was previously reported to be used in 194 formulations in 2005.[2] Sodium Cocoamphoacetate is reported to be used in 121 formulations, and all other ingredients are reported to be used in 73 formulations or less. The results of the 2021 concentration of use survey conducted by Council indicate that Disodium Cocoamphodiacetate has the highest concentration of use in rinse-off products; it is used at up to 20% in cleansing products.[14] Disodium Lauroamphodiacetate has the highest concentration of use reported in leave-on products; it is used at up to 5.4% in other hair preparations. In 2006, the ingredient with the highest reported concentration of use was Sodium Cocoamphoacetate (used at up to 18% in bath soaps and detergents).

Several of these ingredients are reported to be used in products that are applied near the eye; for example, Sodium Lauroamphoacetate is used at 1.3% in eye makeup removers. In addition, these ingredients are reported to be used in products that may result in mucous membrane exposure (e.g., Disodium Cocoamphodiacetate is reported to be used in other personal cleanliness products at up to 3.3%) and in baby products (Disodium Cocoamphodiacetate is used in baby shampoos at up to 5.4%).

Disodium Lauroamphodiacetate is used in a perfume (concentration not reported) and could possibly be inhaled. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The amphoacetates reviewed in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[15]

Non-Cosmetic

Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate are used in cleaning products (all-purpose, oven, floor, dishwashing, metal, and hard-surface) and in the caustic lye peeling of fruit and potatoes.[1] Disodium Cocoamphodiacetate is used at 0.2% in pharmaceutical glaucoma treatment, and in bandage materials. Disodium Cocoamphodipropionate is used at 0.35% in hemorrhoid treatment formulations and up to 0.04% in contact lens disinfecting solutions.

Sodium Lauroamphoacetate is used as a surfactant in various industrial and household cleaning products, including dishwashing and laundry detergents.[4,16] This ingredient is used as an FDA-approved sanitizing agent for food-processing equipment and utensils (21CFR178.1010). Disodium Cocoamphodiacetate is reported to be used as an inactive ingredient in a pharmaceutical shampoo formulation at 5%.[17]

TOXICOKINETIC STUDIES

Toxicokinetics studies were not found in the published literature, and unpublished data were not submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal acute toxicity assays were performed in rabbits using shampoo creams containing 4% Disodium Cocoamphodiacetate (24-h application; occlusive conditions; undiluted).[1] Signs of clinical toxicity (depression, labored respiration, phonation, tremors) and dermal toxicity (reversible gross dermal lesions, atonia, desquamation, fissures, sloughing) were observed during the 14-d observation period. Several acute oral toxicity assays were performed using Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate (as commercially supplied) in mice and rats. All test substances were considered to be nontoxic (median lethal dose (LD_{50}s) ranged from >5 to 28 ml/kg).

Oral

The acute oral toxicity studies on Sodium Lauroamphoacetate summarized here are described in Table 7. An LD_{50} of 6116 mg/kg for Sodium Lauroamphoacetate (% solids not stated; water and sodium chloride) was determined in mice.[4] The lowest LD_{50} in rats was reported to be > 2000 mg/kg bw Sodium Lauroamphoacetate (50% solids; water and sodium

chloride; tested as provided). The same LD_{50} was reported for a 20% aqueous dilution of Sodium Lauroamphoacetate (35% solids; water, sodium chloride, sodium glycolate).

Subchronic Toxicity Studies

Oral

Disodium Cocoamphodiacetate

Wistar Han rats (10/sex/group in main study; 5/sex/group in recovery group) were given Disodium Cocoamphodiacetate (47.2 - 48% solids) in water, via gavage, in doses of either 0, 100, 300, or 1000 mg/kg bw/d for 90 d.[4] Recovery groups received either the vehicle only or 1000 mg/kg bw/d of the test substance, for 90 d, followed by a 28-d treatment-free period. Body weight changes, food consumption, mortality, behavior, ophthalmological, hematological, gross pathological, reproductive, and histopathological parameters were evaluated. No deaths occurred throughout the study. Mild respiratory difficulty, fur loss, and hunched posture were observed in several animals of treated groups. Lowered body weight compared to controls was observed in males treated with 1000 mg/kg bw/d. Slightly lower food consumption was observed in treated males (at all test concentrations). Histopathological changes included non-adverse squamous cell hyperplasia accompanied with hyperkeratosis in the stomach of female rats (dosed with 300 mg/kg bw/d and higher) and goblet cell hyperplasia of the rectum of a few male rats (dosed with 1000 mg/kg bw/d). In addition, higher kidney and liver weights were noted in females dosed with 1000 mg/kg bw/d. Histopathological and organ weight changes were fully reversed at the end of the recovery period. No toxicologically-relevant adverse effects were noted in any of the remaining parameters evaluated. The no-observed-adverse-effect-level (NOAEL) was determined to be 1000 mg/kg bw/d. The reproductive effects evaluated in this assay are found in the Developmental and Reproductive Toxicity section of this report.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

The oral developmental and reproductive toxicity studies summarized here can be found in Table 8. A reproductive toxicity assay was performed on Disodium Cocoamphodiacetate (0, 100, 300, or 1000 mg/kg bw/d; in water; gavage administration; treated days 6 - 20 post-coitum) using female Wistar Han rats (22/group).[4] No maternal toxicity was observed in this assay (maternal NOAEL = 1000 mg/kg bw/d). Severe cardiac abnormalities were observed in fetuses in all test groups (not including control), in a non-dose-dependent manner; accordingly, the developmental NOAEL could not be determined. Disodium Cocoamphodiacetate (0, 100, 300, or 1000 mg/kg bw/d; in water; gavage administration) was given to Wistar Han rats (10/sex/group) to evaluate parental toxicity. In this assay, males were treated for 29 d (before, during, and after mating), and females were treated for 50 - 54 d (before and during mating, throughout pregnancy, and during lactation). Females without offspring were treated for 41 d. No reproductive toxicity was observed in either the parent or F1 generation. The reproductive NOAEL was determined to be 1000 mg/kg bw/d. Wistar Han rats (10/sex/dose) were treated with Disodium Cocoamphodiacetate (47 - 48% solids; in water; 0, 100, 30, or 1000 mg/kg bw/d; 90-d gavage administration). Animals were evaluated for changes in reproductive parameters such as estrous cycle length, spermatogenesis, and histopathology of reproductive organs; no adverse effects were observed. [Results for the non-reproductive parameters evaluated in this study can be found in the Subchronic Toxicity section of this report.] A reproductive NOAEL of 1000 mg/kg bw/d was established in a reproductive toxicity assay performed in Wistar Han rats (10/sex/group) using Sodium Cocoamphoacetate (0, 100, 300, or 1000 mg/kg bw/d; in water; gavage administration). A developmental and maternal NOAEL of 1000 mg/kg bw was established in a developmental toxicity assay performed in female Wistar Han rats (22/group) given Sodium Lauroamphoacetate (0, 100, 300, or 1000 mg/kg bw/d; in water; gavage administration).

GENOTOXICITY STUDIES

Ames assays were performed with Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, and Sodium Cocoamphoacetate (up to 1 µl/plate; with and without metabolic activation) using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100.[1] The test substances were not considered to be mutagenic.

Details on the in vitro genotoxicity assays summarized here can be found in Table 9. The genotoxic potential of Sodium Lauroamphoacetate was evaluated in three in vitro assays.[4] Sodium Lauroamphoacetate (35% solids; water, sodium chloride, and sodium glycolate; up to 4375 µg/plate) was considered to be non-genotoxic in an Ames assay performed on *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100. Similarly, no genotoxicity was observed in an Ames assay performed on Sodium Lauroamphoacetate (water and sodium chloride; up to 5000 µg/plate) using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* WP2 uvr A. Sodium Lauroamphoacetate (water, sodium chloride, and sodium glycolate; up to 250 µg/ml) was considered non-clastogenic in a mammalian chromosome aberration assay performed using human peripheral blood lymphocytes. All assays were performed with and without metabolic activation.

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Corneal Epithelium Impairment

Disodium Cocoamphodiacetate

The following study is included as it may be helpful in addressing cosmetic safety concerns following ocular exposure to Disodium Cocoamphodiacetate. The right eye of C5BL/6 mice (n = 8) was anesthetized with isoflurane, and either the control (10 µl phosphate-buffered saline (PBS)), 0.1% Disodium Cocoamphodiacetate in PBS, or 1% Disodium Cocoamphodiacetate in PBS was administered.[18] Treatment was performed once per day, for 7 or 14 consecutive days. Morphological and pathological changes in the murine ocular surface were evaluated. After one day of treatment, slit lamp images revealed that no obvious alterations were observed in corneas treated with 0.1% Disodium Cocoamphodiacetate; however, corneas treated with 1% Disodium Cocoamphodiacetate manifested diffuse sodium fluorescein staining in the central area. After 7 d of treatment punctuate staining of fluorescein was observed in 0.1% Disodium Cocoamphodiacetate-treated animals, and haze appeared in the central cornea of 1% Disodium Cocoamphodiacetate-treated animals. Hematoxylin and eosin staining performed on eyes treated with 0.1% Disodium Cocoamphodiacetate and control eyes for 14 d revealed a statistically significant decrease of epithelial thickness in the Disodium Cocoamphodiacetate-treated group compared to the control ($P < 0.05$). To determine if the test substances promoted corneal epithelial apoptosis, a TdT-dUTP terminal nick-end labeling (TUNEL) assay was performed after 14 d of treatment. Very few TUNEL-positive cells were observed in the control group, while an increased number of TUNEL-positive cells were found in the Disodium Cocoamphodiacetate-treated groups, in a dose-dependent manner.

Co-Reactivity of Surfactant Allergens

Disodium Lauroamphodiacetate

The following study is included as it may be helpful in addressing irritation/hypersensitivity concerns following exposure to Disodium Lauroamphodiacetate. Previously patch-tested, surfactant-positive subjects (n = 47) were patch-tested with 1 and 2% aqueous Disodium Lauroamphodiacetate, screening surfactants (cocamidopropyl betaine, amidoamine, dimethylaminopropylamine, cocamide diethanolamine, oleamidopropyl dimethylamine, and decyl glucoside), the novel surfactants sodium lauroyl sarcosinate and isostearamidopropyl morpholine lactate, and a hypoallergenic liquid cleanser.[19] Patch testing occurred for 5-8 d under occlusive conditions for all test substances except for the hypoallergenic liquid cleanser, which was tested in a semi-open fashion. Doubtful, mild, and moderate reactions to Disodium Lauroamphodiacetate (concentration at which reactions were noted was not specified) were observed in 7, 2, and 1 subjects, respectively. Of the three participants who displayed a mild or moderate reaction to Disodium Lauroamphodiacetate, 2 reacted to isostearamidopropyl morpholine lactate and 1 reacted to dimethylaminopropylamine, oleamidopropyl dimethylamine, amidoamine, cocamidopropyl betaine, or sodium lauroyl sarcosinate.

Reactivity to Irritants in Atopic and Non-Atopic Patients

Sodium Cocoamphoacetate

The following study is included as it may be helpful in addressing irritation concerns following exposure to Sodium Cocoamphoacetate. Patch testing was performed in 40 healthy volunteers and 480 atopic subjects (affected by atopic dermatitis, psoriasis, or eczema) using several irritants, including 15 µl aqueous solutions of Sodium Cocoamphoacetate (3 and 5%).[20] Patch tests were applied to the back for 2 d (level of occlusion not stated). Readings were performed 1 h after patch removal. No reactions were observed in healthy subjects treated with 3% Sodium Cocoamphoacetate; however, 2 healthy subjects displayed positive reactions to 5% Sodium Cocoamphoacetate. Three and 11 atopic subjects displayed positive reactions to 3% Sodium Cocoamphoacetate and 5% Sodium Cocoamphoacetate, respectively.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Single patch tests were performed using Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate (ingredients were as commercially supplied) in rabbits (occlusive conditions; abraded and unabraded skin; 24-h applications).[1] Disodium Cocoamphodiacetate and Sodium Cocoamphoacetate ranged from non-irritating to severely irritating. Disodium Cocoamphopropionate was observed to be non-irritating in rabbits, and slight irritation was observed in assays performed using Sodium Cocoamphopropionate. Dermal irritation was also evaluated in rabbits via a single intradermal injection of Disodium Cocoamphodiacetate (tested at 1%), Disodium Cocoamphodipropionate (tested at 1%), and Sodium Cocoamphopropionate (tested at 0.1%). All test substances resulted in less irritation compared to control shampoos (olive oil castile shampoo). Cleansing creams containing 5% Disodium Cocoamphodipropionate very mildly irritating in 12 subjects in a 21-d cumulative irritation assay (occlusive), and were non-irritating when products were applied daily for 2 wk (n = 24) or 1 mo (n = 53). A facial cleanser containing 25% Disodium Cocoamphodiacetate (45.6% solids) that was routinely used by subjects (n = 54) for 1 mo produced no adverse effects.

A human repeated insult patch test (HRIPT) evaluating the sensitization potential of 10% Sodium Cocoamphoacetate and 10% Sodium Cocoamphopropionate in human subjects yielded negative results (n = 141; non-occlusive conditions). No sensitization was observed in a maximization assay performed in 25 subjects using a diluted hair product containing 0.1%

Disodium Cocoamphodipropionate. A cleansing cream containing 5% Disodium Cocoamphodipropionate was non-irritating and non-sensitizing in an HRIPT. In addition, no sensitization was observed in an HRIPT using Disodium Cocoamphodiacetate (32% solids), under semi-occlusive conditions; however, some irritation was noted under occlusive conditions.

Details regarding the animal and human dermal irritation and sensitization studies summarized here can be found in Table 10. Test substances were considered to be non-irritating in two irritation assays performed in rabbits using Sodium Lauroamphoacetate (35-50% solids).[4] Severe dermal irritation was noted in two assays performed in the intact and abraded skin of New Zealand albino rabbits using a trade name mixture containing Sodium Lauroamphoacetate (36 - < 67.9%).[21,22] Test substances (Disodium Cocoamphodiacetate (up to 5%), Sodium Cocoamphoacetate (up to 5%), and Sodium Lauroamphoacetate (35% solids; tested undiluted)) produced none to slight irritation in irritation assays performed in humans.[4,16,23,24] Erythema and scaling was observed in in a 48-h occlusive patch test performed in 12 subjects using Sodium Cocoamphoacetate (10%) in citrate buffer.[25] Irritation was observed in a soap chamber and epicutaneous dermal irritation assay using 1% Sodium Lauroamphoacetate and 2% Sodium Lauroamphoacetate, respectively.[16]

No sensitization was observed in a guinea pig maximization test using Sodium Cocoamphoacetate (water, sodium chloride, and sodium glycolate).[4] The test substance was evaluated as a 1% (0.394% solids), 5%, and 75% dilution in water for the intradermal, epicutaneous, and challenge exposures, respectively. A two-part local lymph node assay was performed in female CBA/J mice (4/group). Animals were exposed to the test article (Sodium Lauroamphoacetate (water and sodium chloride)), in propylene glycol, at up to 30% in experiment 1 and up to 50% in experiment 2. No signs of hypersensitivity was observed in experiment 1; however, delayed contact hypersensitivity was noted at concentrations of 50%. A guinea pig maximization test was performed using Sodium Lauroamphoacetate (0.18 - 17.5% solids). The test substance, tested at 0.5% for the intradermal induction, 50% for the epicutaneous induction, and at 20% for the challenge exposure, was considered to be non-sensitizing. The sensitization potential of a 0.5% aqueous solution of Sodium Lauroamphoacetate (0.15% solids) was evaluated in an HRIPT in 99 subjects.[4] Subjects were exposed to the test substance, under occlusive conditions for 9, 24-h induction periods, followed by a 24-h challenge exposure. The test substance was considered to be non-irritating and non-sensitizing.

Photosensitization/Phototoxicity

Sodium Cocoamphoacetate, Sodium Cocoamphopropionate, and Disodium Cocoamphoacetate (tested at 10% in distilled water) did not cause photo-allergic reactions or delayed contact hypersensitivity in an assay performed in 30 subjects.[1]

OCULAR IRRITATION STUDIES

Several ocular irritation assays were performed using Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate (ingredients were as commercially supplied; 0.1 ml), predominantly via the Draize method, using rabbits.[1] For some assays, rinse-out procedures were performed prior to scoring irritation. Disodium Cocoamphodiacetate was considered to be moderately to severely irritating when the test substance was not rinsed from the eyes, and minimally to mildly irritating when the test substance was rinsed from the eyes. Disodium Cocoamphopropionate was non-irritating under unrinsed conditions. Sodium Cocoamphoacetate was considered to be minimally to severely irritating under unrinsed conditions. Sodium Cocoamphopropionate was non-irritating to minimally irritating under unrinsed conditions. In some assays, Disodium Cocoamphodiacetate was observed to have an anti-irritation effect on rabbit corneas. In a human ocular irritation assay, a shampoo containing 28.1% Disodium Cocoamphodiacetate (diluted up to 10% in distilled water) was evaluated in 30 subjects. Irritation was similar among the test substance and control-treated groups (treated with distilled water).

Details regarding the ocular irritation studies summarized here are provided in Table 11. The majority of in vitro ocular irritation assays performed using Disodium Cocoamphodiacetate (up to 3%), Sodium Cocoamphodiacetate (up to 3%), and Sodium Lauroamphoacetate (up to 3%) reported no to slight irritation; however, a red blood cell test using 1% Disodium Cocoamphodiacetate resulted in moderate irritation.[16] However, severe irritation potential was observed with higher concentrations. Severe irritation was noted in an EpiOcular™ assay evaluating the ocular irritation potential of 50% Disodium Cocoamphodiacetate.[26] Severe ocular irritation was also observed in a hen's egg test-chorioallantoic membrane (HET-CAM) assay using 40% Sodium Lauroamphoacetate.[27] In several studies, Sodium Lauroamphoacetate (tested as 10 - 50% solids; water and sodium chloride; tested undiluted) was not considered to be an ocular irritant based on Classification, Labelling, and Packaging (CLP) criteria in three assays performed in New Zealand White rabbits (n = 3 - 6). However, in one study Sodium Lauroamphoacetate (50% solids; water and sodium chloride; tested undiluted) was considered to be a category 2 ocular irritant (based on CLP criteria) when evaluated in 3 New Zealand White rabbits. All signs of irritation were fully reversible within 7 d post-administration. No symptoms of eye irritation were observed in assays performed in humans (n = 10), in which subjects were reported to use a micellar water cleanser containing Disodium Cocoamphodiacetate (0.4 and 1.2%) once per day for 21 d.[28]

CLINICAL STUDIES

Case Reports

Disodium Cocoamphodipropionate

A 28-yr-old woman with a history of eczema reported worsened dermatitis following dermal exposure to contact lens solution (containing 38-40% Disodium Cocoamphodipropionate).[29] Patch tests were performed using the undiluted contact lens fluid, as well as the contact lens fluid ingredients, including Disodium Cocoamphodipropionate (0.1 - 1%; aqueous solution). Positive reactions were observed following testing with Disodium Cocoamphodipropionate at all tested concentrations, as well as the undiluted contact lens fluid. Twenty-one non-atopic control individuals were patch tested with a 1% aqueous solution of Disodium Cocoamphodipropionate. No positive reactions were observed.

Disodium Lauroamphodiacetate

A 46-yr-old massage therapist with a history of contact allergies presented with hand dermatitis following use of a hypoallergenic liquid cleanser.[30] In addition, a 57-yr-old woman with a history of hand dermatitis displayed atopic symptoms following the use of the same cleanser. Semi-open patch tests were performed on both individuals using the liquid cleanser itself (1, 10, and 100%; aqueous solution), and the cleanser ingredients, including Disodium Lauroamphodiacetate (1 and 2%; aqueous solution). Patch tests were also performed in 10 healthy control subjects. Positive responses were observed in both atopic patients following testing with Disodium Lauroamphoacetate (at both test concentrations), and the liquid cleanser (tested at 100%). No positive responses were observed in control subjects.

Sodium Cocoamphoacetate

A 45-yr-old woman with a history of eczema and rhinoconjunctivitis reported facial dermatitis following the use of a makeup remover containing Sodium Cocoamphoacetate (concentration not specified).[31] Patch tests were performed using the eye makeup remover and Sodium Cocoamphoacetate (1 and 2%; aqueous solution). Thirty-three non-atopic control subjects underwent the same patch testing. Positive reactions were observed in the atopic individual for both concentrations of Sodium Cocoamphoacetate, and the eye makeup remover. Some weak irritant reactions were noted in control subjects treated with 2% Sodium Cocoamphoacetate. No reactions were observed in control subjects following testing with 1% Sodium Cocoamphoacetate. It was not stated whether control subjects elicited a response to the eye makeup remover formulation.

Sodium Cocoamphopropionate

Four individuals reported hand and forearm dermatitis following use of a skin protection cream containing Sodium Cocoamphopropionate.[32] One of the four individuals had a history of atopic disease (allergic rhinoconjunctivitis). Occlusive patch tests (24-h) were performed on the individuals using the cream itself, as well as the cream ingredients, including Sodium Cocoamphopropionate (1%; aqueous solution). Positive reactions were observed in all individuals following testing with the cream and 1% Sodium Cocoamphopropionate. Eczema improved in all patients following elimination of exposure to Sodium Cocoamphopropionate.

Sodium Lauroamphoacetate

Four cases of atopic dermatitis were reported in individuals following exposure to detergents containing amphoacetates.[11] Patch tests of aqueous solutions of Sodium Lauroamphoacetate (1, 5, and 10%), as well as undiluted Sodium Lauroamphoacetate, were administered to patients under occlusive conditions, for 2 d. Other substances tested include ethylenediamine (concentration not reported) and AEEA (1%). Twenty non-allergic control subjects were patch tested with Sodium Lauroamphoacetate (1, 5, 10, and 100%) and AEEA (1%). All four atopic individuals displayed positive reactions to Sodium Lauroamphoacetate and AEEA at all tested concentrations. Six of the 20 non-atopic control subjects responded with an irritation reaction to Sodium Lauroamphoacetate tested at 100%. No other reactions were reported in control subjects.

Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, Sodium Cocoamphopropionate, and Sodium Lauroamphoacetate

A 34-yr-old nurse working in a surgical department reported hand and forearm dermatitis following use of a disinfectant hand cleanser containing 2% Sodium Cocoamphopropionate.[33] Patch tests of the diluted hand soap (3.2 – 20%), as well as patch tests of the individual hand soap ingredients, including Sodium Cocoamphopropionate (1 – 10%), were performed. Related surfactants that were not ingredients of the hand soap were also patch tested (Sodium Cocoamphoacetate (1 – 10%), Sodium Lauroamphoacetate (1 – 10%), Disodium Cocoamphodipropionate (10%), and AEEA (0.1 – 1%)). Positive patch test results were observed for the hand cleanser (at all concentrations), Sodium Cocoamphopropionate (at 3.2% and higher), Sodium Cocoamphoacetate (at 3.2% and higher), Sodium Lauroamphoacetate (at 3.2% and higher), and AEEA (at 0.32% and higher). Four fast-food restaurant workers also reported atopic dermatitis following exposure to the same hand cleanser containing 2% Sodium Cocoamphopropionate. Patch tests were performed in these individuals according to similar procedures as mentioned above. Positive reactions were observed for all tested substances (hand cleanser (at all concentrations), Sodium Cocoamphopropionate (at all concentrations), Sodium Cocoamphoacetate (at 3.2% and higher),

Sodium Lauroamphoacetate (at 3.2% and higher), Disodium Cocoamphodipropionate (at all concentrations), and AEEA (at all concentrations). Other reports of hand irritation following use of this hand cleanser were reported in 24-yr-old and 27-yr old fast-food workers with recurrent eczema.[34] These patients were patch tested with several materials including ethylenediamine (1%), the hand soap (100%), and Sodium Cocoamphopropionate (1%; aqueous solution). Both patients showed positive reactions to all test substances. Sodium Cocoamphopropionate (1%; aqueous solution) was also tested in 20 non-atopic control individuals. No irritation or allergic reactions were observed.

SUMMARY

The safety of 11 amphoacetate ingredients is reviewed in this safety assessment. These ingredients are reported to function as various types of surfactants (cleansing agents, foam boosters, hydrotropes) and hair-conditioning agents in cosmetics. Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate have been previously reviewed by the Panel and were considered safe in the present practices of use and concentration as described in the safety assessment published in 1990. This conclusion was re-affirmed in 2008.

According to 2023 VCRP survey data, Disodium Cocoamphodiacetate has the highest frequency of use (220 total formulations; 40 leave-on formulations, 179 rinse-off formulations, and 1 formulation diluted for bath use. Sodium Lauroamphoacetate is reported to be used in 202 total formulations (183 rinse-off formulations; 17 rinse-off formulations; and 2 formulations diluted for bath use). All other ingredients are reported to be used in 121 formulations or less. The results of the 2021 concentration of use survey conducted by Council indicate that Disodium Lauroamphodiacetate has the highest concentration of use in leave-on products; it is used at up to 5.4% in other hair preparations.

Acute oral toxicity studies were performed using Sodium Lauroamphoacetate in mice and rats. An LD_{50} of 6116 mg/kg for Sodium Lauroamphoacetate (% solids not stated; water and sodium chloride) was determined in mice. The lowest LD_{50} in rats was reported to be > 2000 mg/kg bw (using Sodium Lauroamphoacetate (50% solids; water and sodium chloride; tested as provided) and Sodium Lauroamphoacetate (35% solids; water, sodium chloride, sodium glycolate; tested as a 20% aqueous dilution). An NOAEL of 1000 mg/kg bw/d was established in a 90-d oral subchronic toxicity assay in which Wistar Han rats (10/sex/group in main study; 5/sex/group in recovery group) were given Disodium Cocoamphodiacetate (47.2 – 48% solids), in water, via gavage, in doses of up to 1000 mg/kg bw/d.

A maternal NOAEL of 1000 mg/kg bw/d was established in a reproductive toxicity assay in which Disodium Cocoamphodiacetate (up to 1000 mg/kg bw/d; in water; gavage administration; treated days 6 - 20 post-coitum) was given to female Wistar Han rats (22/group). Severe cardiac abnormalities were observed in fetuses in all treated test groups (not including control group). A parental NOAEL of 300 mg/kg bw/d was determined in an assay in which Disodium Cocoamphodiacetate (up to 1000 mg/kg bw/d; in water; gavage administration) was given to Wistar Han rats (10/sex/dose). Males were treated before, during, and after mating, and females were treated before and during mating, throughout pregnancy, and during lactation. No reproductive toxicity was observed in either the parent or F1 generation. No adverse effects regarding estrous cycle length, spermatogenesis, and histopathology of reproductive organs were observed in an assay in which Wistar Han rats (10/sex/dose) were treated with Disodium Cocoamphodiacetate (47 - 48% solids; in water; up to 1000 mg/kg bw/d; 90-d gavage administration). A parental NOAEL of 1000 mg/kg bw/d was established in a reproductive toxicity assay performed in Wistar Han rats (10/sex/group) using Sodium Cocoamphoacetate (up to 1000 mg/kg bw/d; in water; gavage administration). Similarly, a developmental and maternal NOAEL of 1000 mg/kg bw was established in a developmental toxicity assay performed in female Wistar Han rats (22/group) given Sodium Lauroamphoacetate (up to 1000 mg/kg bw/d; in water; gavage administration).

No genotoxicity was observed in Ames assays performed using Sodium Lauroamphoacetate (35% solids; water, sodium chloride, and sodium glycolate; up to 4375 µg/plate) and Sodium Lauroamphoacetate (water and sodium chloride; up to 5000 µg/plate). Similarly, Sodium Lauroamphoacetate (water, sodium chloride, and sodium glycolate; up to 250 µg/ml) was considered to be non-clastogenic in a mammalian chromosome aberration assay. All assays were performed with and without metabolic activation.

In an assay performed to evaluate the potential corneal epithelium impairment effects of Disodium Cocoamphodiacetate, C5BL/6 mice (n = 8) were administered either the control (10 µl phosphate-buffered saline (PBS)), 1% Disodium Cocoamphodiacetate in PBS, or 0.1% Disodium Cocoamphodiacetate in PBS, in the right eye, once a day, for 7 or 14 d. Treatment with both 0.1 and 1% Disodium Cocoamphodiacetate resulted in corneal impairment (e.g., decreased thickness, increased apoptosis of corneal cells).

Previously patch-tested, surfactant-positive subjects (n = 47) were patch-tested (5 - 8 d testing duration) with several types of surfactants, including Disodium Lauroamphodiacetate (aqueous solution; 1 and 2%). Doubtful, mild, and moderate reactions to Disodium Lauroamphodiacetate (concentration at which reactions were noted was not specified) were observed in 7, 2, and 1 subjects.

Patch testing was performed in 40 healthy volunteers and 480 atopic subjects (affected by atopic dermatitis, psoriasis, or eczema) using several irritants, including Sodium Cocoamphoacetate (aqueous solution; 3 and 5%). No reactions were observed in healthy subjects treated with 3% Sodium Cocoamphoacetate; however, 2 healthy subjects displayed positive

reactions to 5% Sodium Cocoamphoacetate. Three and 11 atopic subjects displayed positive reactions to 3% Sodium Cocoamphoacetate and 5% Sodium Cocoamphoacetate, respectively.

Test substances were considered to be non-irritating in two irritation assays performed in rabbits using Sodium Lauroamphoacetate (35-50% solids). Severe dermal irritation was noted in two assays performed in the intact and abraded skin of New Zealand albino rabbits using a trade name mixture containing Sodium Lauroamphoacetate (36 - < 67.9%). Test substances (Disodium Cocoamphodiacetate (up to 5%), Disodium Cocoamphodiacetate (up to 2%), Sodium Cocoamphoacetate (up to 5%), and Sodium Lauroamphoacetate (35% solids)) produced none to slight irritation in irritation assays performed in humans. Erythema and scaling were observed in in a 48-h occlusive patch test performed in 12 subjects using Sodium Cocoamphoacetate (10%) in citrate buffer. Irritation was observed in a soap chamber and epicutaneous dermal irritation assay using 1% Sodium Lauroamphoacetate and 2% Sodium Lauroamphoacetate, respectively.

No sensitization was observed in a guinea pig maximization test using Sodium Cocoamphoacetate (water, sodium chloride, and sodium glycolate; tested as a 1% (0.394% solids), 5%, and 75% dilution in water for the intradermal, epicutaneous, and challenge exposures, respectively). Delayed contact hypersensitivity was observed in a local lymph node assay performed in mice using Sodium Lauroamphoacetate (water and sodium chloride; vehicle of propylene glycol) when tested at 50%. No hypersensitivity was observed when this test substance was used at 30%. No sensitization was observed in a guinea pig maximization test performed using Sodium Lauroamphoacetate (0.18 – 17.5% solids; water, sodium chloride and sodium glycolate (tested at 0.5% for the intradermal induction, 50% for the epicutaneous induction, and at 20% for the challenge exposure)). A 0.5% aqueous solution of Sodium Lauroamphoacetate (0.15% solids) was considered to be non-irritating and non-sensitizing in an HRIPT performed in 99 subjects.

The majority of in vitro ocular irritation assays performed using Disodium Cocoamphodiacetate (up to 3%), Sodium Cocoamphodiacetate, (up to 3%) and Sodium Lauroamphoacetate (up to 3%) reported none to slight irritation; however, a red blood cell test using 1% Disodium Cocoamphodiacetate resulted in moderate irritation. However, severe irritation potential was observed with higher concentrations. Severe irritation was noted in an EpiOcular™ assay evaluating the ocular irritation potential of 50% Disodium Cocoamphodiacetate. Severe ocular irritation was also observed in a HET-CAM assay using 40% Sodium Lauroamphoacetate. Sodium Lauroamphoacetate (tested as 10 - 50% solids; water and sodium chloride; tested undiluted) was not considered to be an ocular irritant when tested in rabbits. However, Sodium Lauroamphoacetate (50% solids; water and sodium chloride; tested undiluted) was considered to be a category 2 ocular irritant when evaluated in rabbits. No eye irritation was observed in assays performed in humans (n = 10), in which subjects were reported to use a micellar water cleanser containing Disodium Cocoamphodiacetate (0.4% and 1.2%) once per day for 21 d.

Several case reports were found in the literature regarding dermatitis following the use of products containing amphoacetates. A positive patch test reaction to Disodium Cocoamphodipropionate (0.1 – 1%; aqueous solution) was observed in a 28-yr-old woman experiencing dermatitis following exposure to a contact lens solution containing Disodium Cocoamphodipropionate. Two women presented with hand dermatitis following exposure to a cleanser containing Disodium Lauroamphodiacetate. Positive patch tests were observed in both patients for both the cleanser and Disodium Lauroamphodiacetate (1 and 2%; aqueous solution). A 45-yr-old woman reported facial dermatitis following the use of a makeup remover containing Sodium Cocoamphoacetate. Patch tests for the eye makeup remover and for Sodium Cocoamphoacetate (1 and 2%; aqueous solution) were positive. Four individuals with a history of allergies reported dermatitis following the use of a cream containing Sodium Cocoamphopropionate. All subjects had positive patch test reactions to the cream and 1% Sodium Cocoamphopropionate (aqueous solution). Four cases of atopic dermatitis were reported in individuals following exposure to detergents containing amphoacetates. All four individuals displayed positive patch test reactions to Sodium Lauroamphoacetate (1, 5, 10, and 100%; aqueous solutions) and AEEA (1%). Several cases of dermatitis have been reported following exposures to hand cleansers containing amphoacetates. Patch testing using several amphoacetates (Disodium Cocoamphodipropionate (1 - 10%) Sodium Cocoamphoacetate (1 - 10%), Sodium Cocoamphopropionate (1 - 10%), Sodium Lauroamphoacetate (1 - 10%)), performed in these individuals, yielded positive results.

INFORMATION SOUGHT

The following information on the amphoacetates reviewed in this report is being sought for use in the resulting safety assessment:

- Composition and impurities data on all ingredients; specifically, the constituents and percent solids of these ingredients as finished solutions
- Method of manufacturing data
- Dermal absorption data; if absorbed, additional toxicity studies may be needed
- Irritation and sensitization data, at maximum concentrations of use

TABLES

Table 1. INCI names, definitions, structures, and functions of the amphoacetate ingredients reviewed in this safety assessment[3]

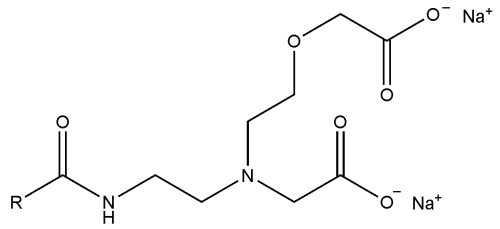
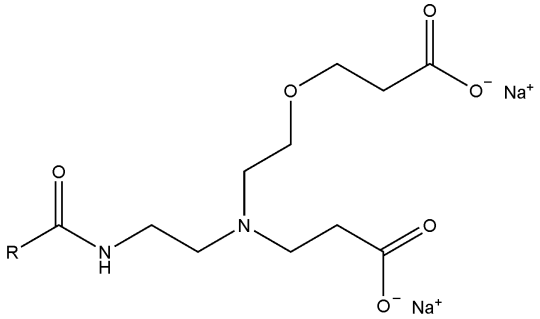
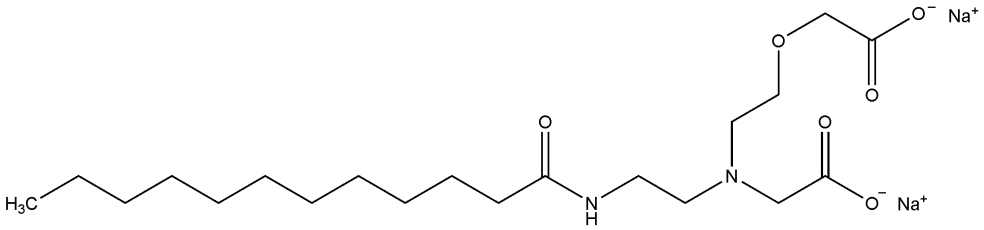
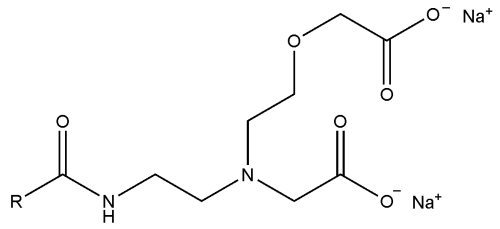
Ingredient	Definition	Function
Disodium Cocoamphodiacetate [CAS: 68650-39-5]	Disodium Cocoamphodiacetate is the amphoteric organic compound that conforms generally to the structure:  where RC(O)- represents the acyl groups derived from coconut oil.	Hair Conditioning Agents; Surfactants – Cleansing Agents; Surfactants – Foam Boosters; Surfactants – Hydrotropes
Disodium Cocoamphodipropionate [CAS: 68411-57-4; 86438-79-1]	Disodium Cocoamphodipropionate is the amphoteric organic compound that conforms generally to the structure:  where RC(O)- represents the acyl groups derived from coconut oil.	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants - Foam Boosters; Surfactants - Hydrotropes
Disodium Lauroamphodiacetate [CAS: 14350-97-1]	Disodium Lauroamphodiacetate is the amphoteric organic compound that conforms generally to the formula: 	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants - Foam Boosters; Surfactants - Hydrotropes
Disodium Wheatgermamphodiacetate	Disodium Wheatgermamphodiacetate is the organic compound that conforms to the formula:  where RC(O)- represents the acyl groups derived from wheat germ oil.	Hair Conditioning Agents Surfactants - Cleansing Agents Surfactants - Foam Boosters Surfactants - Hydrotropes

Table 1. INCI names, definitions, structures, and functions of the amphoacetate ingredients reviewed in this safety assessment[3]

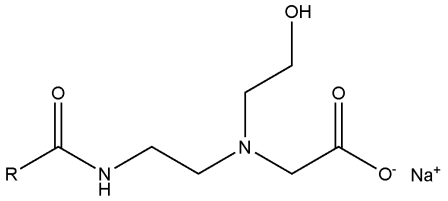
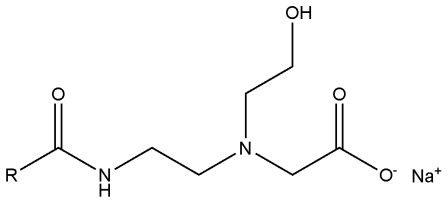
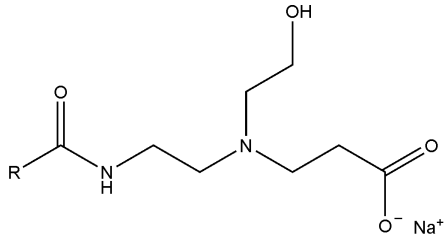
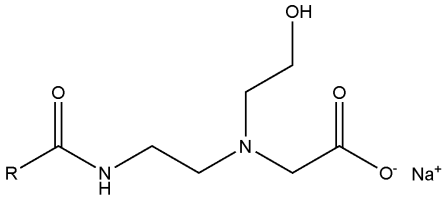
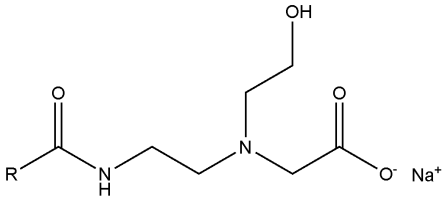
Ingredient	Definition	Function
Sodium Arganamphoacetate	Sodium Arganamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from Argania Spinosa Kernel Oil.	Surfactants - Cleansing Agents
Sodium Cocoamphoacetate [CAS: 90387-76-1; 68334-21-4; 68608-65-1]	Sodium Cocoamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from coconut oil.	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants - Foam Boosters
Sodium Cocoamphopropionate	Sodium Cocoamphopropionate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from coconut oil.	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants - Foam Boosters; Surfactants - Hydrotropes
Sodium Cottonseedamphoacetate	Sodium Cottonseedamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from cottonseed oil.	Surfactants - Cleansing Agents
Sodium Lauroamphoacetate [CAS: 68608-66-2; 156028-14-7; 66161-62-4]	Sodium Lauroamphoacetate is the amphoteric organic compound that conforms generally to the structure in *Figure 1*.	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants - Foam Boosters
Sodium Olivamphoacetate	Sodium Olivamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from olive oil.	Hair Conditioning Agents Surfactants - Cleansing Agents Surfactants - Foam Boosters

Table 1. INCI names, definitions, structures, and functions of the amphoacetate ingredients reviewed in this safety assessment[3]

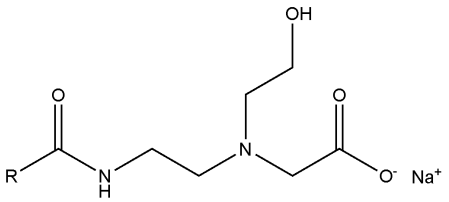
Ingredient	Definition	Function
Sodium Sweetalmondamphoacetate	Sodium Sweetalmondamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from sweet almond oil.	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants - Foam Boosters

Table 2. Chemical properties

Property	Value	Reference
Disodium Cocoamphodiacetate		
Physical Form	liquid	1
Color	light tan	1
Odor	faintly fruity	1
Specific Gravity (@ 25ºC)	1.17	35
Water Solubility	soluble	1
Alcohol Solubility	insoluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Disodium Cocoamphodipropionate		
Physical Form	liquid	1
Color	light amber	1
Odor	faintly fruity	1
Molecular Weight (g/mol)	292.24	36
Specific Gravity (@ 25ºC)	1.05	37
Vapor Pressure (mmHg @ 25ºC)	0.0000225	38
Boiling Point (ºC)	≥ 100; ≤ 101	38
log K_{ow}	-7.57	38
Water Solubility	soluble	1
Alcohol Solubility	soluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Disodium Lauroamphodiacetate		
Physical Form	liquid	39
Formula Weight (g/mol)	446.5	39
Disodium Wheatgermamphodiacetate		
Physical Form	liquid	1
Color	clear-amber	1
Odor	mild organic	1
Formula Weight (g/mol)	525 – 531	1
Specific Gravity	1.02	1
Boiling Point (ºC)	105	1
log K_{ow}	0.5	1
Sodium Cocoamphoacetate		
Physical Form	liquid	40
Color	clear – light amber	1
Odor	faintly fruity	1
Formula Weight (g/mol)	270.62	40
Water Solubility	soluble	1
Alcohol Solubility	insoluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Sodium Cocoamphopropionate		
Physical Form	liquid	1
Color	light amber	1
Odor	faintly fruity	1
Water Solubility	soluble	1
Alcohol Solubility	soluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Sodium Lauroamphoacetate		
Physical Form	powder	4

Table 2. Chemical properties

Property	Value	Reference
Disodium Cocoamphodiacetate		
Physical Form	liquid	[1]
Color	light tan	[1]
Odor	faintly fruity	[1]
Specific Gravity (@ 25ºC)	1.17	[35]
Water Solubility	soluble	[1]
Alcohol Solubility	insoluble	[1]
Nonpolar Organic Solvent Solubility	insoluble	[1]
Disodium Cocoamphodipropionate		
Physical Form	liquid	[1]
Color	light amber	[1]
Odor	faintly fruity	[1]
Molecular Weight (g/mol)	292.24	[36]
Specific Gravity (@ 25ºC)	1.05	[37]
Vapor Pressure (mmHg @ 25ºC)	0.0000225	[38]
Boiling Point (ºC)	≥ 100; ≤ 101	[38]
log K_{ow}	-7.57	[38]
Water Solubility	soluble	[1]
Alcohol Solubility	soluble	[1]
Nonpolar Organic Solvent Solubility	insoluble	[1]
Disodium Lauroamphodiacetate		
Physical Form	liquid	[39]
Formula Weight (g/mol)	446.5	[39]
Disodium Wheatgermamphodiacetate		
Physical Form	liquid	[1]
Color	clear-amber	[1]
Odor	mild organic	[1]
Formula Weight (g/mol)	525 – 531	[1]
Specific Gravity	1.02	[1]
Boiling Point (ºC)	105	[1]
log K_{ow}	0.5	[1]
Sodium Cocoamphoacetate		
Physical Form	liquid	[40]
Color	clear – light amber	[1]
Odor	faintly fruity	[1]
Formula Weight (g/mol)	270.62	[40]
Water Solubility	soluble	[1]
Alcohol Solubility	insoluble	[1]
Nonpolar Organic Solvent Solubility	insoluble	[1]
Sodium Cocoamphopropionate		
Physical Form	liquid	[1]
Color	light amber	[1]
Odor	faintly fruity	[1]
Water Solubility	soluble	[1]
Alcohol Solubility	soluble	[1]
Nonpolar Organic Solvent Solubility	insoluble	[1]
Sodium Lauroamphoacetate		
Color	light yellow	[4]
Formula Weight (g/mol)	349.5	[41]
Specific Gravity (@ 20ºC)	1.09	[4]
Vapor Pressure (mmHg @ 20ºC)	< 0.000011	[4]
Melting Point (ºC)	40	[4]
Water Solubility (g/l @ 20ºC)	1000	[4]

Table 3. Fatty acid compositions (%)[8,42]

Fatty Acids	Argan	Coconut	Cottonseed	Olive	Sweet Almond	Wheat Germ
Caproic (C6)		0.008 – 1.2				
Caprylic (C8)		3.4 – 15				
Capric (C10)		3.2 – 15				
Lauric (C12)		41 – 51.3				
Myristic (C14)		13 – 23	2		1	
Palmitic (C16)	10 – 15	4.2 – 18	21	7.5 – 20	4 – 9	11 – 16
Heptadecanoic (C17)					0.2	
Stearic (C18)	5 – 6.5	1.6 – 4.7	trace	0.5 – 3.5		1 – 6
Oleic (C18:1)	45 – 55	3.4 – 12	30	53 – 86	62 – 86	8 – 30
Linoleic (C18:2)		0.9 – 3.7	45	3.5 – 20	20 – 30	44 – 65
Arachidic (C20)		1.03	trace		0.2	
Palmitoleic (C16:1)				0.3 – 3.5	0.8	4 – 10
Stearic (C18)					2 – 3	
Linolenic (C18:3)	28 – 36			0 – 1.5	0.4	
Eicolenoic (C20:1)					0.3	
Behenic (C22)					0.2	
Erucic (C22:1)					0.1	
Other					< C16 = 0.1	0 – 1.2 (C20 – C22 saturated acids)

Table 4. Tradename mixtures of amphoacetates

Ingredient	Composition	Reference
Disodium Cocoamphodiacetate	47.5-52.5% Disodium Cocoamphodiacetate, 37.5-40% water, 11-12.5% sodium chloride, 0.02% dichloroacetic acid, and 0.01% chloroacetic acid	[43]
Disodium Cocoamphodipropionate	30-40% Disodium Cocoamphodipropionate, 60-70% water, <0.1% other components (not specified)	[44]
Disodium Lauroamphodiacetate	30-60% Sodium Lauroamphoacetate and < 0.1% dichloracetic acid (remaining components not stated)	[45]
Sodium Cocoamphoacetate	30% pure active surfactant, 59% water, 7% sodium chloride, 1-2% glycolic acid, <1% fatty acid, < 0.6% diamide, 0.5% amidoamine , < 10 ppm dichloroacetic acid, and < 5 ppm monochloroacetic acid	[46]
Sodium Lauroamphoacetate	30 – 32% Sodium Lauroamphoacetate, 1-5% amidoamine, 1-5% glycolate, <70% water/inert materials	[7]

Table 5. Frequency (2023) and concentration (2021) of use according to likely duration and exposure and by product category[13,14,47]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Disodium Lauroamphodiacetate		Disodium Wheatgermamphodiacetate		Sodium Arganamphoacetate		Sodium Cottonseedamphoacetate	
Totals	**10**	**0.18 – 5.4**	**NR**	**0.93**	**1**	**NR**	**1**	**NR**
summarized by likely duration and exposure*								
Duration of Use								
Leave-On	*1*	*1.6 – 5.4*	*NR*	*NR*	*1*	*NR*	*NR*	*NR*
Rinse-Off	*9*	*0.18 – 1.3*	*NR*	*0.93*	*NR*	*NR*	*1*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type*								
Eye Area	2	0.18	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	1[a]	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	1[a]	NR	NR	NR
Dermal Contact	9	0.18 – 1.6	NR	NR	1	NR	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	1.3 – 5.4	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	0.93	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	1	NR
Baby Products	1	1.3 – 1.6	NR	NR	NR	NR	NR	NR
as reported by product category								
Baby Products								
Baby Shampoos	NR	1.3						
Baby Lotions/Oils/Powders/Creams								
Other Baby Products	1	1.6						
Bath Preparations (diluted for use)								
Bubble Baths								
Other Bath Preparations								
Eye Makeup Preparations								
Eye Makeup Remover	2	0.18						
Other Eye Makeup Preparations								
Fragrance Preparations								
Perfumes								
Hair Preparations (non-coloring)								
Hair Conditioner								
Hair Spray (aerosol fixatives)								
Hair Straighteners								
Permanent Waves								
Shampoos (non-coloring)	1	NR						
Tonics, Dressings, and Other Hair Grooming Aids								
Other Hair Preparations	NR	5.4						
Hair Coloring Preparations								
Hair Dyes/Colors (all types requiring caution statements and patch tests)			NR	0.93				
Hair Shampoos (coloring)								
Other Hair Coloring Preparations								
Makeup Preparations								
Other Makeup Preparations								
Manicuring Preparations (Nail)								
Other Manicuring Preparations								

Table 5. Frequency (2023) and concentration (2021) of use according to likely duration and exposure and by product category[13,14,47]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Personal Cleanliness Products								
Bath Soaps and Detergents								
Douches								
Feminine Deodorants								
Other Personal Cleanliness Products							1	NR
Shaving Preparations								
Preshave Lotions (all types)								
Shaving Cream								
Skin Care Preparations								
Cleansing	6	0.2						
Face and Neck (exc shave)					1	NR		
Body and Hand (exc shave)								
Moisturizing								
Paste Masks (mud packs)								
Other Skin Care Preparations								
	Sodium Lauroamphoacetate		**Sodium Olivamphoacetate**		**Sodium Sweetalmondamphoacetate**			
Totals	**202**	**0.46 – 9.9**	**25**	**NR**	**15**	**NR**		
summarized by likely duration and exposure*								
Duration of Use								
Leave-On	*17*	*0.8 – 1.1*	*NR*	*NR*	*NR*	*NR*		
Rinse-Off	*183*	*0.46 – 9.9*	*25*	*NR*	*15*	*NR*		
Diluted for (Bath) Use	*2*	*0.72 – 1.3*	*NR*	*NR*	*NR*	*NR*		
Exposure Type*								
Eye Area	3	1.3	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR	NR	NR		
Incidental Inhalation-Spray	1; 1[b]	NR	NR	NR	NR	NR		
Incidental Inhalation-Powder	1[c]	NR	NR	NR	NR	NR		
Dermal Contact	183	0.46 – 9.9	15	NR	15	NR		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	17	0.75 – 4.4	10	NR	NR	NR		
Hair-Coloring	2	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	NR	NR	NR		
Mucous Membrane	112	0.72 – 5.3	15	NR	15	NR		
Baby Products	8	0.8 – 1.1	NR	NR	NR	NR		
as reported by product category								
Baby Products								
Baby Shampoos	2	0.8						
Baby Lotions/Oils/Powders/Creams	1	1.1						
Other Baby Products	5	0.8						
Bath Preparations (diluted for use)								
Bubble Baths	NR	0.72						
Other Bath Preparations	2	1.3						
Eye Makeup Preparations								
Eye Makeup Remover	2	1.3						
Other Eye Makeup Preparations	1	NR						
Fragrance Preparations								
Perfumes	1	NR						
Hair Preparations (non-coloring)								
Hair Conditioner			1	NR				
Hair Spray (aerosol fixatives)								

Table 5. Frequency (2023) and concentration (2021) of use according to likely duration and exposure and by product category[13,14,47]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Hair Straighteners	1	0.75						
Permanent Waves								
Shampoos (non-coloring)	13	0.8 – 4.4	9	NR				
Tonics, Dressings, and Other Hair Grooming Aids	1	NR						
Other Hair Preparations								
Hair Coloring Preparations								
Hair Dyes/Colors (all types requiring caution statements and patch tests)								
Hair Shampoos (coloring)	2	NR						
Other Hair Coloring Preparations								
Makeup Preparations								
Other Makeup Preparations								
Manicuring Preparations (Nail)								
Other Manicuring Preparations								
Personal Cleanliness Products								
Bath Soaps and Detergents	107	0.8 – 5.3	15	NR	15	NR		
Douches								
Feminine Deodorants								
Other Personal Cleanliness Products	3	0.8 – 2.8						
Shaving Preparations								
Preshave Lotions (all types)								
Shaving Cream								
Skin Care Preparations								
Cleansing	53	0.46 – 9.9						
Face and Neck (exc shave)								
Body and Hand (exc shave)								
Moisturizing								
Paste Masks (mud packs)	NR	1.2						
Other Skin Care Preparations	8	NR						

NR – not reported

*likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

**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.

[a] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 6. Current and historical frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[13]	**2005[2]**	**2022[14]**	**2006[2]**	**2023[13]**	**2005[2]**	**2022[14]**	**2006[2]**	**2023[13]**	**2005[2]**	**2022[14]**	**2006[2]**	**2023[13]**	**2005[2]**	**2022[14]**	**2006[2]**
	Disodium Cocoamphodiacetate				**Disodium Cocoamphodipropionate**				**Sodium Cocoamphoacetate**				**Sodium Cocoamphopropionate**			
Totals	**220**	**194**	**0.1 - 20**	**0.0006 – 12**	**73**	**72**	**0.8 – 1.8**	**0.008 - 15**	**121**	**46**	**0.03 – 4.5**	**0.09 – 18**	**21**	**7**	**0.84 – 7.5**	**0.3 – 10**
summarized by likely duration and exposure*																
Duration of Use																
Leave-On	*40*	*18*	*0.1 – 3.4*	*0.0006 – 10*	*29*	*20*	*NR*	*0.8 - 1*	*20*	*NR*	*0.56 – 0.93*	*0.1 – 4*	*15*	*4*	*NR*	*NR*
Rinse-Off	*179*	*168*	*0.1 – 20*	*0.005 – 12*	*40*	*52*	*0.8 – 1.8*	*0.008 – 15*	*101*	*42*	*0.03 – 4.5*	*0.7 – 18*	*6*	*3*	*0.84 – 7.5*	*0.3 – 8*
Diluted for (Bath) Use	*1*	*8*	*1.2*	*4 – 8*	*4*	*NR*	*NR*	*NR*	*NR*	*4*	*NR*	*0.09*	*NR*	*NR*	*NR*	*10*
Exposure Type*																
Eye Area	3	15	NR	0.005 – 0.8	3	NR	NR	NR	3	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	6[a]; 22[b]	5[a]; 3[b]	2.3 – 2.7[a]	0.004 – 0.06[a]; 0.03 – 0.2[b]	2[a]	4[a]	NR	1; 0.8[a]	4[a]; 13[b]	NR	0.56[a]	0.1[a]	NR	2[a]	NR	NR
Incidental Inhalation-Powder	22[b]	3[b]	3.4[c]	0.03 – 0.2[b]	NR	NR	NR	NR	13[b]	NR	0.93[c]	NR	NR	NR	NR	NR
Dermal Contact	141	97	0.1 – 20	0.0006 – 12	10	9	0.8 – 1.8	0.5 – 8	81	29	0.93 – 4.5	0.09 – 18	17	22	2	10
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	64	92	0.9 – 6.9	2 – 8	61	60	NR	0.2 – 15	40	15	0.03 – 4.5	0.1 – 6	4	6	0.84 – 7.5	0.3 – 8
Hair-Coloring	2	5	NR	5	2	3	NR	0.008	NR	2	2.1	0.7	NR	NR	2.4	NR
Nail	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	60	20	0.1 – 3.3	0.05 – 9	5	3	NR	0.5 – 8	21	26	3.3	0.09 – 18	NR	2	NR	10
Baby Products	7	8	0.56 – 5.4	2 - 7	NR	1	NR	NR	6	NR	2.8	4	NR	NR	NR	NR
as reported by product category																
Baby Products																
Baby Shampoos	4	NR	0.9 – 5.4	NR					5	NR	2.8	NR				
Baby Lotions/Oils/Powders/Creams																
Other Baby Products	3	NR	0.56	4	NR	1	NR	NR	1	NR	NR	4				
Bath Preparations (diluted for use)																
Bubble Baths	NR	4	1.2	0.09					NR	4	NR	0.09				
Other Bath Preparations	1	NR	NR	NR	4	15	NR	NR					NR	NR	NR	10
Eye Makeup Preparations																
Eye Makeup Remover	2	NR	NR	NR	1	NR	NR	NR	3	NR	NR	NR				
Other Eye Makeup Preparations	1	NR	NR	NR	2	NR	NR	NR								
Fragrance Preparations																
Perfumes																
Hair Preparations (non-coloring)																
Hair Conditioner	3	3	NR	2	15	14	NR	0.2	1	3	1	2	NR	NR	2 – 7.5	3 - 5
Hair Spray (aerosol fixatives)					NR	NR	NR	1								
Hair Straighteners																
Permanent Waves	NR	1	NR	NR					NR	1	NR	NR	NR	NR	0.84	0.3
Shampoos (non-coloring)	55	11	1.4 – 6.9	1 – 6	19	27	NR	15	30	11	0.03 – 4.5	1 – 6	4	3	2.4	8
Tonics, Dressings, and Other Hair Grooming Aids	NR	NR	2.3 – 2.7	0.1	2	4	NR	0.8	3	NR	0.56	0.1	NR	2	NR	NR
Other Hair Preparations	2	NR	NR	NR	25	NR	NR	NR	1	NR	NR	NR	NR	2	NR	0.3 – 10
Hair Coloring Preparations																
Hair Dyes and Colors (all types requiring caution statements and patch tests)	2	NR	NR	0.7	NR	3	NR	0.008	NR	NR	NR	0.7				
Hair Shampoos (coloring)									NR	NR	2.1	NR	NR	NR	2.4	NR
Other Hair Coloring Preparation	NR	2	NR	NR	2	NR	NR	NR	NR	2	NR	NR				

Table 6. Current and historical frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[13]	**2005[2]**	**2022[14]**	**2006[2]**	**2023[13]**	**2005[2]**	**2022[14]**	**2006[2]**	**2023[13]**	**2005[2]**	**2022[14]**	**2006[2]**	**2023[13]**	**2005[2]**	**2022[14]**	**2006[2]**
Makeup Preparations																
Other Makeup Preparations	NR	NR	NR	3					1	NR	NR	3				
Manicuring Preparations (Nail)																
Other Manicuring Preparations	1	NR	NR	NR												
Personal Cleanliness Products																
Bath Soaps and Detergents	22	4	2.1	3 – 18	NR	3	NR	8	15	4	3.3	3 – 18				
Douches	12	NR	NR	0.8 – 2					NR	NR	NR	0.8 – 2				
Feminine Deodorants	1	NR	NR	NR												
Other Personal Cleanliness Products	24	18	0.1 – 3.3	NR	1	NR	NR	0.5	6	18	NR	NR				
Shaving Preparations																
Preshave Lotions (all types)					NR	NR	1.8	NR					NR	NR	2	NR
Shaving Cream	3	NR	0.99	NR					1	NR	NR	NR				
Skin Care Preparations																
Cleansing	52	3	0.77 - 20	2 – 5	2	5	0.8	7	38	3	1.6 – 4.5	2 - 5	2	NR	NR	NR
Face and Neck (exc shave)	3	NR	3.4 (not spray)	NR					8	NR	0.93 (not spray)	NR				
Body and Hand (exc shave)	18	NR	NR	NR					5	NR	NR	NR				
Moisturizing	6	NR	NR	NR					1	NR	NR	NR				
Paste Masks (mud packs)									2	NR	1.5	NR				
Other Skin Care Preparations	5	NR	0.1	NR									15	NR	NR	NR

NR – not reported

*likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

**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.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

Table 7. Acute oral toxicity studies on Sodium Lauroamphoacetate[4]

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/ Results
Sodium Lauroamphoacetate (water and sodium chloride)	No vehicle	Carworth mice (10/group; sex not specified)	100%; 10, 12.5, 15 ml/kg bw	OECD TG 401; gavage administration; 5 d observation period	One, four, and eight animals died in groups given 10, 12.5, and 15 ml/kg bw of the test substance, respectively. The LD_{50} was determined to be 12.7 ml/kg for the aqueous solution. This corresponds to 14,224 mg/kg for the aqueous solution and 6116 mg/kg for the undiluted test substance.
Sodium Lauroamphoacetate (50% solids; water and sodium chloride)	Water and 0.5% carboxymethylcellulose	Hsd: Sprague-Dawley rats (3/sex)	20%; 10 ml/kg	OECD TG 423; gavage administration; 14 d observation period	LD_{50} > 10 ml/kg (corresponding to 2000 mg/kg bw)
Sodium Lauroamphoacetate (35% solids; water, sodium chloride, sodium glycolate)	Water	Wistar rats (5/sex)	20% aqueous dilution; 10 ml/kg	OECD TG 401; gavage administration; 14 d observation period	LD_{50} > 10 ml/kg (corresponding to 2000 mg/kg bw)
Sodium Lauroamphoacetate (50% solids; water and sodium chloride)	Water	Charles River rats (5/sex/group)	50% aqueous dilution; 5, 5.5, 6.25, and 6.5 ml/kg bw;	OECD TG 401; gavage administration; 7 d observation period	One and 3 animals died in groups given 5 and 5.5 ml/kg bw test substance, respectively. Seven animals died in the group receiving 6.25 ml/kg test substance, and 7 animals died in the group receiving 6.5 ml/kg bw test substance. The acute oral LD_{50} was calculated to be 5.85 ml/kg. This corresponds to 6844 mg/kg for the aqueous solution and 3422 mg/kg for the undiluted test substance.
Sodium Lauroamphoacetate (50% solids; water, and sodium chloride)	Water	Sprague-Dawley rats (5/sex)	50% aqueous dilution; 15 ml/kg bw	OECD TG 401; gavage administration; 14 d observation period	LD_{50} determined to be > 15 ml/kg; corresponds to an LD_{50} > 7500 mg/kg for the undiluted test substance.

LD_{50} = median lethal dose; OECD TG: Organisation for Economic Cooperation and Development Test Guidelines

Table 8. Oral reproductive and developmental toxicity studies[4]

Test Article	Vehicle	Animals/Group	Dose	Procedure	Results
Disodium Cocoamphodiacetate	Water	female Wistar Han rats (22/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 414; animals treated via gavage on days 6-20 post-coitum; animals killed on day 21; control animals treated with water only; clinical observations performed throughout study; reproductive organs evaluated post-mortem (gravid uterine weight, number of corpora lutea, implantations, early and late resorptions); fetal examinations included external, soft tissue, skeletal, and head examinations, anogenital distance, body weights, survival rate, sex ratio, developmental variations	No treatment-related mortality or adverse effects in dams were observed. Visceral examination of fetuses revealed severe cardiovascular malformations in all test groups (non-dose-dependent; not including control group). In the 1000 mg/kg bw/d group, one fetus had a right-sided aortic arch, ventricular septum defect, and no eyes. At 300 mg/kg bw/d, one fetus had a ventricular septum defect, absence of the ductus arteriosus, situs inversus, and abnormal lung lobation. At 100 mg/kg bw/d, two fetuses were viscerally malformed; one fetus had abnormal lung lobation and transposition of the great vessels, and the other fetus presented with situs inversus, abnormal lung lobation, interrupted aortic arch, retroesophageal ductus arteriosus, and ventricular septum defect. Mean litter incidences of a 7th cervical ossification site were 1.5, 5.3, 4.6, and 11.3% per litter in the 0, 100, 300, and 1000 mg/kg bw/d groups, respectively. No other adverse effects relating to developmental parameters evaluated were observed. The maternal NOAEL was determined to be 1000 mg/kg bw/d. A developmental NOAEL could not be determined as severe cardiovascular malformations were observed at all doses tested, in a non-dose-dependent manner.
Disodium Cocoamphodiacetate	Water	Wistar Han rats (10/sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 422; animals treated via gavage; control animals treated with water only; males treated for 29 d (2 wk prior to mating, during mating, and up to necropsy); females treated for 50-54 d (2 wk prior to mating, during mating, post-coitum, and 14-16 d of lactation); females without offspring were treated for 41 d; animals were observed for mortality, estrous cycle lengths, sperm parameters, mating index, fertility index, gestation index, precoital time, and duriation of gestation, and histopathology of reproductive organs; offspring viability indices evaluated include the post-implantation index, live birth index, sex ratio, and lactation index	Treatment with the test substance did not cause any adverse morphological effects in reproductive organs. No adverse effects were noted in any of the parameters evaluated. A high mortality rate was observed in females (4/10), and one death was reported in males. These deaths were concluded to be related to regurgitation, and thus, secondary to the test item; however, it is possible that the physical/chemical properties of the test item solution in combination with the route of administration could have resulted in these deaths. No treatment related abnormalities were observed in the F1 generation. Because the mortalities reported, the NOAEL was determined to be 300 mg/kg bw/d and the reproductive NOAEL was determined to be 1000 mg/kg bw/d.
Disodium Cocoamphodiacetate (47.2 – 48% solids)	Water	Wistar Han rats (10/sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 408; animals treated via gavage for 90 d; estrous cycle length, spermatogenesis, and weight/ appearance/histopathology of reproductive organs evaluated	No adverse effects relating to the parameters evaluated were observed.

Table 8. Oral reproductive and developmental toxicity studies[4]

Test Article	Vehicle	Animals/Group	Dose	Procedure	Results
Sodium Cocoamphoacetate	Water	Wistar Han rats (10/sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 422; animals treated via gavage; control animals treated with water only; males treated for 29 d (2 wk prior to mating, during mating, and up to and including the day before necropsy); females treated for 50-56 d (14 d prior to mating, the time to conception, duration of pregnancy, and 13 or 15 d after delivery, up to and including the day before necropsy); females without offspring were treated for 53 d (no evidence of mating) or 42-43 d (not pregnant or implantation site only); animals were observed for mortality, estrous cycle lengths, sperm parameters, mating index, fertility index, gestation index, precoital time, and duriation of gestation, and histopathology of reproductive organs; offspring viability indices evaluated include the post-implantation index, live birth index, sex ratio, and lactation index	No test-item related abnormalities in estrous cycle length and regularity were observed. One male at 300 mg/kg bw/d showed tubular atrophy in the testes and reduced luminal sperm with luminal cell debris in the epididymis. No treatment-related effects in the F1 generation were observed. The reproductive NOAEL was determined to be 1000 mg/kg bw/d.
Sodium Lauroamphoacetate	Water	female Wistar Han (22/group)	0, 100, 300, and 1000 mg/kg bw/d	OECD TG 414; animals treated from day 6 to day 20 post-coitum via gavage; animals killed on day 21; control animals treated with water only; clinical observations performed throughout study; reproductive organs evaluated post-mortem (gravid uterine weight, number of corpora lutea, implantations, early and late resorptions); fetal examinations included external, soft tissue, skeletal, and head examinations, anogenital distance, body weights, survival rate, sex ratio, developmental variations	Abnormal breathing sounds, temporary slight weight loss and decreased food consumption, and salivation were observed in dams dosed with 300 and 1000 mg/kg bw/d. Body weight and food intake recovered throughout dosing. A statistically significant decrease of T3 (thyroid hormone) blood concentration was observed in dams dosed with 1000 mg/kg bw/d; however, values were within the historical control database values of the laboratory. Irregular surface of the non-glandular stomach was noted in 12/22 females treated with 1000 mg/kg bw/d. Dark red foci on the glandular stomach were observed in 1 animal in this group. No other adverse effects relating to maternal parameters investigated were observed (uterine content, gravid uterine weight, corpora lutea, implantation sites, pre-/post-implantation loss). No adverse effects relating to developmental parameters were observed in fetuses. The maternal and developmental NOAEL was determined to at least 1000 mg/kg bw/d.

NOAEL = no-observed-adverse-effect-level; OECD TG = Organisation for Economic Cooperation and Development test guidelines

Table 9. Genotoxicity studies[4]

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results
Sodium Lauroamphoacetate (35% solids; water, sodium chloride, and sodium glycolate)	Water	Experiment 1: 7, 35, 175, 875 and 4375 µg/plate Experiment 2: 5.5, 21.9, 87.5, 350 and 1400 µg/plate	*S. typhimurium* TA1535, TA1537, TA1538, TA98, and TA100	OECD TG 471; Ames assay performed with and without metabolic activation; 2-part experiment; Experiment 1 conducted on *S. typhimurium* strains TA1535, TA1537, and TA100; Experiment 2 conducted on *S. typhimurium* strains TA1538 and TA98; positive (sodium azide, 9-aminoacride, 4-nitro-o-phenyldiamine, or 2-aminoanthracene) and negative controls (water) were used in both experiments	Non-genotoxic; valid controls
Sodium Lauroamphoacetate (water and sodium chloride)	Water	Experiment 1 and 2: 313, 625, 1250, 2500 and 5000 µg/plate (TA1535, TA1537, TA98 and WP2 uvrA) and 156, 313, 625, 1250 and 2500 µg/plate (TA100) Experiment 3: 39.1, 78.1, 156, 313, 625 and 1250 µg/plate (TA1535 and TA1537) and 39.1, 78.1, 156, 313 and 625 µg/plate (TA100 without S9-mix)	*S. typhimurium* TA1535, TA1537, TA98, and TA100; *E. coli* WP2 uvr A	OECD TG 471; Ames assay performed with and without metabolic activation; 3-part experiment; 1st experiment conducted using a plate-incorporation method; 2nd experiment conducted with a pre-incubation step; 3rd experiment conducted with pre-incubation step at lower test concentrations; positive (substance not stated) and negative controls (water) were used in all experiments	Non-genotoxic; valid controls
Sodium Lauroamphoacetate (water, sodium chloride, and sodium glycolate)	Water	Experiment 1: 30, 65, 130, 146, 162, 190, 200 and 250 µg/ml Experiment 2: 30, 65, 125, 140, 155, 170, 185, and 200 µg/ml	Human peripheral blood lymphocytes	OECD 473; in vitro mammalian chromosome aberration assay performed with and without metabolic activation; 2-part experiment; in the 1st experiment, cells were treated for 4 h (with and without metabolic activation) and for 20 h (without metabolic activation); in the 2nd experiment, cells were treated for 4 h (with metabolic activation) at lower test concentrations; positive (substance not stated) and negative controls (water) were used in both experiments	Non-clastogenic; valid controls

OECD TG = Organisation for Economic Cooperation and Development test guidelines

Table 10. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
Animal						
Sodium Lauroamphoacetate (35% solids; water, sodium chloride, and sodium glycolate)	No vehicle	100%; 0.5 ml	3 male Chbb:Hm rabbits	OECD TG 404; semi-occlusive dressing; single patch application for 4 h; evaluation 1, 24, 48, and 72 h after patch removal	Non-irritating	[4]
Sodium Lauroamphoacetate (50% solids; water and sodium chloride)	No vehicle	100%; 0.5 g	3 female New Zealand white rabbits	OECD TG 404; semi-occlusive dressing; single patch application for 4 h; evaluation 1, 24, 48, and 72 h after patch removal	Non-irritating; very slight erythema observed 24 h after patch removal, fully reversed within 72 h	[4]
Trade name mixture consisting of Sodium Lauroamphoacetate, sodium trideceth sulfate, isopropyl alcohol (2%), and water (67.9%) (concentration of Sodium Lauroamphoacetate and sodium trideceth sulfate combined: 30.1%)	No vehicle	100%; 0.5 ml	3 New Zealand albino rabbits (sex not specified)	Test substance placed on abraded and intact skin under 2.5 cm^2 gauze patches; occlusive conditions; patches left on for 24 h; sites evaluated 24 and 72 h after patch removal	severe primary irritant in intact and abraded skin; primary irritation score of 6.75 (score of > 5.1 indicates severe irritation)	[21]
Trade name mixture containing Sodium Lauroamphoacetate (36%) and water (64%)	No vehicle	100%; 0.5 ml	3 New Zealand albino rabbits (sex not specified)	Test substance placed on abraded and intact skin under 2.5 cm^2 gauze patches; occlusive conditions; patches left on for 24 h; sites evaluated 24 and 72 h after patch removal	severe primary irritant in intact and abraded skin; primary irritation score of 5.84 (score of > 5.1 indicates severe irritation)	[22]
Human						
Disodium Cocoamphodiacetate	Water	0.5%; 40 µl	105 subjects	The test substance as applied to the skin under occlusive conditions for 48 h; readings were performed 15 min and 24 h after patch removal; parameters measured include erythema and edema	Non-irritating	[24]
Disodium Cocoamphodiacetate	Water	1%; 100 µl	22 subjects	Soap chamber test; test substance applied to forearm under occlusive conditions; repeated patching was performed for 24 h, followed by a 6 h patch period per day, for the next 4 d; first assessment occurred 15 min after patch removal on day 2; all other assessments were performed prior to reapplication on days 3-5, and on day 8	Non-irritating; total irritation score: 4.42 (score ≤ 10 indicates very slightly or not irritating)	[16]
Disodium Cocoamphodiacetate	Water	2%; 75 µl	20 subjects	Epicutaneous patch test; test substance applied to back under occlusive conditions; patches removed after 24 h; sites evaluated 6, 24, 48, and 72 h after removal	Slightly irritating; total irritation score: 14.14 (score of 10 - ≤ 25 indicates slightly irritating)	[16]
Disodium Cocoamphodiacetate	NR	5%	8 subjects	Test areas (approximately 3 cm^2 each) were marked on the forearm. Three successive washings were performed. For each wash, a technician poured 4 ml of 1 surfactant solution into both palms, rubbed solution into the hands, and used three fingers in a to rub the solution into the predesignated test area for 1 min with the lather. The area was then rinsed for 15 sec, followed by a 30-min rest period. This process was repeated 2 additional times. The degree of irritation was evaluated at baseline and after each washing. A water washing control and non-treatment site were used for comparison. Erythema was quantified by skin color reflectance measurements using a colorimeter.	Clinical scores did not reveal any significant differences between treated and untreated sites.	[23]
Sodium Cocoamphoacetate	Water	1%; 100 µl	21 subjects	Soap chamber test; test substance applied to forearm under occlusive conditions; repeated patching was performed for 24 h, followed by a 6 h patch period per day, for the next 4 d; first assessment occurred 15 min after patch removal on day 2; all other assessments were performed prior to reapplication on days 3-5, and on day 8	Slightly irritating; total irritation score: 13.46 (score of 10 - < 15 indicates slightly irritating)	[16]

Table 10. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Sodium Cocoamphoacetate	Water	2%; 75 µl	20 subjects	Epicutaneous patch test; test substance applied to back under occlusive conditions; patches removed after 24 h; sites evaluated 6, 24, 48, and 72 h after removal	Non-irritating; total irritation score: 8.51 (score ≤ 10 indicates very slightly or not irritating)	[16]
Sodium Cocoamphoacetate	NR	5%	8 subjects	Test areas (approximately 3 cm^2 each) were marked on the forearm. Three successive washings were performed. For each wash, a technician poured 4 ml of 1 surfactant solution into both palms, rubbed solution into the hands, and used three fingers in a to rub the solution into the predesignated test area for 1 min with the lather. The area was then rinsed for 15 sec, followed by a 30-min rest period. This process was repeated 2 additional times. The degree of irritation was evaluated at baseline and after each washing. A water washing control and non-treatment site were used for comparison. Erythema was quantified by skin color reflectance measurements using a colorimeter.	Clinical scores did not reveal any significant differences between treated and untreated sites.	[23]
Sodium Cocoamphoacetate	Citrate buffer (diluted to citrate concentration of 5 mM; pH 6 ± 0.5)	10% (274 mM); 50 µl	12 subjects	48-h occlusive patch test; Finn chambers were applied to the volar forearm; applications sites were evaluated 1 h, 24 h, 5 d, 9 d, and 14 d after patch removal for erythema (on a scale of 1 (slight redness) to 4 (fiery red with edema)) and scaling (on a scale of 1 (fine) to 3 (severe with large flakes)). SLS (2%) was included in the study for comparison. Citrate buffer (10 mM) served as the negative control.	At 1 h after patch removal, the visual erythema score (as % of total) was 33; the scores were 10, 4, 0, and 4 at 24 h and 5, 9, and 14 d after patch removal, respectively. Scaling scores (as % of total) were 0, 3, 22, 22, and 14 at 1 h, 24 h, and 5, 9, and 14 d after patch removal, respectively. For SLS, erythema scores ranged from 58 at 1 h to 17 at 14 d after patch removal, and scaling scores ranged from 0 after 1 h to 22 at 14 d, with a max of 47 at 5 d after patch removal.	[25]
Sodium Lauroamphoacetate	Water	1%; 100 µl	21 subjects	Soap chamber test; test substance applied to forearm under occlusive conditions; repeated patching was performed for 24 h, followed by a 6 h patch period per day, for the next 4 d; first assessment occurred 15 min after patch removal on day 2; all other assessments were performed prior to reapplication on days 3-5, and on day 8	Irritating; total irritation score: 20.93 (score of 20 - < 30 indicates irritating)	[16]
Sodium Lauroamphoacetate	Water	2%; 75 µl	20 subjects	Epicutaneous patch test; test substance applied to back under occlusive conditions; patches removed after 24 h; sites evaluated 6, 24, 48, and 72 h after removal	Moderately irritating; total irritation score: 27.19 (score of 25 - < 50 indicates moderately irritating)	[16]
Sodium Lauroamphoacetate (35% solids; water, sodium chloride, and sodium glycolate)	Water	50 and 100%; dose not reported	20 subjects	The test substance was applied to the skin, under open conditions, every 30 sec for 30 min. All applications occurred under open conditions.	Non-irritating	[4]

Table 10. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
SENSITIZATION						
Animal						
Sodium Cocoamphoacetate (water, sodium chloride, and sodium glycolate)	Water	Intradermal induction: 5% (% solids not stated) Epicutaneous induction: 75% (% solids not stated) Challenge exposure: 1% (0.394% solids)	female Himalayan spotted guinea pigs (control: 5/group; test: 10/group)	-Guinea pig maximization test performed according to OECD TG 406 -Intradermal injections of adjuvant and physiological saline, test substance diluted to 5% in water, and the test substance diluted to 5% by emulsion in a mixture of adjuvant and physiological saline (control groups given mixtures of adjuvant and physiological saline or water) -Topical application on day 7 for epicutaneous induction, aqueous dilutions, under occlusive conditions, for 48 h (control animals treated with water only) -Challenge exposure on day 21, aqueous dilution, under occlusive conditions, for 24 h	Non-sensitizing	4
Sodium Lauroamphoacetate (water and sodium chloride)	Propylene glycol	1, 3, 6, 12, and 30% (experiment 1); 30, 40, and 50% (experiment 2)	4 female CBA/J mice/group	-Local lymph node assay performed according to OECD TG 429 -First experiment: animals treated with the test substance in dilutions of 1, 3, 6, 12, and 30% in propylene glycol (25 µl); animals received this treatment for 3 consecutive days, on one ear -Second experiment: animals treated with the test substance in dilutions of 30, 40, and 50% in propylene glycol; animals received this treatment for 3 consecutive days, on one ear -First and second experiments utilized a positive (hexylcinnamaldehyde) and negative (propylene glycol) group -On day 6, animals received an injection of 0.9% sodium chloride containing 20 µCi of 3H-TdR via the tail vein -Animals were killed 5 h after injection, lymph nodes were pooled, and proliferation evaluated -Ear thickness and local reactions were observed on days 1, 2, and 3 (before application), and on day 6 (after animals were killed)	No adverse effects or lymphoproliferation was observed in experiment 1. In experiment 2, an 11.34% increase in ear thickness was observed after treatment with the test substance at 50%. The test substance was found to induce delayed contact hypersensitivity at concentrations of 50%. The result was considered to be inconclusive as surfactants have clear irritating effects, and may lead to false positives.	4
Sodium Lauroamphoacetate (0.18 – 17.5% solids; water, sodium chloride, and sodium glycolate)	Physiological saline	Intradermal induction: 0.5% (0.18% solids) Epicutaneous induction: 50% (17.5 % solids) Challenge exposure: 20% (7% solids)	2-3 female Pirbright white guinea pigs/group	-Guinea pig maximization test performed according to OECD TG 406 -Intradermal injections of adjuvant and physiological saline, test substance diluted to 5% in physiological saline, and the test substance diluted to 5% by emulsion in a mixture of adjuvant and physiological saline (control groups given mixtures of adjuvant and physiological saline or water) -Topical application on day 7 of the test substance diluted to 50% in physiological saline, under occlusive conditions, for 48 h (control animals treated with water only) -Challenge exposure on day 21 with test substance diluted to 20% in physiological saline, under occlusive conditions, for 24 h	Positive reactions were observed in 5 of 20 test animals during challenge. The test substance was classified to be non-sensitizing.	4
Human						
Sodium Lauroamphoacetate (0.15% solids)	Water	0.5%; 200 µl	99 subjects	HRIPT -9 total induction exposures; 24 h induction periods -2-wk rest period followed by a challenge exposure -all exposures were performed under occlusive conditions	Non-irritating and non-sensitizing	4

HRIPT = human repeated-insult patch test; NR = not reported; OECD TG = Organisation for Economic Cooperation and Development test guidelines; SLS = sodium lauryl sulfate

Table 11. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO			
Disodium Cocoamphodiacetate	Water	0.6%	3 skin samples	30 µl of test substance applied to reconstituted human corneal epithelial tissues and incubated; cell viability evaluated via MTT assay	Non-irritating	[16]
Disodium Cocoamphodiacetate	Water	1%	3 trials	Red blood cell test (evaluates hemolysis and protein denaturation in porcine erythrocytes)	Moderately irritating; H_{50}/DI = 7.77 (score of 1 - ≤ 10 indicates moderately irritating)	[16]
Disodium Cocoamphodiacetate	Water	3%	6 eggs	HET-CAM assay	Slightly irritating; irritation quotient = 0.63 (quotient ≤ 0.8 indicates slightly irritating)	[16]
Disodium Cocoamphodiacetate	Water	50%	6 eggs	EpiOcular™ assay; tissues treated with 100 µl of test article and incubated; MTT assay following incubation	Severe/extreme ocular irritant; ET_{50} < 2 (score < 3 indicates severely/extremely irritating)	[26]
Sodium Cocoamphoacetate	Water	0.6%	3 skin samples	30 µl of test substance applied to reconstituted human corneal epithelial tissues and incubated; cell viability evaluated via MTT assay	Slightly irritating	[16]
Sodium Cocoamphoacetate	Water	1%	3 skin samples	Red blood cell test	Non-irritating; H_{50}/DI = 102.40 (score > 100 indicates non-irritating)	[16]
Sodium Cocoamphoacetate	Water	3%	6 eggs	HET-CAM assay	Slightly irritating; irritation quotient = 0.42 (quotient ≤ 0.8 indicates slightly irritating)	[16]
Sodium Lauroamphoacetate	Water	1%	3 trials	Red blood cell test	Non-irritating; H_{50}/DI = 222.13 (score > 100 indicates non-irritating)	[16]
Sodium Lauroamphoacetate	Water	3%	6 eggs	HET-CAM assay	Slightly irritating; irritation quotient: 0.79 (quotient ≤ 0.8 indicates slightly irritating)	[16]
Sodium Lauroamphoacetate	Water	40%	6 eggs	HET-CAM assay	Severely irritating; irritation quotient: 3.41 (quotient ≥ 2 indicates severely irritating)	[27]
			ANIMAL			
Sodium Lauroamphoacetate (10% solids: water and sodium chloride; 10% aqueous dilution)	No vehicle	100%; 0.1 ml	3 rabbits (strain and sex not specified)	The test material was placed in one eye of each animal in an amount of 0.1 ml. The left eye served as a control. Eyes were evaluated 24, 48, and 72 h after test substance administration. Eyes were also evaluated on day 7 after administration. OECD TG 405.	The test substance was not considered to be an ocular irritant based on CLP criteria. Mean corneal opacity, iris, conjunctivae irritation and chemosis scores were 0/4, 0/2, 0.2/3, and 0/4, respectively. The slight conjunctival irritation was fully reversed by day 7.	[4]
Sodium Lauroamphoacetate (15% solids; water and sodium chloride; 30% aqueous dilution)	No vehicle	100%; 0.1 ml	3 rabbits (strain and sex not specified)	Assay performed according to the same procedure as above.	The test substance was not considered to be an ocular irritant based on CLP criteria. Mean corneal opacity, iris, conjunctivae irritation and chemosis scores were 0/4, 0/2, 0.7/3, and 1.1/4, respectively. All effects were fully reversible within 7 d.	[4]
Sodium Lauroamphoacetate (50% solids; water and sodium chloride; 50% aqueous dilution)	No vehicle	100%; 0.1 ml	3 female New Zealand White rabbits	Assay performed according to the same procedure as above.	The test substance was considered to be a Category 2 irritant based on CLP criteria. Mean corneal opacity, iris, conjunctivae irritation and chemosis scores were 1.2/4, 0/2, 1.7/3, and 0/4, respectively. All effects were fully reversible within 7 d.	[4]

Table 11. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Sodium Lauroamphoacetate (50% solids; water and sodium chloride; 50% aqueous dilution)	No vehicle	100%; 0.1 ml	6 female New Zealand White rabbits	Assay performed according to the same procedure as above, with the exception that a day 7 evaluation was not performed.	The test substance was not considered to be an irritant based on CLP criteria. Mean corneal opacity, iris, conjunctivae irritation and chemosis scores were 0.06/4, 0.1/2, 0.7/3, and 0.6/4, respectively. All effects were fully reversible within 72 h.	[4]
HUMAN						
Micellar water cleanser containing 0.4% Disodium Cocoamphodiacetate and 3% poloxamer 184 (remaining product composition not stated)	No vehicle	100%	10	Subjects instructed to use each product once a day (as an eye makeup remover) for 21 d; reaction responses evaluated at 24 h, 7, and 21 d	No symptoms of eye irritation or adverse effects were noted.	[28]
Micellar water cleanser containing 1.2% Disodium Cocoamphodiacetate and 1% cetearyl alcohol (remaining product composition not stated)	No vehicle	100%	10	Subjects instructed to use each product once a day (as an eye makeup remover) for 21 d; reaction responses evaluated at 24 h, 7, and 21 d	No symptoms of eye irritation or adverse effects were noted.	[28]

CLP = Classification, Labeling, and Packaging; DI = denaturation index: ET_{50} = effective time of exposure to reduce tissue viability to 50%; H_{50} = half-maximal effective concentration for hemolysis; HET-CAM = hen's egg test-chorioallantoic membrane; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; OECD TG = Organisation for Economic Cooperation and Development test guidelines

REFERENCES

1. Andersen F.A. (ed). Final Report on the Safety Assessment of Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoamphodipropionate. *J Am Coll Toxicol*. 1990;9(2):121-142.

2. Andersen F.A. (ed). Annual Review of Cosmetic Ingredient Safety Assessments: 2005/2006. Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoamphodipropionate. *Int J Toxicol*. 2008;27(Suppl 1):98-101.

3. Nikitakis J, Kowcz A. wINCI: *International Cosmetic Ingredient Dictionary and Handbook*. http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC: Personal Care Products Council. Last Updated 2023. Accessed March 1, 2023.

4. European Chemicals Agency (ECHA). Acetic acid, chloro-, sodium salt, reaction products with 4,5-dihydro-2-undecyl-1H-imidazole-1-ethanol and sodium hydroxide. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/13724. Last Updated 2021. Accessed August 19, 2021.

5. Andersen F.A. (ed). Final Report of the Safety Assessment of Glycolic Acid, Ammonium, Calcium, Potassium, and Sodium Glycolates, Methyl, Ethyl, Propyl, and Butyl Glycolates, and Lactic Acid, Ammonium, Calcium, Potassium, Sodium, and TEA-Lactates, Methyl, Ethyl, Isopropyl, and Butyl Lactates, and Lauryl, Myristyl, and Cetyl Lactates. *Int J Toxicol*. 1998;17(Suppl 1):1-241.

6. Fiume MM, Bergfeld WF, Belsito DV, et al. 40th Anniversary Overview and Rereview Summaries from 2011 to 2015. Alpha Hydroxy Acids. *Int J Toxicol*. 2017;36(Suppl 2):15S - 21S.

7. Parchem. Sodium Lauroamphoacetate: Safety Data Sheet. 2016. https://www.parchem.com/siteimages/Attachment/GHS%20Sodium%20Lauroamphoacetate%20MSDS.pdf. Accessed November 30, 2022.

8. Burnett CL, Bergfeld WF, Belsito DV, et al. Final Report of the Cosmetic Ingredient Review Expert Panel on the Safety Assessment of Cocamidopropyl Betaine (CAPB). *Int J Toxicol*. 2012;31(Suppl 1):77S-111S.

9. Zhang Y, Xu H, Lu S. Preparation and application of layered double hydroxide nanosheets. *RSC Adv*. 2021;11:24254-24281.

10. Farn RJ. Chemistry and Technology of Surfactants. In: Oxford, UK: Blackwell Published Ltd.; 2006. 175.

11. Foti C, Bonamonte D, Mascolo G, Tiravanti G, Rigano GA. Aminoethylethanolamine: a new allergen in cosmetics? *Contact Dermatitis*. 2001;45(3):129-133.

12. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Full Public Report: Disodium Wheatgermamphodiacetate. 1998. https://www.industrialchemicals.gov.au/sites/default/files/NA601%20Public%20Report%20PDF.pdf. Accessed March 24, 2023.

13. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2023. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2023; received February 2, 2023).

14. Personal Care Products Council. 2021. Concentration of Use by FDA Product Category: Additions to Sodium Lauroamphoacetate Report. Unpublished data submitted by Personal Care Products Council on January 10, 2022.

15. EUR-Lex. Access to European Union Law. Last Updated 2023. Accessed 03/29/2023.

16. Mehling A, Kleber M, Hensen H. Comparative studies on the ocular and dermal irritation potential of surfactants. *Food Chem Toxicol*. 2007;45(5):747-758.

17. U.S. Food and Drug Administration. Inactive Ingredient Search for Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Last Updated 2022. Accessed November 10, 2022.

18. Wu J, Wu T, Zheng S, Huang Y, Wang L. Low-dose repeated exposure to chemical surfactant impairs corneal epithelium: When personal cleaning products entering the eye. *Exp Eye Res*. 2021 Sep;210:108696.

19. Grey KR, Hanson JL, Hagen SL, Hylwa SA, Warshaw EM. Epidemiology and Co-Reactivity of Novel Surfactant Allergens: A Double-Blind Randomized Controlled Study. *Dermatitis*. 2016;27(6):348-354.

20. Santucci B, Cannistraci C, Lesnoni I, et al. Cutaneous response to irritants. *Contact Dermatitis*. 2003;48(2):69-73.

21. Rhone-Poulenc Inc. Initial Submission: Internal Research Screening Skin Irritation Study of Miranol MHT in Rabbits with Cover Letter Dated 061992. Prod Safety Labs; 1992. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0541043.xhtml. Accessed March 24, 2023.

22. Rhone-Poulenc Inc. Initial Submission: Internal Research Screening Skin Irritation Study with Sodium Lauroamphoacetate in Rabbits with Cover Letter Dated 060892. Product Safety Labs; 1992. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0540016.xhtml. Accessed March 24, 2023.

23. Zhai H, Fautz R, Fuchs A, Branco N, Maibach HI. Assessment of the subclinical irritation of surfactants: a screening open assay model. *Exog Dermatol*. 2002;1:238-241.

24. Corazza M, Lauriola MM, Bianchi A, Zappaterra M, Virgili A. Irritant and sensitizing potential of eight surfactants commonly used in skin cleansers: an evaluation of 105 patients. *Dermatitis*. 2010;21(5):262-268.

25. Bárány E, Lindberg M, Lodén M. Biophysical characterization of skin damage and recovery after exposure to different surfactants. *Contact Dermatitis*. 1999;40(2):98-103.

26. Stern M, Klausner M, Alvarado R, Renskers K, Dickens M. Evaluation of the EpiOcular((TM)) Tissue Model as an Alternative to the Draize Eye Irritation Test. *Toxicol In Vitro*. 1998;12(4):455-461.

27. Scheel J, Kleber M, Kreutz J, et al. Eye irritation potential: usefulness of the HET-CAM under the Globally Harmonized System of classification and labeling of chemicals (GHS). *Regul Toxicol Pharmacol*. 2011;59(3):471-492.

28. Rivero MN, Lenze M, Izaguirre M, et al. Comparison between HET-CAM protocols and a product use clinical study for eye irritation evaluation of personal care products including cosmetics according to their surfactant composition. *Food Chem Toxicol*. 2021 Jul;153:112229.

29. de Groot AC, Weijland W. Contact allergy to disodium cocoamphodipropionate. *Contact Dermatitis*. 1996;35(4):248-249.

30. Hanson JL, Warshaw EM. Contact allergy to surfactants in a hypoallergenic liquid cleanser. *Dermatitis*. 2015;26(6):284-286.

31. Goossens A, Bruze M, Gruvberger B, Gielen K, Stoskute L. Contact allergy to sodium cocoamphoacetate present in an eye make-up remover. *Contact Dermatitis*. 2006;55(5):302-304.

32. Skudlik C, Markthaler M, John SM. Occupational contact allergy to sodium cocoamphopropionate in a skin protection cream. *Contact Dermatitis*. 2018;78(4):295-296.

33. Pesonen M, Suomela S, Kuuliala O, Aalto-Korte K. Occupational contact allergy to sodium cocoamphopropionate in a hand cleanser. *Contact Dermatitis*. 2016;74(4):246-248.

34. Hagvall L, Brared-Christensson J, Inerot A. Occupational contact dermatitis caused by sodium cocoamphopropionate in a liquid soap used in fast-food restaurants. *Contact Dermatitis*. 2014;71(2):122-124.

35. ATAMAN Chemicals. Disodium Cocoamphodiacetate. https://www.atamanchemicals.com/disodium-cocoamphodiacetate_u24965/. Last Updated 2020. Accessed October 28, 2021.

36. PubChem. beta-Alanine, N-(2-aminoethyl)-N-(2-(2-carboxyethoxy)ethyl)-, N-coco acyl derivs., disodium salts. https://pubchem.ncbi.nlm.nih.gov/compound/6455953. Last Updated 2021. Accessed October 28, 2021.

37. Stepan. AMPHOSOL® 2CSF. https://www.stepan.com/content/stepan-dot-com/en/products-markets/product/AMPHOSOL2CSF.html. Last Updated 2021. Accessed October 28, 2021.

38. European Chemicals Agency (ECHA). β-Alanine, N-(2-aminoethyl)-N-[2-(2-carboxyethoxy)ethyl]-, N-coco acyl derivs., disodium salts. https://echa.europa.eu/da/registration-dossier/-/registered-dossier/27215/4/2. Last Updated 2022. Accessed February 23, 2022.

39. PubChem. Disodium 1-[2-(carboxymethoxy)ethyl]-1-(carboxymethyl)-4,5-dihydro-2-undecyl-1H-imidazolium hydroxide. https://pubchem.ncbi.nlm.nih.gov/compound/84372. Last Updated 2021. Accessed October 28, 2021.

40. PubChem. Acetic acid, chloro-, sodium salt, reaction products with 4,5-dihydro-1H-imidazole-1-ethanol 2-norcoco alkyl derivs. and sodium hydroxide. https://pubchem.ncbi.nlm.nih.gov/compound/155132. Last Updated 2021. Accessed October 28, 2021.

41. PubChem. Sodium lauroamphoacetate (Compound). https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-lauroamphoacetate#section=Chemical-and-Physical-Properties. Last Updated 2021. Accessed August 20, 2021.

42. Burnett CL, Fiume MM, Bergfeld WF, et al. Safety Assessment of Plant-Derived Fatty Acid Oils. *Int J Toxicol*. 2017;36(Suppl 3):51S-129S.

43. Parchem. Safety Data Sheet: Disodium Cocoamphodiacetate. 2015. https://www.parchem.com/siteimages/Attachment/GHS%20Disodium%20Cocoamphodiacetate%20MSDS.pdf. Accessed November 29, 2022.

44. Stepan. Safety Data Sheet: Amphosol 2CSF-AF. 2018. https://pt.stepan.com/content/dam/stepan-dot-com/webdam/website-product-documents/safety-data-sheets/sds-us/en/01005600.pdf. Accessed November 30, 2022.

45. Colonial Chemical. Safety Data Sheet: Cola®Teric J49. 2017. https://colonialchem.me/wp-content/uploads/2020/10/ColaTeric-J49-SDS-US.pdf. Accessed November 30, 2022.

46. Leidreiter HI, Gruning B, Kaseborn D. Amphoteric surfactants: processing, product composition and properties. *Int J Cosmet Sci*. 1997;19(5):239-253.

47. Personal Care Products Council. 2021. Concentration of Use by FDA Product Category: Sodium Lauroamphoacetate. Unpublished data submitted by Personal Care Products Council on September 8, 2021.