Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	May 19, 2023
Panel Meeting Date:	June 12-13, 2023

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., and the Senior Director is Monice Fiume. This safety assessment was prepared by Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

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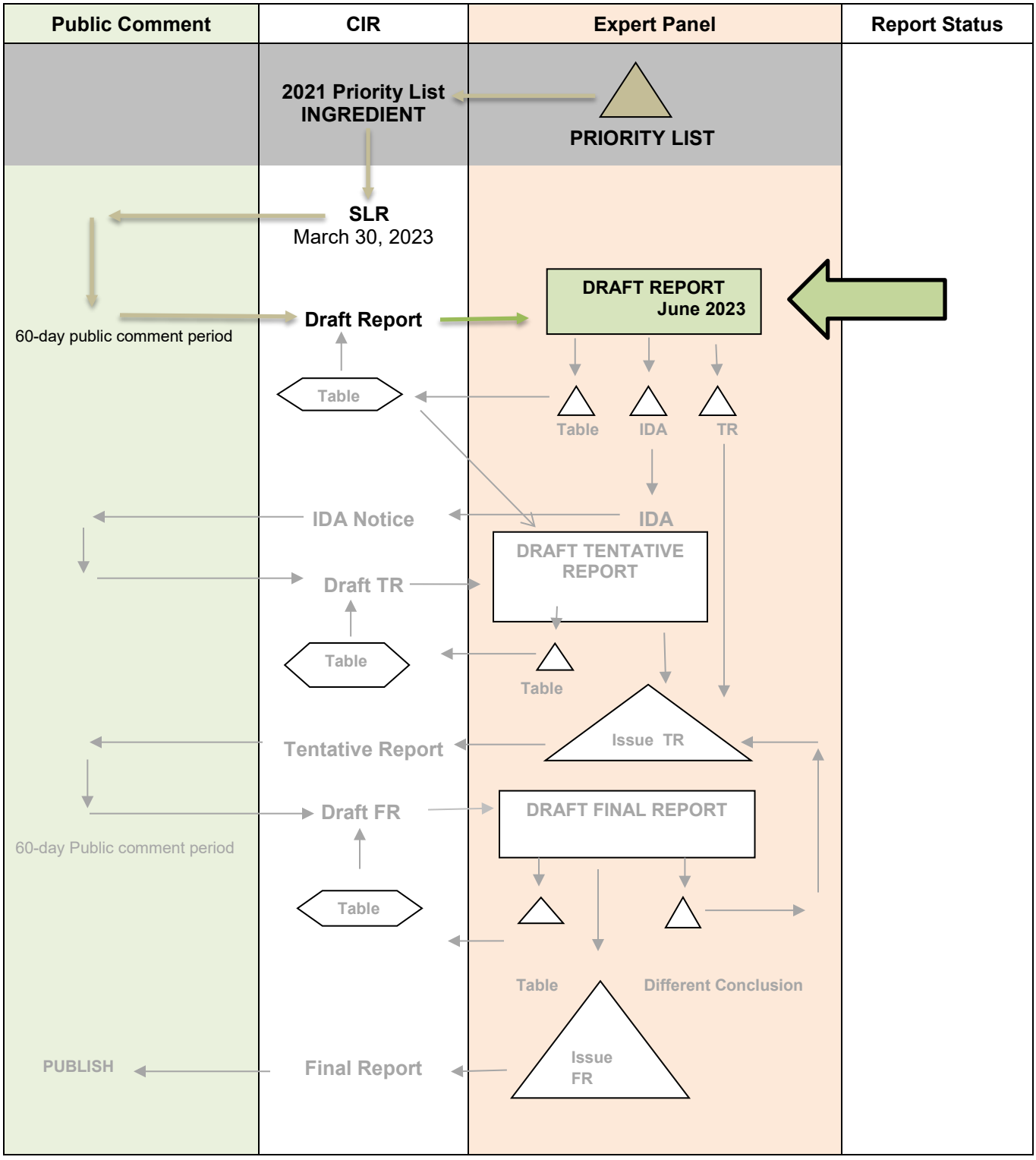
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Amphoacetate Group

MEETING June 2023



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR
Date: May 19, 2023
Subject: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics

Enclosed is the Draft Report of the Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (identified in the pdf as *report_FattyAmphocarboxylates_062023*). The 11 fatty amphocarboxylates reviewed in this report include the following:

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

Sodium Lauroamphoacetate was included on the 2021 Priority List due to high reported frequencies of use. It was noted that 4 related ingredients previously reviewed by the Panel in a report published in 1990 and re-reviewed in 2008, i.e., Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate, would soon be considered for another re-review. Accordingly, the Panel deemed it appropriate to include the 4 previously-reviewed ingredients in this new safety assessment. (The Panel had concluded that these 4 ingredients are safe in cosmetics in the present practices of use and concentration, as described in the 1990 safety assessment.) The 1990 report (*originalreport_FattyAmphocarboxylates_062023*), 2008 re-review (*re-review_FattyAmphocarboxylates_062023*) along with corresponding minutes of the deliberations (*originalminutes_FattyAmphocarboxylates_062023)* have been included herein.

Comments on the SLR provided by Council (*PCPCcomments_FattyAmphocarboxylates_062023*) were addressed, as indicated in the responses to these comments (*response-PCPCcomments_FattyAmphocarboxylates_062023*).

The following documents are also included in this packet:

- 2021 concentration of use data (*data1_FattyAmphocarboxylates_062023*) (data on Sodium Lauroamphoacetate)
- 2022 concentration of use data (*data2_FattyAmphocarboxylates_032023*) (remaining ingredients that were not surveyed in 2021)
- report history (*history_FattyAmphocarboxylates_062023*)
- data profile (*dataprofile_FattyAmphocarboxylates_062023*)
- search strategy (*search_FattyAmphocarboxylates_062023*)
- flow chart (*flow_FattyAmphocarboxylates_062023*)

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: April 12, 2023

SUBJECT: Scientific Literature Review: Safety Assessment of Amphoacetates as Used in Cosmetics (release date: March 30, 2023)

The Personal Care Products Council respectfully submits the following comments on the Scientific Literature Review Safety Assessment of Amphoacetates as Used in Cosmetics.

Title – Since there are two amphopropionate ingredients in the report, is the current title sufficient?

Abbreviations – Please delete the duplicate "European Chemicals Agency ECHA" row.

Introduction – Rather than just saying "forward" when describing the literature search, it would be helpful to state the date it was completed, so those looking at the report when it is published will know the date of the search. It will also be helpful to have the search date when these ingredients are reviewed again.

Composition and Impurities – Please include the references for the "chemical safety data sheets on trade name products".

Acute, Oral; Summary – Although the percent solids may not have been stated, the LD_{50} for the study in mice was stated as both 12.7 ml/kg of the dosing solution, as well as 6116 mg Sodium Lauroamphoacetate/kg. Both values should be stated in the text. Because the result in terms of Sodium Lauroamphoacetate is stated, % solids is not needed.

Developmental and Reproductive Toxicology; Summary; Table 8 – It would be helpful to also include the OECD TG numbers in the text. In the text and table for the results of the Disodium Cocoamphodiacetate OECD 414 study, it would be helpful to indicate that dossier says: "a test item-related effect could not be excluded as in the case of right-sided aortic arch the incidence was above historical control data range." Other visceral malformations observed were within the historical control data range.

Co-Reactivity of Surfactant Allergens – As the authors of reference 19 also considered Disodium Lauroamphodiacetate to be a "novel surfactant", it is not necessary to call sodium lauroyl sarcosinate and isostearamidopropyl morpholine lactate "novel".

Dermal Irritation and Sensitization – Please indicate if the studies described in the following sentence were completed in humans. "Irritation was observed in a soap chamber and epicutaneous dermal irritation assay using 1% Sodium Lauroamphoacetate and 2% Sodium Lauroamphoacetate, respectively."

Case Reports, Sodium Lauroamphoacetate – It is misleading to state that the subjects were tested with 100% Sodium Lauroamphoacetate. The abstract of reference 11 states: "Patch testing showed positive reactions to sodium lauroamphoacetate (Miranol HM Special, Rhodia, England) as is or diluted at decreasing concentration (10%, 5% and 1%) in water and to aminoethylethanolamine (AEE) at the concentration of 1% in various vehicles (ethanol, acetone, and sodium laurylethersulfate 1% aqueous solution) and at decreasing concentrations ranging from 1% to 0.005% in water." As the SLR states, these surfactants are sold as liquids with 30-60% of the active ingredient. Current information on Miranol HM Special was not found, but product data sheet on Miranol HMD https://glenncorp.com/wp-content/uploads/2013/08/MIRANOL-HMD1.pdf indicates that it has 33-36% solids. The 100% concentration represents the concentration of Miranol HM Special, not Sodium Lauroamphoaceate. Therefore, the tested concentrations of Sodium Lauroamphoacetate were closer to 40%, 4%, 2% and 0.4%.

Table 2 – There are two versions of Table 2 in the SLR. The second table includes more information on Sodium Lauroamphoacetate than the first Table 2. The first Table 2 should be deleted.

Table 3 – Reference 8 is the CIR report on CAPB. It is not an appropriate reference for this table. The title of this table should be revised to indicate why the fatty acid composition of these oils is included in this report.

Table 4 – Please revise the title of this table to: "Composition of Tradename Mixtures of Amphoacetate and Amphopropionate Ingredients".

Table 7 – In the results column of the first study, it would be clearer to state "6116 mg/kg for Sodium Lauroamphoacetate" (rather than "for the undiluted test substance")

Table 8 – In the second study, please state the doses at which deaths were observed.

Table 10 – At the beginning of Table 10 there should be headings, Irritation and Human. In the last animal sensitization study, although they completed the study in small groups of guinea pigs, overall, there were 20 test and 10 control guinea pigs. Please revise the Test Population column.

Table 11, In Vitro – The Test Population column for the assays in corneal epithelial cells should say ocular tissue model (or corneal epithelial cells) not "skin samples". The Test Population

column should not say “6 eggs” for the EpiOcular assay. The Test Population column should not say “3 skin samples” for the red blood cell test (likely that porcine red blood cells were used – which should be stated rather than “3 trials”).

Table 11, Animal – It is not clear why the Concentration/Dose column says 100%, when the Test Article column says “30% aqueous dilution” (suggests a tested concentration of 4.5%) and “50% aqueous dilution” (this is in two studies) (suggests a tested concentration of 25%).

Fatty Amphocarboxylates - June 2023 – Priya Cherian	
Comment Submitter: PCPC **Date of Submission: April 12, 2023**	
Comment	**Response/Action**
Title – Since there are two amphopropionate ingredients in the report, is the current title sufficient?	Addressed – report re-named Fatty Amphocarboxylates
Abbreviations – Please delete the duplicate "European Chemicals Agency ECHA" row.	Addressed
Introduction – Rather than just saying "forward" when describing the literature search, it would be helpful to state the date it was completed, so those looking at the report when it is published will know the date of the search. It will also be helpful to have the search date when these ingredients are reviewed again	Date search was conducted was provided (April 2022), and represents the time period for which literature was searched for (1985-2022)
Composition and Impurities – Please include the references for the "chemical safety data sheets on trade name products".	Addressed
Acute, Oral; Summary – Although the percent solids may not have been stated, the LD50 for the study in mice was stated as both 12.7 ml/kg of the dosing solution, as well as 6116 mg Sodium Lauroamphoacetate/kg. Both values should be stated in the text. Because the result in terms of Sodium Lauroamphoacetate is stated, % solids is not needed.	Left unchanged in report. Percent solids is stated for consistency.
Developmental and Reproductive Toxicology; Summary; Table 8 – It would be helpful to also include the OECD TG numbers in the text. In the text and table for the results of the Disodium Cocoamphodiacetate OECD 414 study, it would be helpful to indicate that dossier says: "a test item-related effect could not be excluded as in the case of right-sided aortic arch the incidence was above historical control data range." Other visceral malformations observed were within the historical control data range.	Details such as OECD test guideline information are placed in the table.
Co-Reactivity of Surfactant Allergens – As the authors of reference 19 also considered Disodium Lauroamphodiacetate to be a "novel surfactant", it is not necessary to call sodium lauroyl sarcosinate and isostearamidopropyl morpholine lactate "novel".	Addressed
Dermal Irritation and Sensitization – Please indicate if the studies described in the following sentence were completed in humans. "Irritation was observed in a soap chamber and epicutaneous dermal irritation assay using 1% Sodium Lauroamphoacetate and 2% Sodium Lauroamphoacetate, respectively."	Addressed
Case Reports, Sodium Lauroamphoacetate – It is misleading to state that the subjects were tested with 100% Sodium Lauroamphoacetate. The abstract of reference 11 states: "Patch testing showed positive reactions to sodium lauroamphoacetate (Miranol HM Special, Rhodia, England) as is or diluted at decreasing concentration (10%, 5% and 1%) in water and to aminoethylethanolamine (AEE) at the concentration of 1% in various vehicles (ethanol, acetone, and sodium laurylethersulfate 1% aqueous solution) and at decreasing concentrations ranging from 1% to 0.005% in water." As the SLR states, these surfactants are sold as liquids with 30- 60% of the active ingredient. Current information on Miranol HM Special was not found, but product data sheet on Miranol HMD https://glenncorp.com/wpcontent/uploads/2013/08/MIRANOL-HMD1.pdf indicates that it has 33-36% solids. The 100% concentration represents the concentration of Miranol HM Special, not Sodium Lauroamphoaceate. Therefore, the tested	Addressed – test substance changed to "trade name mixture containing Sodium Lauroamphoacetate"

concentrations of Sodium Lauroamphoacetate were closer to 40%, 4%, 2% and 0.4%	
Table 2 – There are two versions of Table 2 in the SLR. The second table includes more information on Sodium Lauroamphoacetate than the first Table 2. The first Table 2 should be deleted	Addressed
Table 3 – Reference 8 is the CIR report on CAPB. It is not an appropriate reference for this table. The title of this table should be revised to indicate why the fatty acid composition of these oils is included in this report.	CIR report reference kept in report – title of table addressed – fatty acid compositions were included as there are relevant to the botanically-sourced mixtures
Table 4 – Please revise the title of this table to: "Composition of Tradename Mixtures of Amphoacetate and Amphopropionate Ingredients".	Addressed
Table 7 – In the results column of the first study, it would be clearer to state "6116 mg/kg for Sodium Lauroamphoacetate" (rather than "for the undiluted test substance")	Addressed
Table 8 – In the second study, please state the doses at which deaths were observed	Addressed
Table 10 – At the beginning of Table 10 there should be headings, Irritation and Human. In the last animal sensitization study, although they completed the study in small groups of guinea pigs, overall, there were 20 test and 10 control guinea pigs. Please revise the Test Population column.	The headings are placed appropriately in the table.
Table 11, In Vitro – The Test Population column for the assays in corneal epithelial cells should say ocular tissue model (or corneal epithelial cells) not "skin samples". The Test Population 3 column should not say "6 eggs" for the EpiOcular assay. The Test Population column should not say "3 skin samples" for the red blood cell test (likely that porcine red blood cells were used – which should be stated rather than "3 trials").	Addressed
Table 11, Animal – It is not clear why the Concentration/Dose column says 100%, when the Test Article column says "30% aqueous dilution" (suggests a tested concentration of 4.5%) and "50% aqueous dilution" (this is in two studies) (suggests a tested concentration of 25%)	Addressed

History – Fatty Amphocarboxylates

1990

- Report published on Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate

2008

- Re-review published on Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate

September 2021

- Concentration of use data received on Sodium Lauroamphoacetate

January 2022

- Concentration of use data received on remaining 10 amphoacetate ingredients

March 2023

- SLR announced

April 2023

- Comments on SLR received from PCPC

June 2023

- Panel reviews Draft Report

Fatty Amphocarboxylates Data Profile – June 2023 – Writer, Priya Cherian

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation			Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal		Retrospective/ Multicenter	Case Reports
Disodium Cocoamphodiacetate	**XO**	**O**	X				O	O			X			X	O					O	XO			O	O	X	O	X		
Disodium Cocomphodipropionate	**XO**	**O**		X				O							O					O	O			O			O			X
Disodium Lauroamphodiacetate	**X**																													X
Disodium Wheatgermamphodiacetate	**X**		X	X																										
Sodium Arganamphoacetate	**X**																													
Sodium Cocoamphoacetate	**XO**	**O**	X					O						X	O					O	X		X	O	O	X	O			X
Sodium Cocoamphopropionate	**XO**	**O**						O												O				O	O		O			X
Sodium Cottonseedamphoacetate	**X**																													
Sodium Lauroamphoacetate	**X**		X					X						X	X					X	X		X	X		X	X			X
Sodium Olivamphoacetate	**X**																													
Sodium Sweetalmondamphoacetate	**X**																													

* "X" indicates that data were available in a category for the ingredient
* "O" indicates that data were available from the previous 1990 report

Search Strategy: Fatty Amphocarboxylates – Priya Cherian

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Disodium Cocoamphodiacetate	68650-39-5	x	x		x	x	x						x						
Disodium Cocoamphodipropionate	68411-57-4 86438-79-1	x																	
Disodium Lauroamphodiacetate	14350-97-1	x																	
Disodium Wheatgermamphodiacetate		x										x							
Sodium Cocoamphoacetate	90387-76-1; 68334-21-4; 68608-65-1	x																	
Sodium Cocoamphopropionate		x																	
Sodium Cottonseedamphoacetate		x																	
Sodium Isostearoamphopropionate		x																	
Sodium Lauroamphoacetate	68608-66-2; 156028-14-7; 66161-62-4	x	x				x						x						x
Sodium Olivamphoacetate		x																	
Sodium Stearoamphoacetate	30473-39-3	x																	
Sodium Sweetalmondamphoacetate		x																	

Search Strategy

Search terms below were searched for in the websites listed above. If useful information was found, an "x" is noted.

Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- metabolism
- dermal
- inhalation
- skin
- toxicity
- drugs
- medicine
- irritation
- ocular
- eye
- sensitization
- allergy
- manufacture
- cancer

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

In the ensuing discussion, it was suggested the Expert Panel make a direct request to the company for the study details. However, it was noted this would necessitate a change in the procedures, which were established to insulate the Panel from industry.

By majority vote, the Panel accepted and approved the following data request relating to Drometrizole:

(1) 90-day subchronic oral toxicity

(2) Mutagenicity testing in two systems other than the Ames assay and the mouse bone marrow micronucleus test

or, in lieu of the above,

(1) Detailed results of an unpublished long-term feeding study in rats referenced in Schmid et al. (1980)[a] and cited as Hunter et al. (1975)[b], report submitted to Ciba-Geigy AG, Basel.

(a) Schmid, K., Schweizer, W., Staeubli, W., and Waechter, F. (1980). Effect of 2-(2'-hydroxy-5'-methylphenyl) benzotriazole on rat liver. Food Cosmet. Toxicol. 18(3):245-52.

(b) Hunter, B., Graham, C., Street, A.E., Heywood, R., and Cherry, C.P. (1975). Unpublished report submitted to Ciba-Geigy AG, Basel.

The Insufficient Data Announcement will shortly be issued for a 90-day public comment period.

Cocoamphoglycinate Group

The issuance of an Insufficient Data Announcement for all four ingredients of this group was recommended by the Bergfeld Team.

The Panel unanimously accepted and approved a request for the following data relating to these ingredients:

(1) Cocoamphoglycinate (Cocoamphoacetate) and Cocoamphopropionate - mutagenicity and clinical irritation, sensitization, and photosensitization.

(2) Cocoamphocarboxyglycinate (Cocoamphodiacetate) - mutagenicity and clinical photosensitization.

(3) Cocoamphocarboxypropionate (Cocoamphodipropionate) - mutagenicity and clinical irritation, sensitization, and photosensitization.

The Insufficient Data Announcement will shortly be issued for a 90-day public comment period.

data submitted were acceptable, clinical photosensitization data were still lacking. She stated that her team was therefore recommending an insufficient conclusion on the basis of lack of clinical photosensitization data, lack of impurity data, and an inadequate response from industry.

A discussion ensued concerning the adequacy of the UV spectrum. Dr. Hoffmann stated that, as the composition of Tragacanth Gum includes esters, there should be absorption at 250 nm due to the carbonyl band; however, as no absorption was seen at this wavelength, it indicated that the sensitivity of the spectrophotometer was too low. He also noted that the gum has a yellow-brown color and should therefore have some absorption. He pointed out that the UV spectrum had not been run using the standard procedures previously set out by the Panel and that more than one concentration should be used.

Dr. Hoffmann cautioned that the company should not assume that a UV spectrum correctly run would satisfy the insufficiency as the Panel's request was for photosensitivity data. It was noted that the Panel's practice is to consider a UV spectrum (if adequately run); however, if this shows significant absorption, photosensitivity data would still be required. Dr. McEwen requested to have this reflected in the discussion of the report.

Subject to minor textual revisions, the Panel unanimously accepted and approved an Insufficient Data conclusion based on the lack of clinical photosensitization data.

The Tentative Final Report will shortly be announced for a 90-day comment period.

Cocoamphoglycinates

Dr. Bergfeld reported that the Panel had issued an IDA on July 2, 1985, requesting mutagenicity and clinical photosensitization data on all four

ingredients as well as clinical irritation and sensitization data on the three ingredients CAG, CAP, and CACP. Subsequently, an additional submission of data was received from industry, of which, only clinical irritation and sensitization data on products containing CACP were supplied in response to the Panel's request. She stated that the Bergfeld team was therefore recommending an Insufficient Data conclusion based on the lack of mutagenicity and clinical photosensitization data on all ingredients as well as lack of clinical irritation and sensitization data on CAG and CAP.

Dr. Schroeter questioned the possibility of separating out CACP and CACG and requesting photosensitivity and mutagenicity data only; however, it was pointed out that an IDA had already gone out and industry had not adequately responded.

Mr. Eiermann noted that these compounds were once assigned a cyclical structure, although they are now considered to be linear.

The Panel then unanimously accepted and approved the Insufficient Data conclusion as recommended by the Bergfeld team.

The Tentative Final Report will shortly be announced for a 90-day comment period.

Drometrizole

Dr. Bergfeld reported that the Panel had issued an IDA on Drometrizole July 2, 1985, requesting a 90-day subchronic oral study and mutagenicity testing in two systems other than the Ames assay and the mouse bone marrow micronucleus test, or, in lieu of these data, detailed results of an unpublished long-term feeding study in rats. She stated that no response had been received from industry, but an attempt had been made by CIR staff and Dr. Hoffmann to translate a Russian article referring to a one-year oral study in

It was noted that Tragacanth Gum had already had the 90-day public comment period and that the final review would be by mail ballot.

Dr. Shank wanted to add a discussion on the Bachmann et al. (1978) and Anderson et al. (1984) studies in which low doses of Tragacanth Gum caused heart problems in some rats; however, this was not repeated in further studies. It was the consensus of the Panel that this anomaly was to be resolved in the text and not in a discussion.

Cocoamphoglycinate Group

Dr. Elder reported on the status of this group. A new submission of data had been received (a summary was distributed at the meeting); however, these data were not responsive to the Panel's request. A letter had also been received from Mona Industries expressing interest in supplying the data still lacking and requesting guidance from the Panel regarding the proper test methods.

In response to the letter from Mona, the Panel concurred that the Ames test would suffice for mutagenicity (unless it gave positive results) and that an acceptable photosensitization test (RIPT) should be used. It was decided that CAA (Cocoamphoacetate) and CAP (Cocoamphopropionate) could be grouped together chemically and that CADA (Cocoamphodiacetate) and CADP (Cocoamphodipropionate) could also be grouped. Therfore, a test on one of the two chemicals in each group would suffice for the clinical data needed.

In summary, the data needed was as set forth here:

1) Mutagenicity on all four chemicals - using two tester strains both with and without metabolic activation
2) Clinical irritation, sensitization and photosensitization (repeated insult patch test) on CAA or CAP
3) Photosensitization on CADA or CADP.

There was some discussion of the confusion surrounding the concentration of these ingredients as they are supplied at varying active concentrations (normally 30 to 40 percent). Dr. Berndt requested that "a concentration of 100 percent" be changed to "as commercially supplied" with the active concentration given in parentheses, even if unknown.

Raymond Mayhew, of Mona Industries, introduced himself and offered some information on this group of compounds. He stated that the acetates are usually

supplied at concentrations of 35-37 percent. While propionates are supplied at concentrations of 38-39 percent. These products are definitely mixtures, containing glyconic acid and some free alcohol. He also indicated that the structures may not be correct. The Japanese have done some recent structural work and he believes they may be right. Much discussion has taken place at CTFA and the current structure is probably a compromise.

It was noted that the discussion on the varying active concentrations of these compounds would be reflected in the discussion of the report.

This report will be delayed, awaiting the completion of the necessary testing by Mona Industries.

Panel Procedure Discussion

The Panel discussed the wording and context of two informal guidelines: the informal team data request and the suggested procedures following various responses to an Insufficient Data Announcement. These were changed to reflect the Panel's comments (see attached).

Dr. Elder expressed his concern that with the use of the informal data request (with a set date), many documents would be released too soon in that they would become public as of their set date.

Dr. Bergfeld responded that as the Panel was expecting the industry to respond by a certain date, it was only fair that the teams clean up their documents by the same date.

Dr. Elder also expressed his concern that a person/company may undertake the testing requested by the team, in good faith, and then may get hit at the Panel meeting with a request for further data and an Insufficient Data Announcement. It was suggested that team documents may be referred to the other team for concurrence prior to full Panel review; however, this was considered to be too handicapping due to the amount of editing and time involved. It was concluded that, in the future, a document may be cross referred only if a very unusual request has been made by a team.

Isopropanolamines

Dr. Bergfeld briefly reviewed the status of this report. All of the data informally requested had been supplied by industry and were incorporated into

Cocoamphoacetate, Cocoamphodiacetate, Cocoamphodipropionate, Cocoamphopropionate

Dr. Bergfeld opened the discussion with a history of the Cocoamphoacetates report. In 1985, an insufficient data report was issued. In 1986, Mona Industries requested information on the data the Panel had requested. In 1988, data on mutagenicity, clinical irritation and sensitization, and photosensitization were received. She noted that the report now contained enough data to make a decision on the safety of the four ingredients in this group. She stated that it was the recommendation of her team that based upon the available data included in this report the Expert Panel should consider Cocoamphoacetate, Cocoamphodiacetate, Cocoamphodipropionate, and Cocoamphopropionate safe as cosmetic ingredients in the present practices of use. She then requested that a statement be included in the discussion section of the report noting that the degree of ocular irritation caused by these ingredients is influenced by the pH of those ingredients.

Dr. Hoffmann added that it should be noted that no mutagenicity data were received on CAA, but that the results of mutagenicity data on the other three ingredients were negative, and he would not delay the report because of this since structure analogies would indicate that CAA was not likely to be mutagenic. He stated that a statement concerning the lack of mutagenicity data should be included somewhere in the report.

Dr. Bergfeld stated that the minutes could reflect this concern.

Dr. Elder asked if this should also be included in the summary of the report.

Dr. Bergfeld replied that if Dr. Hoffmann felt that the subject needed clarification, it should be included in the discussion along with the statement about the relationship between ocular irritation and pH.

Dr. Hoffmann replied that a statement recognizing that no mutagenicity data were received on CAA should be included in the discussion. He also suggested that from now on all CIR reports contain an impurities section, and that when impurites data are not available then a statement under the heading of impurites would reflect that situation.

There was general agreement that an impurities section would be included in every report.

Dr. Bergfeld noted that she had made a motion that the Panel would accept the report with a conclusion of safe in the present practices of use.

Dr. Carlton seconded the motion.

Dr. Boutwell added that the Panel had requested that a discussion be included in the report.

Dr. Shank then called for a vote on the motion to accept the report with the addition of a discussion and with the conclusion that the cocoamphoacetates are safe for use as ingredients in cosmetics in present practices of use. The motion was carried unanimously.

APRIL 3 – 4, 2006 (RE-REVIEW)

Dr. Belsito stated that a Final Report with the following conclusion on this group of ingredients was published in 1989: Based upon the available data included in this report, the Expert Panel concludes that CAA, CAP, CADA, and CADP are safe as cosmetic ingredients in the present practices of use.

He added that since the Final Report was published, the names of the ingredients have been changed (as indicated above). Furthermore, he noted that use frequencies have increased, but that the current use concentrations are consistent with the use concentration data in the published Final Report. It also appears that ingredient use in leave-on products has increased, compared to use primarily in rinse-off products in the published report. This is based on current use concentration data that were provided by CTFA.

However, in light of the frequency of use and use concentration data in the re-review document, Dr. Belsito said that the studies included in the published Final Report are sufficient for documenting the safety of these ingredients in leave-on products. Dr. Belsito added that his Team determined that the Final Report does not need to be reopened.

The Panel unanimously concluded that the Final Report on the Sodium Cocoamphoacetate ingredient family should not be reopened.

Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: May 19, 2023
Panel Meeting Date: June 12-13, 2023

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., and the Senior Director is Monice Fiume. This safety assessment was prepared by Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

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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
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 fatty amphocarboxylates 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 Expert Panel for Cosmetic Ingredient Safety (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 fatty amphocarboxylate 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 search was las conducted April 2022. 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 in the literature, 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 ≤ 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 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 issues of impurities (e.g., amidoamine) and mechanisms of toxicity similar 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:

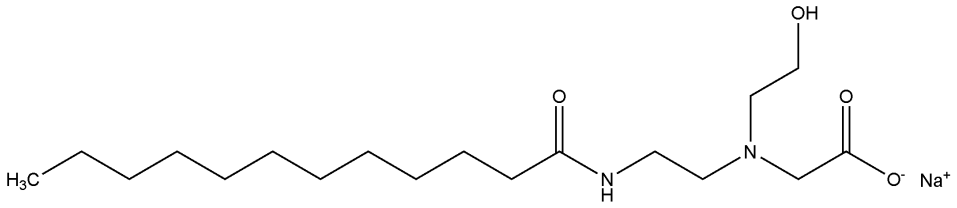


Figure 1. Sodium Lauroamphoacetate

The definitions and structures of all the fatty amphocarboxylates 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

The fatty amphocarboxylates reviewed in this report are prepared by reacting fatty acid derivatives (e.g., coco fatty acid for Sodium Cocoamphoacetate) with hydroxyethyl ethylenediamine or aminoethylethanolamine (AEEA).[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 fatty amphocarboxylates are provided in Table 3.

Composition and Impurities

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 mixtures (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]

Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Disodium Lauroamphodiacetate, Sodium Cocoamphoacetate, and Sodium Lauroamphoacetate

The compositions of these fatty amphocarboxylates 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.[7,12-15] The compositions, per those datasheets, can be found in Table 4. The majority of these ingredients consist of mixtures containing 30 - 60% of the ingredients in question.

Disodium Wheatgermamphodiacetate

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.[16] 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).[17] 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 concentration of use survey initiated by the Council in 2021 indicate that Disodium Cocoamphodiacetate has the highest concentration of use in rinse-off products; it is used at up to 20% in cleansing products.[18] 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 ingredients reviewed in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[19]

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.[4,20] 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%.[21]

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.[22] 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 surfactants sodium lauroyl sarcosinate and isostearamidopropyl morpholine lactate, and a hypoallergenic liquid cleanser.[23] 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%).[24] 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 were 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%).[25,26] 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.[4,20,27,28] Erythema and scaling was observed in in a 48-h occlusive patch test performed in 12 subjects using Sodium Cocoamphoacetate (10%) in citrate buffer.[29] Irritation was observed in a soap chamber and epicutaneous dermal irritation assay using 1% Sodium Lauroamphoacetate (n = 21 subjects) and 2% Sodium Lauroamphoacetate (n = 20 subjects), respectively.[20]

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 were 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 Cocoamphodiacetate (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.[20] 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.[30] Severe ocular irritation was also observed in a hen's egg test-chorioallantoic membrane (HET-CAM) assay using 40% Sodium Lauroamphoacetate.[31] 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.[32]

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).[33] 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.[34] 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).[35] 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.[36] 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 fatty amphocarboxylates.[11] Patch tests of aqueous solutions of a trade name mixture containing Sodium Lauroamphoacetate (1, 5, 10, and 100%) 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 (using same concentrations as stated above) 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 the undiluted trade name mixture containing Sodium Lauroamphoacetate. 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.[37] 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.[38] 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 fatty amphocarboxylate 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 LD50 of 6116 mg/kg for Sodium Lauroamphoacetate (% solids not stated; water and sodium chloride) was determined in mice. The lowest LD50 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 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 EpiOcularTM 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 fatty amphocarboxylates. 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 fatty amphocarboxylates. All four individuals displayed positive patch test reactions to a trade name mixture containing Sodium Lauroamphoacetate (1, 5, 10, and 100%) and AEEA (1%). Several cases of dermatitis have been reported following exposures to hand cleansers containing fatty amphocarboxylates. Patch testing using several fatty amphocarboxylates (Disodium Cocoamphodipropionate (1 - 10%) Sodium Cocoamphoacetate (1 - 10%), Sodium Cocoamphopropionate (1 - 10%), Sodium Lauroamphoacetate (1 - 10%)), performed in these individuals, yielded positive results.

DISCUSSION

To be developed

CONCLUSION

To be determined.

TABLES

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

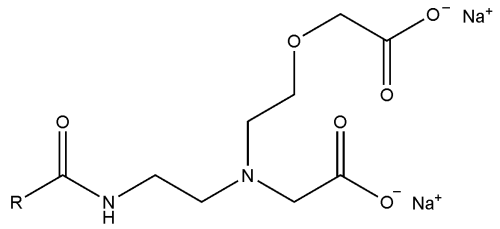
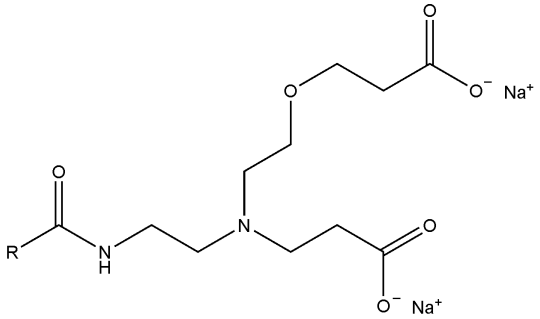
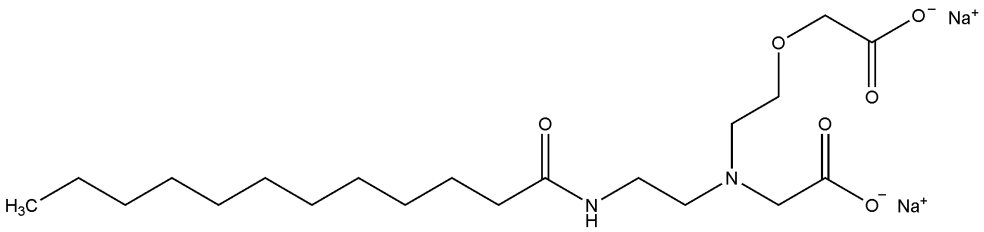
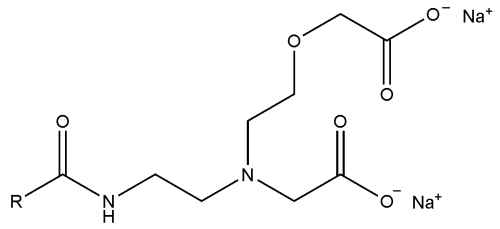
Ingredient	Definition	Function
Disodium Cocoamphodiacetate [CAS: 68650-39-5]	Disodium Cocoamphodiacetate is the amphoteric organic compound that conforms generally to the structure:  where RC(O)- represents the acyl groups derived from coconut oil.	Hair Conditioning Agents; Surfactants – Cleansing Agents; 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 ingredients reviewed in this safety assessment[3]

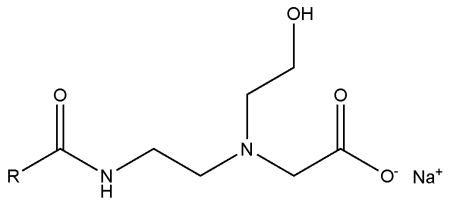
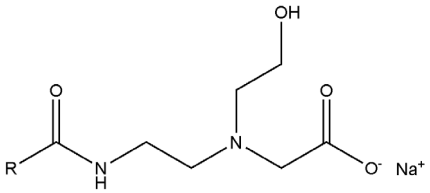
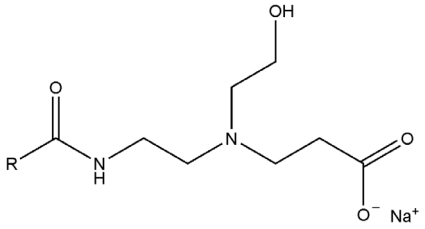
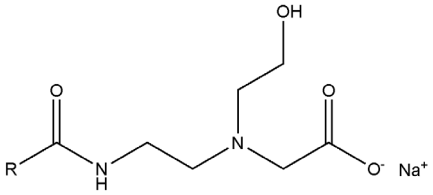
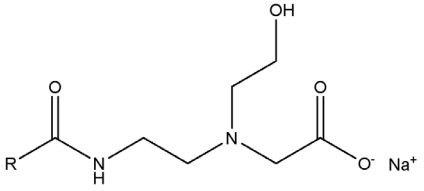
Ingredient	Definition	Function
Sodium Arganamphoacetate	Sodium Arganamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from Argania Spinosa Kernel Oil.	Surfactants - Cleansing Agents
Sodium Cocoamphoacetate [CAS: 90387-76-1; 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 ingredients reviewed in this safety assessment[3]

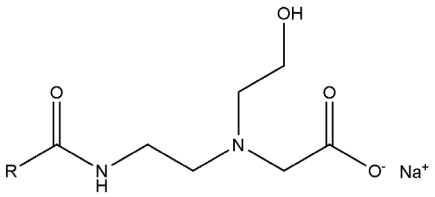
Ingredient	Definition	Function
Sodium Sweetalmondamphoacetate	Sodium Sweetalmondamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from sweet almond oil.	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants - 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	39
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	40
Specific Gravity (@ 25ºC)	1.05	41
Vapor Pressure (mmHg @ 25ºC)	0.0000225	42
Boiling Point (ºC)	≥ 100; ≤ 101	42
log K_{ow}	-7.57	42
Water Solubility	soluble	1
Alcohol Solubility	soluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Disodium Lauroamphodiacetate		
Physical Form	liquid	43
Formula Weight (g/mol)	446.5	43
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	44
Color	clear – light amber	1
Odor	faintly fruity	1
Formula Weight (g/mol)	270.62	44
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

Table 2. Chemical properties

Property	Value	Reference
Sodium Lauroamphoacetate		
Physical Form	powder	[4]
Color	light yellow	[4]
Formula Weight (g/mol)	349.5	[45]
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 chain length distributions (%)[8,46]

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. Composition of tradename mixtures of fatty amphocarboxylate ingredients

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	[13]
Disodium Cocoamphodipropionate	30-40% Disodium Cocoamphodipropionate, 60-70% water, <0.1% other components (not specified)	[12]
Disodium Lauroamphodiacetate	30-60% Sodium Lauroamphoacetate and < 0.1% dichloracetic acid (remaining components not stated)	[14]
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	[15]
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[17,18,47]

	# 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[17,18,47]

	# 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 (not powder)						
Other Baby Products	5	0.8 (baby bubble bath)						
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[17,18,47]

	# 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

*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.

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

[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. Frequency (2023; 2005) and concentration (2022; 2006) 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[17]	**2005[2]**	**2022[18]**	**2006[2]**	**2023[17]**	**2005[2]**	**2022[18]**	**2006[2]**	**2023[17]**	**2005[2]**	**2022[18]**	**2006[2]**	**2023[17]**	**2005[2]**	**2022[18]**	**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. Frequency (2023; 2005) and concentration (2022; 2006) 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[17]	**2005[2]**	**2022[18]**	**2006[2]**	**2023[17]**	**2005[2]**	**2022[18]**	**2006[2]**	**2023[17]**	**2005[2]**	**2022[18]**	**2006[2]**	**2023[17]**	**2005[2]**	**2022[18]**	**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

*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.

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

[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[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 Sodium Lauroamphoacetate.
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. A test-item related effect could not be excluded as the right-sided aortic arch incidence was above historical control range. Other visceral malformations observed were within the historical control data range. 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 duration 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) at the 1000 mg/kg bw/d dose level, 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 duration 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	Tested neat; 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	Tested neat; 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	Tested neat; 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)	[25]
Trade name mixture containing Sodium Lauroamphoacetate (36%) and water (64%)	No vehicle	Tested neat; 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)	[26]
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	[28]
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)	[20]
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)	[20]
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.	[27]
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)	[20]

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)	[20]
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.	[27]
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.	[29]
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)	[20]
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)	[20]
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)	20 (test) and 10 (control) female Pirbright white guinea pigs	-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	30 µl of test substance applied to reconstituted human corneal epithelial tissues and incubated; cell viability evaluated via MTT assay	Non-irritating	[20]
Disodium Cocoamphodiacetate	Water	1%	3	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)	[20]
Disodium Cocoamphodiacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient = 0.63 (quotient ≤ 0.8 indicates slightly irritating)	[20]
Disodium Cocoamphodiacetate	Water	50%	6	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)	[30]
Sodium Cocoamphoacetate	Water	0.6%	3	30 µl of test substance applied to reconstituted human corneal epithelial tissues and incubated; cell viability evaluated via MTT assay	Slightly irritating	[20]
Sodium Cocoamphoacetate	Water	1%	3	Red blood cell test	Non-irritating; H_{50}/DI = 102.40 (score > 100 indicates non-irritating)	[20]
Sodium Cocoamphoacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient = 0.42 (quotient ≤ 0.8 indicates slightly irritating)	[20]
Sodium Lauroamphoacetate	Water	1%	3	Red blood cell test	Non-irritating; H_{50}/DI = 222.13 (score > 100 indicates non-irritating)	[20]
Sodium Lauroamphoacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient: 0.79 (quotient ≤ 0.8 indicates slightly irritating)	[20]
Sodium Lauroamphoacetate	Water	40%	6	HET-CAM assay	Severely irritating; irritation quotient: 3.41 (quotient ≥ 2 indicates severely irritating)	[31]
			ANIMAL			
Sodium Lauroamphoacetate (10% solids: water and sodium chloride; 10% aqueous dilution)	No vehicle	Tested neat; 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	Tested neat; 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	Tested neat; 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	Tested neat; 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	Tested neat	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.	[32]
Micellar water cleanser containing 1.2% Disodium Cocoamphodiacetate and 1% cetearyl alcohol (remaining product composition not stated)	No vehicle	Tested neat	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.	[32]

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

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1

Final Report on the Safety Assessment of Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoamphodipropionate

Cocoamphoacetate (CAA), Cocoamphopropionate (CAP), Cocoamphodiacetate (CADA), and Cocoamphodipropionate (CADP) are imidazoline-derived amphoteric organic compounds. These amphoteric compounds are used in cosmetics as surfactants, mild foaming and cleansing agents, detoxifying agents, and conditioners at concentrations ranging from ≤ 0.1 to 50 percent.

In acute oral toxicity studies, CADA and CAA were nontoxic in rats and mice, CADP was nontoxic in rats, and CAP was nontoxic in mice. An oral LD_{50} of 7.8 ml/kg was reported for mice dosed with 70% CADP.

The results of ocular irritation studies of these compounds, as commercially supplied, varied widely. CADA was moderately to severely irritating when eyes were not rinsed and practically nonirritating to mildly irritating when rinsed. CADP was practically nonirritating under unrinsed conditions. CAA was minimally to severely irritating and CAP was practically nonirritating to minimally irritating under unrinsed conditions. In a clinical ocular study, 1, 3, and 10% dilutions of a shampoo containing 28.1% CADA were nonirritating to the human eye.

CAP, CADA, and CADP were nonmutagenic in the Ames assay, both with and without metabolic activation.

CAA and CAP, at a concentration of 10%, were neither irritants nor sensitizers in a repeated insult patch test on 141 subjects.

Based upon the available data, it is concluded that CAA, CAP, CADA, and CADP are safe for use as cosmetic ingredients.

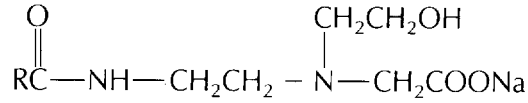
INTRODUCTION

The following report encompasses the four ingredients represented by the old nomenclature of Amphoterics-1 and -2: Cocoamphoacetate, Cocoamphopropion-

ate, Cocoamphodiacetate, and Cocoamphodipropionate.* Amphoteric-6, a complex of Amphoteric-2 and sodium lauryl sulfate, is currently regarded as a simple mixture and has been withdrawn from the third edition of the *CTFA Cosmetic Ingredient Dictionary*.[1]

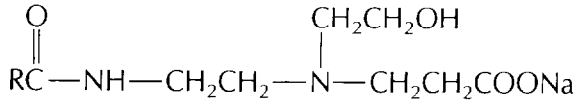
CHEMICAL AND PHYSICAL PROPERTIES

Cocoamphoacetate (CAA), Cocoamphopropionate (CAP), Cocoamphodiacetate (CADA), and Cocoamphodipropionate (CADP) are amphoteric organic compounds generally conforming to the following structural formulas:[2]



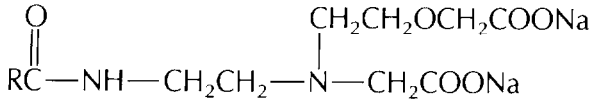
Cocoamphoacetate

I

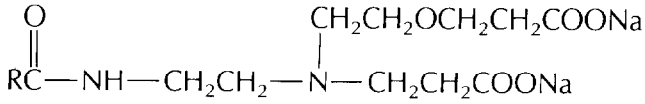


Cocoamphopropionate

II



Cocoamphodiacetate



Cocoamphodipropionate

where RCO– represents the mixed coconut acid moieties. The alkyl imidazolines were previously thought to be ring structured; however, they now are known to have a linear structure.[2–4] Cosmetic suppliers do not agree on the representation of the structures for CADA and CADP. In the opinion of some chemists, the second carboxylate group may be unattached to the amphoteric structure.[1]

These products are prepared by reacting coconut acid with aminoethylethanolamine and appear to form an imidazoline as an intermediate. The cocoimidazoline is

*New designations in supplement to the 3rd edition of the *CTFA Cosmetic Ingredient Dictionary:* Cocoamphoacetate formerly Cocoamphoglycinate (CAG), Cocoamphodiacetate formerly Cocoamphocarboxyglycinate (CACG); Cocoamphodiapropionate formerly Cocoamphocarboxypropionate (CACP). These substances are used as sodium salts in cosmetics.

then reacted with monochloracetic acid or monochloropropionic acid in the presence of sodium hydroxide to form the sodium salts either of a mono- (CAA and CAP) or dicarboxylated (CADA and CADP) product.[1,5,6]

These compounds are supplied as amber liquids, usually containing 40 to 50 percent solids, with a faintly fruity odor. Their viscosity can be controlled by the addition of sodium chloride (the more sodium chloride added, the more viscous the solution becomes). All of these products are soluble in water and insoluble in nonpolar organic solvents. CAP and CADP, containing only traces of sodium chloride ($\leq 0.02\%$), are also soluble in alcohol.[1,2] The pH range for solutions of these ingredients has been reported to be from 8.1 to 10.2 (Table 1).[2]

CAA, CAP, CADA, and CADP can be positively identified by close match to standard infrared spectra.[2] Another analytical method is based on the ionization curves formed by plotting pH changes upon addition of acids and alkalis to the amphoteric solution. Each ionization curve is unique and allows for immediate identification as well as giving information about the purity and degree of carboxylation of the compound.[7]

IMPURITIES

No information is available on impurities.

USE

Cosmetic

CAA, CAP, CADA, and CADP are used in cosmetics as surfactants, mild foaming and cleansing agents, detoxifying agents, and conditioners.[1,5,8–10]

Blends of cosmetic amphoterics and anionics act synergistically to reduce irritation potential, improve viscosity, and enhance foam volume and longevity.[11,12] Ampho-

TABLE 1. Physicochemical Properties

Property	*Cocoamphoacetate*	*Cocoamphopropionate*	*Cocoamphodiacetate*	*Cocoamphodipropionate*
Description (in aqueous solution)	Clear, viscous, light amber solution[1,2]	Clear, light amber solution[1,2]	Viscous, light tan solution[1,2]	Clear, light amber solution[1,2]
Odor	Faintly fruity[2]	Faintly fruity[2]	Faintly fruity[2]	Faintly fruity[2]
pH at 30°C	9.0–9.5[2]	9.8–10.2[2]	8.1–8.3[2] (of 20% aqueous soln)	9.4–9.8[2]
Solubility				
Water	S[1,2,5]	S[1,2,5]	S[2,5]	S[2,5]
Alcohol	I[2]	S[2]	I[2]	S[2]
Nonpolar organic solvents	I[2]	I[2]	I[2]	I[2]
Chloride (as NaCl)	7.0–7.7%[2]	0.02% maximum[2]	11.2–11.8%[2]	0.02% maximum[2]
Nitrogen	2.4–2.6%[2]	2.7–2.9%[2]	2.3–2.5%[2]	2.4% minimum[2]
Non-volatiles	43% minimum[2]	36–38%[2]	49% minimum[2]	38% minimum[2]

terics have less severe defatting effects compared with anionics and promote hair and skin substantivity at acid pH when they become cationic in character.[11] Goddard et al.[13] studied the effect of CAP on the adsorption of Polymer JR-400 on bleached and unbleached hair. CAP increased adsorption with each successive shampooing; CAP-Polymer JR-400 was one of the surfactant-polymer systems with the highest deposition on the hair.

The FDA product formulation data for CAA, CAP, CADA, and CADP are summarized in Table 2.[14] The cosmetic product formulation data, made available by the FDA, are compiled through voluntary filing in accordance with Title 21 part 720.4 (d)(1) of the Code of Federal Regulations.[15] Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. CAA and CADA are used in cosmetic products at concentrations of $\geq$ 1.0 to 10.0% and $\leq$ 0.1 to 50.0%, respectively, and, CADP, at concentrations of $>$ 1.0 to 25.0%. There are no reported cosmetic uses of CAP.[14]

TABLE 2. Product Formulation Data

Product Category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*						
			>25-50	*>10-25*	*>5-10*	*≥5*	*>1-5*	*>0.1-1*	*≤0.1*
Cocoamphoacetate									
Hair shampoos (noncoloring)	859	5	—	—	2	—	3	—	—
1989 Totals		5	—	—	2	—	3	—	—
Cocoamphopropionate									
1989 Totals	—	0	—	—	—	—	—	—	—
Cocoamphodiacetate									
Hair shampoo	878	13	1	7	4	—	1	—	—
Skin cleansing preparations	1298	10	—	1	—	—	7	1	1
Miscellaneous other cosmetics	2134	7	—	—	2	—	—	4	1
1989 Totals		30	1	8	6	—	8	5	2
Cocoamphodipropionate									
Hair shampoo	859	8	—	1	6	—	1	—	—
Other hair products	772	7	—	1	—	—	6	—	—
Skin cleansing preparations	751	2	—	—	1	—	1	—	—
1989 Totals		17	—	2	7	—	8	—	—

Source: From Ref. 14.

The formulation data presented in Table 2 indicate that cosmetic products containing these amphoterics may contact all external body surfaces and hair, conjunctivae, and other mucous membranes. These products may be used daily or occasionally over a period of up to several years. The frequency and duration of application could result in continuous exposure.

Noncosmetic

CAA, CAP, CADA, and CADP are widely used in heavy-duty liquid, steam, pressure, metal, and all-purpose cleaners.[5,16] They are used in the caustic lye peeling of fruit and potatoes and are commonly found in household products such as oven cleaners, wash and wax floor polishes, dishwashing machine compounds, copper and silver cleaners, and hard-surface cleaners.[5]

Other uses of these amphoterics include pharmaceutical formulations for the treatment of glaucoma (CADA, 0.2%) and hemorrhoids (CADP, 0.25%), contact lens disinfecting solution (CADP, 0.0035–0.04%), and in material for bandages (CADA).[17–20]

GENERAL BIOLOGY

Hirai et al.[21] studied the effects of surfactants on the nasal absorption of insulin in rats. The addition of 1% CADA to the solution administered nasally to rats significantly enhanced insulin absorption as measured by a 56.9% decrement in plasma glucose concentration from 0 to 4 h. The absolute bioavailability of insulin was increased from 5 to 30% by the addition of a surfactant such as CADA. The surfactants appeared to promote nasal absorption either by increasing the permeability of the nasal mucosa or by reducing the activities of proteolytic enzymes.

A blend containing CADA, sodium lauryl sulfate, and hexylene glycol was tested for antimicrobial activity and inhibition of the formation of *in vitro* plaque by oral bacteria. The blend had antimicrobial activity against *Actinomyces viscosus, A. naeslundii,* and *Streptococcus mutans.* However, it was significantly less effective than other detergents tested and had an ID_{50} (dose resulting in 50% inhibition of bacterial growth) of 2.0 to 5.0 $\times 10^{-5}$ M. The blend was not active against *A. viscosus* in the plaque assay and had very limited activity against *A. naeslundii* and *S. mutans* with ID_{50}s of 10^{-1}M or greater.[22]

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

CADA, CADP, CAA, and CAP, as commercially supplied, have all been evaluated for acute oral toxicity using rats or mice. LD_{50} values ranged from >5.0 to 16.60 g/kg for CADA, >5.0 to 16.30 g/kg for CADP, 15.9 to 28.0 ml/kg for CAA, and a value of 20.0 ml/kg was reported for CAP in two studies. Results of these and other acute oral toxicity tests are reported in Table 3.

Additionally, CADA and CADP were each fed to albino rats (number unspecified) at concentrations of 0.25 and 0.50% in the diet for 10 days. Control groups were

TABLE 3. Acute Oral Toxicity

Ingredient	*Animal*	*LD_{50} Value*	*Comments*	*Reference*
CADA: As commercially supplied	Rats: 5 females	>5.0 g/kg	No toxic effects	23
CADA: As commercially supplied	Rats: 10	>5.0 ml/kg	—	26
CADA: As commercially supplied	Mice: 3 groups of 10	>15 ml/kg	—	27
CADA: As commercially supplied	Rats: groups of 10	16.60 g/kg	Nontoxic	24
CADA:				24
0.50% in the diet	Rats: unspecified no.	—	Rats fed daily for 10 days; nontoxic	
0.25% in the diet	Rats: unspecified no.	—	Rats fed daily for 10 days; nontoxic	24
CADP: As commercially supplied	Rats: groups of 10	16.30 g/kg	Nontoxic	25
CADP: As commercially supplied	Rats: 5 males 5 females	>5.0 ml/kg	—	28
CADP: 70% active (as commercially supplied)	Mice: 3 groups of 10	7.8 ml/kg	—	29
CADP:				25
0.50% in the diet	Rats: unspecified no.	—	Rats fed for 10 days; nontoxic	
0.25% in the diet	Rats: unspecified no.	—	Rats fed for 10 days; nontoxic	25
CAA: As commercially supplied	Mice: 3 groups of 5 males and 5 females each	28.0 ml/kg	—	30
CAA: As commercially supplied	Mice: 4 groups of 10	15.9 ml/kg	—	30
CAA: 25% (of supplied) in water	Rats: 10	>5.0 ml/kg	Nontoxic	31
CAP: As commercially supplied	Mice: 10	20.0 ml/kg	—	32
CAP: As commercially supplied	Mice: 4 groups of 10	20.0 ml/kg	—	33
CADA with sodium lauryl sulfate and hexylene glycol: 30%	Rats: groups of 10	10.25 g/kg	Nontoxic	34
CADA: 4% in a shampoo cream	Rats: 5 males 5 females	>5.0 ml/kg	No signs of systemic toxicity; no gross pathological effects	35
CADA: 4% in a shampoo cream	Rats: 5 males 5 females	>5.0 ml/kg	No signs of systemic toxicity; no gross pathological effects	35

maintained on a standard diet. At the end of the 10-day period, the rats were weighed and observed for changes in behavior, general appearance and activity. The rats on the test diets did not differ from the controls in any of the above parameters. CADA and CADP were considered nontoxic when fed to rats daily for ten days at concentrations of 0.25 and 0.50%.[24,25]

Dermal

Two shampoo creams, each containing 4.0% CADA, were evaluated for acute dermal toxicity in rabbits. Each test group consisted of two male and two female New Zealand albino rabbits. A single application of each undiluted shampoo was applied to the clipped, intact skin of the back of each rabbit at a dose of 10.0 ml/kg. Test sites were covered for 24 h with an impervious plastic binder and tape. Upon removal of the binders, excess test material was removed. Animals were observed for signs of systemic toxicity and dermal irritation for 14 days. No deaths occurred, although clinical signs of systemic toxicity included depression, labored respiration, phonation upon handling, tremors, and weight loss (in one animal only). At necropsy, six rabbits had no gross lesions and two had changes unrelated to treatment. Gross dermal lesions included moderate to marked erythema and edema accompanied by blanched areas (in two animals) and most of the lesions had cleared by day 8. Moderate to marked atonia and marked desquamation developed during the first week in all animals. Coriaceous areas and fissures were also observed. Sloughing of the damaged skin with eschar formation occurred in two rabbits. Slight to moderate desquamation was noted at termination in all animals and two animals had moderate atonia.[36]

Irritation

Ocular

CADA, CADP, CAA, and CAP, as commercially supplied, have been evaluated for ocular irritation primarily by Draize or modified Draize tests. In all tests, a 0.1 ml sample of the substance was instilled into the conjunctival sac of each rabbit; the other eye served as the untreated control. The eyes of those rabbits designated for testing with a rinse-out procedure were rinsed either 4 seconds after instillation with 20 or 60 ml of water or 10 seconds after instillation with 300 ml of water. Ocular irritation responses were scored according to Draize (max = 110) on days 1, 2, 3, 4, and 7. CADA, at concentrations of 10 to 12% active as well as solutions of unstated activity, was moderately to severely irritating when not rinsed from the eye and practically nonirritating to mildly irritating when tested using rinse-out procedures. CADP, at a concentration of 7.5% active, was practically nonirritating under unrinsed conditions. CAA, at concentrations of 16 to 50% active as well as solutions of unstated activity, was minimally to severely irritating under unrinsed conditions. CAP, at concentrations of 5 and 16% active, was practically nonirritating to minimally irritating under unrinsed conditions. Cosmetic products containing CADA (as supplied) at concentrations of 1.5 to 28.1% and CADP (as supplied) at concentrations of 25 to 36% also have been evaluated by the Draize test. All ocular irritation test results are given in Table 4.

North-Root et al.[37] also investigated the cellular toxicity of cationic, anionic, nonionic, and amphoteric surfactants *in vitro* using an established line of rabbit corneal cells and compared the results with those from an *in vivo* ocular irritation test in New Zealand albino rabbits. CADP had an LC_{50} of 35.5 ppm for the SIRC rabbit corneal cells (other surfactant LC_{50}s ranged from 2.2 to 36000 ppm); the CADP concentration predicted to cause a Draize score of 20 was approximately 90.0%. A 0.01 ml sample of CADP (at a concentration not exceeding 30%) was administered to the cornea of each of three male and three female rabbits. Corneal, iridial, and conjunctival responses were scored according to Draize 24, 48, and 72 hours after application. Individual

TABLE 4. Ocular Irritation

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADA: As commercially supplied	Draize[a]	6: Unrinsed	HAIS[b] of 32 on day 1, 3 on day 7; moderately irritating	39
CADA: As commercially supplied	Draize	6: Unrinsed	HAIS of 30 on day 1, 3 on day 7; moderately irritating	40
CADA: As commercially supplied	Draize	6: Unrinsed	HAIS of 32 on day 1, 18 on day 7; moderately to severely irritating	41
CADA: As commercially supplied	Draize	3: Rinsed 4 s after instillation w/20 ml water	HAIS of 8 on day 1, eyes normal by day 4; minimally irritating	42
CADA: As commercially supplied	Draize	3: Rinsed 4 s after instillation w/20 ml water	HAIS of 1 on day 1, eyes normal by day 2; practically nonirritating	43
CADA: As commercially supplied	Draize	6: Unrinsed 3: Rinsed 4 s after instillation w/20 ml water	Unrinsed: HAIS of 37.17 on day 1, corneal and iridial irritation at day 7; severely irritating Rinsed: HAIS of 12.00 on day 1, some conjunctival irritation at day 7; mildly irritating	44
CADA: As commercially supplied	Draize (max = 104, discharge category omitted from scoring system)	3: Rinsed 10 s after instillation w/150 ml water/min for 2 min	HAIS of 5.33 for days 1-3, eyes normal by day 5; mildly irritating	45
CADA: 21% aqueous dilution of CADA (as supplied)	Draize	6: Unrinsed 3: Rinsed 4 s after instillation w/20 ml water	Unrinsed: HAIS of 3.67 at day 1, minimal conjunctival irritation at day 7; minimally irritating Rinsed: all scores of 0; nonirritating	46
CADA: 25% dilution of CADA (as supplied)	Draize	3: Unrinsed	HAIS of 5.33 on day 1, eyes normal by day 4; minimally irritating	47
CADA: 12% active (as commercially supplied)	Draize	3: Unrinsed	All scores: 0; nonirritating	48
CADA: 10% active (as commercially supplied)	Draize	3: Unrinsed	HAIS of 4.0 on day 1, eyes normal by day 3; minimally irritating	49
CADA: 5% (as commercially supplied) in water	—	6	Irritation cleared by 24 h	50
CADA: 5% (supplied w/1% $NaBH_4$) in water	—	6	Irritation cleared by 24 h	51
CADA: at 2, 10, and 20% in water	Draize	Groups of 5, unrinsed	Dose response observed; CADA was the second least irritating surfactant tested; 2%, score of 10 at 1 h, 0 at 24 h; 10%, score of 35 at 1 h, 5 at 7 days; 20%, score of 55 at 1 h, 5 at 7 days	52
CADP: 25% dilution of CACP (as commercially supplied) pH adjusted to 8	Draize	6: Unrinsed	HAIS of 1 on day 1, eyes normal by day 2; nonirritating	53

TABLE 4. *Continued*

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADP: 7.5% active (as commercially supplied)	Draize	3: Unrinsed	HAIS of 1.33 on day 2, eyes normal by day 3; practically nonirritating	54
CADP	*In vitro* rabbit corneal cell toxicity test	—	LC_{50} = 35.5 ppm; least irritating amphoteric tested	37
CADP: concentration not > 30%	Draize	6: Unrinsed	CADP was the least irritating amphoteric; order of toxicity was cationic > anionic = amphoteric > nonionic; individual scores not given	37
CAA: As commercially supplied	Draize	6: Unrinsed	HAIS of 5.33 on day 1, eyes normal by day 7; minimally irritating	55
CAA: 50% active (as commercially supplied)	—	6	Draize scoring over 24 h, HAIS of 5.67 at 2 and 8 h, 1.0 at 24 h; minimally irritating	56
CAA: 50% active (as commercially supplied)	Modified Draize	6	HAIS of 29.4 on day 1, corneal and iridial irritation at day 7 in 2 rabbits; severely irritating	57
CAA: 16% active (as commercially supplied) pH adjusted to 7.0	Draize	3: Unrinsed	HAIS of 8.7 on day 1, minimal conjunctival irritation on day 7; minimally irritating	58
CAA: 25% aqueous dilution (of supplied)	Draize	6: Unrinsed	HAIS of 1.7 on day 1, eyes normal by day 2; nonirritating	31
CAA: 20% aqueous solution of 50% active CAG	Draize	6	HAIS of 5.67 on day 1, minimal conjunctival irritation on day 7; minimally irritating	59
CAA: 5% aqueous solution of 50% active CAG	Draize	6	HAIS of 1.0 on day 1, eyes normal by day 3; nonirritating	60
CAP: 16% active (as commercially supplied) pH adjusted to 7.0	Draize	3: Unrinsed	HAIS of 5.33 on day 1, eyes normal by day 4; minimally irritating	61
CAP: 5% active (as commercially supplied)	Draize	3: Unrinsed	HAIS of 1.33 on day 1, eyes normal by day 2; practically nonirritating	62
CADA: 28.1% in a shampoo (32% active)	Draize	6: Unrinsed	HAIS of 2.33 on day 1, eyes normal by day 3; practically nonirritating	63
CADA: 4% in a shampoo cream	Draize	5: Rinsed 4 s after instillation w/60 ml water	HAIS of 10.4 at 1 h, 4.8 by day 1, eyes normal by day 3; minimally irritating	64
CADA: 4% in a shampoo cream	Draize	5: Rinsed 4 s after instillation w/60 ml water	HAIS of 16.4 at 1 h, 5.2 by day 1, eyes normal by day 4; mildly irritating	64
CADA: 4% in an eye cream	Draize	5: Unrinsed	HAIS of 3 at 1 h, 1 by day 1, eyes normal by day 2; minimally irritating	65

TABLE 4. *Continued*

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADA: 1.5% in a facial scrub	Draize	5: Unrinsed 5: Rinsed 4 s after instillation w/60 ml water	Unrinsed: HAIS of 27.4 on day 1, corneal and iridial irritation cleared by day 4, minimal conjunctival irritation at day 7; moderately irritating Rinsed: HAIS of 7.2 at 1 h, 0.4 by day 1, eyes normal by day 3; minimally irritating	66
CADA: at 0.14% with a formulation containing menthol	Draize	Unspecified	Totally eliminated the ocular irritation effects of menthol in the formulation— Draize score reduced to 0 (max = 110)	38
CADA: at 0.14% with a cologne	Draize	Unspecified	Reduced corneal irritation score of the cologne to 0; also reduced total score to 6 and 29 at 72 h and 7 days, respectively	38
CADA: 0.3% blend of CADA with sodium lauryl sulfate and a cologne	Draize	Unspecified	Equivocal reduction of ocular irritation; Draize scores of 7 and 27 for the cornea, 17 and 92 total scores, for 72 h and 7 days, respectively	38
CADP: 36.842% in a shampoo (38% active)	Draize	6: Unrinsed	HAIS of 8 at 1 h, 0 by day 1; not an ocular irritant	67
CADP: 25% in a shampoo (38% active) tested as 10 percent aqueous dilution	Draize	6: Unrinsed	HAIS of 1 on day 1, 0 thereafter; practically nonirritating	68

[a]Maximum score = 110.
[b]HAIS = Highest average irritation score (ocular).

results for CADP were not given. The order of ocular irritancy and cytotoxicity was cationic > anionic = amphoteric > nonionic. A significant correlation existed between relative toxicity in the rabbit corneal cells *in vitro* and relative ocular irritation when tested *in vivo*. CADP was the least irritating amphoteric surfactant; only the three nonionic surfactants were less irritating.

Additionally, Goldemberg[38] found that CADA had anti-irritant activity. CADA eliminated the ocular irritation effects of menthol in a Draize ocular irritation test using a pre-electric shave formulation consisting of 20% butyl stearate in ethanol as the "control." Groups of three rabbits received instillations of the control solution, the control solution with 0.7% menthol, and the control solution with 0.7% menthol and 0.14% CADA. The control formulation had baseline scores of 10, 6.2, and 5.0 at 24, 48, and 72 hours, respectively. The addition of menthol increased the scores to 14.7, 12.4, and 6.5 at 24, 48, and 72 hours, respectively. With addition of CADA, all scores were 0. The determination of the amount of CADA necessary to neutralize the effects of menthol was likened to titration by the investigator. At concentrations of CADA lower than 0.14% some ocular irritation was observed; higher concentrations were not more efficient. The efficiency ratio was 0.14/0.7 indicating that, in this case, 20% CADA neutralized the ocular irritation effects of menthol.

Goldemberg[38] conducted similar studies using a cologne formulation as the "control." Groups of three rabbits received instillations of the cologne alone, the

cologne with 0.14% CADA, and the cologne with 0.3% of a blend containing CADA and sodium lauryl sulfate. The addition of CADA alone was more effective in reducing ocular irritation than the blend. The cologne (96% SDA 39C ethanol) contained approximately 1% diethyl phthalate, which also may have had anti-irritant activity. The effective anti-irritant/irritant ratio for CADA/triethanolamine lauryl sulfate was 1:3.[38]

Dermal

CADA, CADP, CAA, and CAP, as commercially supplied, have been evaluated for dermal irritation primarily by single insult patch test (SIPT) procedures. In each test, an occlusive patch was applied for 24 hours to the clipped skin of the back of the rabbit. Intact or intact and abraded sites were used. In those tests using intact sites only, scores were taken 2 and 24 hours after patch removal on a maximum scale of 4. In those tests using the Draize procedure, with intact and abraded sites, scores were taken at 24 and 72 hours on a maximum scale of 8. CADA, at a concentration of 10 to 12% active, as well as solutions of unstated activity, was nonirritating to severely irritating to rabbit skin. CADP, at concentrations of 7.5 and 70% active, was nonirritating. CAA, at a concentration of 16% active as well as solutions of unstated activity, was nonirritating to severely irritating. CAP, at concentrations of 15 and 16% active, was slightly irritating. Cosmetic products containing CADA (as supplied) at concentrations of 1.5 to 4% and CADP (as supplied) at concentrations of 25 to 36.8% also have been evaluated for dermal irritation by the Draize procedure. Dermal irritation test results are given in Table 5.

These four ingredients also have been evaluated for dermal irritation in rabbits by use of a single intradermal injection. Each injection consisted of 0.5 ml of a 5% solution of CADA, CADP, or CAP (supplied as 20% active solutions—giving actual test concentrations of 1%); CAA was evaluated as a 0.1% solution. In each case, a second group of rabbits received injections of an olive oil castile shampoo as the control. The rabbits were observed for signs of irritation at the injection site 24 hours later and scored on a maximum scale of 4. CADA had a score of 0 and was considered nonirritating.[69] CADP, CAA, and CAP had scores of 1 and were considered less irritating than the control shampoos, which had scores of 2.[70–72]

Sensitization

The Magnusson-Kligman maximization test was used to evaluate the sensitization potential of CAA in 15 guinea pigs. CAA was tested at concentrations of 25, 50, and 100%. Negative (15 guinea pigs) and positive (15 guinea pigs) control groups were tested with distilled water and methylmethacrylate (25, 50, and 100%), respectively. CAA did not induce sensitization in any of the animals tested. Sensitization reactions were observed in the positive control group.[94]

MUTAGENICITY

The mutagenic potentials of CAP, CADA, and CADP were evaluated in the Ames *Salmonella*/microsome assay, using *Salmonella typhimurium* strains: TA-1535, TA-1537, TA-1538, TA-98, and TA-100.[95] CAP, CADA, and CADP (each diluted with deionized water) were tested at concentrations ranging from 0.005 to 1.00 μl per plate. Each test substance was incubated with each bacterial strain (three plates per dose, 37 ± 2°C) for 48 to 72 h in both the presence and absence of metabolic activation. The number of his+ revertant colonies was determined using an automated colony counter.

TABLE 5. Dermal Irritation

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADA: As commercially supplied	SIPT[a]	9	AII[b] = 1.8; mildly irritating	73
CADA: As commercially supplied	SIPT	9	AII = 1.89; mildly irritating	74
CADA: As commercially supplied	SIPT	5	AII = 4.0; severely irritating	75
CADA: As commercially supplied	Draize[c]	6	PII[d] = 4.49; severely irritating	76
CADA: As commercially supplied	Draize	6	PII = 1.5; mildly irritating	48
CADA: 21% aqueous solution of CADA (as commercially supplied)	Draize	6	PII = 0.96; mildly irritating	77
CADA: 12% active (as commercially supplied)	Draize	3	PII = 0; nonirritating	78
CADA: 10% active (as commercially supplied)	Draize	3	PII = 0.85; slightly irritating	49
CADA: 10% in water	Draize	6	PII = 0; nonirritating	79
CADA: 10% in mineral oil	SIPT	9	AII = 0.11; minimally irritating	80
CADA: 2, 10, 20% aqueous solutions	Draize	6	PIIs = 2.25, 2.5, and 3.0 for the 2, 10, and 20% aqueous solutions; 2 and 10% solutions considered moderately irritating; 20% solution considered severely irritating	52
CADA: Actual concentration of 1% (5% of 20% active solution)	SIDI[e]	Unspecified	All scores = 0 (max = 4); nonirritating	69
CADP: 70% active (as commercially supplied)	Draize	3	PII = 0; nonirritating	81
CADP: 25% dilution of the CADP supplied	Draize	6	PII = 0; nonirritating	82
CADP: 7.5% active (as commercially supplied)	Draize	3	PII = 0; nonirritating	83
CADP: actual concentration of 1% (5% of 20% active solution)	SIDI	Unspecified	Score = 1 (max = 4); considered less irritating than control shampoo	72
CAA: As commercially supplied (pH adjusted to 7.0)	Draize	6	PII = 0; nonirritating	84
CAA: 25% (of supplied) in water	Draize	6	PII = 0.08; nonirritating	31
CAA: 16% active (as commercially supplied; pH adjusted to 7.0)	Draize	3	PII = 3.83; severely irritating	85
CAA: 0.1%	SIDI	Unspecified	Score = 1 (max = 4); considered less irritating than control shampoo	70
CAP: 16% active (as commercially supplied—pH adjusted to 7)	Draize	3	PII = 0.5; slightly irritating	86
CAP: 15% active (as commercially supplied)	Draize	6	PII = 0.5; slightly irritating	87
CAP: actual concentration of 1% (5% of 20% active solution)	SIDI	Unspecified	Score = 1 (max = 4); considered less irritating than control shampoo	71

TABLE 5. *Continued*

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADA: 4% in an eye cream	Draize	4	PII = 3.13; severely irritating	88
CADA: 4% in a shampoo cream tested at 2.5% in water	Draize	4	PII = 1.56; mildly irritating	89
CADA: 4% in a shampoo cream tested at:	Draize			89
2.5% in water		4	PII = 2.94; moderately irritating	
1.25% in water		4	PII = 1.63; mildly irritating	
CADA: 1.5% in each of three facial scrubs; tested at	Draize	4	PII = 0.81; slightly irritating	90
1.25% in water		4	PII = 1.06; mildly irritating	
		4	PII = 2.00; moderately irritating	
CADA: with sodium lauryl sulfate and hexylene glycol; unspecified concentration	Draize	3	PII = 0.5; slightly irritating	91
CADP: 36.842% in a shampoo (38% active)	Draize	6	PII = 0.12; slightly irritating	92
CADP: 25% in a shampoo (38% active); tested as 10% aqueous dilution	Draize	6	PII = 0.21; slightly irritating	93

[a]SIPT = Single insult patch test = 24 h occlusive on intact site. Scores taken at 26 and 48 h.
[b]AII = Average irritation index (max = 4).
[c]Draize = Single 24 h occlusive patch on intact and abraded sites. Scores taken at 24 and 72 h.
[d]PII = Primary irritation index (max = 8).
[e]SIDI = Single intradermal injection.

Solvent controls were incubated with 50.0 μl of deionized water. Positive control cultures (all strains, metabolic activation) were incubated with 2-anthramine (2.5 μg/plate). Other positive control cultures (no metabolic activation) were incubated with: sodium azide in water (10.0 μg/plate, TA-1535 and TA-100), 2-nitrofluorene in dimethyl sulfoxide (DMSO) (10.0 μg/plate, TA-1538 and TA-98), and quinacrine mustard in DMSO (5.0 μg/plate, TA-1537). CAP, CADA, and CADP were not mutagenic to any of the strains tested in either the presence or absence of metabolic activation. The positive controls (with and without metabolic activation) induced large increases in the numbers of revertants in all of the strains tested.[96–98]

CLINICAL ASSESSMENT OF SAFETY

Ocular Irritation

A children's shampoo containing 28.1% CADA (32% active) was evaluated for ocular irritation using 30 adult subjects. Three dilutions of the shampoo were tested: 1, 3, and 10%. Each dilution was instilled into the conjunctival sac of one eye of each of 10 subjects; the other eye was treated with sterile distilled water. Positive reactions were noted only at the 30-s posttreatment evaluation. These consisted primarily of mild irritation scores for the bulbar and palpebral conjunctivae for all groups (including water treated); one subject each in the 3 and 10% groups as well as one treated with distilled water had a moderate score for irritation of the bulbar conjunctiva. Stinging

was noted in 1, 3, 4, and 2 subjects in the 1, 3, and 10% groups and water-treated eyes, respectively. When weighted for the number of eyes exposed, no significance was found in the positive responses. In all but seven of the positive reactions to the shampoo dilutions, distilled water elicited a positive reaction in the other eye. This was attributed to the eye sensitivity of individual subjects. None of the shampoo dilutions were considered more irritating than sterile distilled water.[99]

Dermal Irritation and Sensitization

The skin sensitization potential of CAA and CAP was evaluated using 32 male (18–65+ years) and 109 female (18–65 years) subjects. The chemicals were diluted to a concentration of 10% w/v in distilled water prior to testing. During induction, each chemical was applied to the back three times per week for three successive weeks. Sites were covered for 24 h with nonocclusive patches secured with surgical tape. Repeated applications of both chemicals were made to the same test sites. Reactions were scored 48 or 72 h after each induction application according to the Draize[100] scale: 0 (no erythema and eschar formation, no edema) to 4 (severe erythema to slight eschar formation, severe edema). The challenge phase was initiated 10 to 15 days after application of the final induction patch. Challenge patches (nonocclusive) were applied for 24 h to new sites on the back; reactions were scored 48 and 96 h later. CAA and CAP did not induce skin irritation or sensitization in any of the subjects tested.[101] Results of all irritation and sensitization tests are reported in Table 6.

A children's shampoo containing 28.1% CADA (32% active) was evaluated for irritation and sensitization by a Repeated Insult Patch Test (RIPT) using 105 subjects. Occlusive patches containing a 5.0% dilution of the shampoo were applied to the backs of the subjects on Mondays, Wednesdays, and Fridays for the first five inductions; however, due to the large number of irritant reactions, semiocclusive patches were used on a new site for the remaining four inductions. Sites were scored upon patch removal (and prior to next patch application) on a scale of 0–3+. After a two-week nontreatment period, a challenge patch was applied for 48 h to the same site and the site was scored after 48 and 72 h. Under semiocclusive conditions, the shampoo elicited, at most, two ? (barely perceptible erythema) reactions and one 1+ (definite erythema) reaction during induction. Three and one ? reactions were observed 48 and 72 h after the challenge, respectively. The shampoo was nonirritating and nonsensitizing under semiocclusive patch test conditions.[102]

A shampoo cream and a facial scrub containing 4 and 0.61% CADA, respectively, were evaluated for irritation and sensitization by RIPT at a concentration of 1% in water. In each test, a series of eight induction patches was applied to the upper portion of the arm of each subject on four consecutive days per week for two weeks. These patches were semiocclusive and contained 0.3 or 0.2 ml of the shampoo or scrub test solutions, respectively. Patches were removed after 24 h and sites scored on a scale of 0 to 5. After a 2-week nontreatment period, semiocclusive challenge patches were applied to adjacent sites for 24 h. Reactions were scored at 24, 48, and 72 h for both test solutions, and additionally at 96 h for the facial scrub. In both tests, slight erythema (score of 1) was noted during induction, whereas no reactions were observed at challenge. The shampoo and facial scrub were nonirritating and nonsensitizing in the 45 and 53 subjects, respectively, who completed the studies.[103,104]

TABLE 6. Clinical Irritation and Sensitization

Ingredient	*Test method*	*No. of subjects*	*Results*	*References*
CAA: 10% in distilled water	RIPT[a] (nonocclusive)	141	Nonirritating and nonsensitizing	101
CAP: 10% in distilled water	RIPT (nonocclusive)	141	Nonirritating and nonsensitizing	101
CADA: 28.1% in a shampoo (32% active); tested as 5% dilution in water	RIPT (occlusive switched to semiocclusive)	105	Large number of irritant reactions—to induction patches 1-5 under occlusive conditions; switched to semiocclusive patches; nonirritating and nonsensitizing	102
CADA: 4.0% in a shampoo cream and tested at 1% in water	RIPT (semiocclusive)	45	Nonirritating and nonsensitizing	103
CADA: 1.1% in an eye makeup remover (70% active)	RIPT (occlusive)	102	Nonirritating and nonsensitizing	105
CADA: 1.1% in an eye makeup remover (70% active)	RIPT (occlusive)	103	Produced some irritation; nonsensitizing	112
CADA: 0.61% in a facial scrub; tested at 1% in water	RIPT (semiocclusive)	53	Nonirritating and nonsensitizing	104
CADA: 25% in a facial cleanser (45.6% active)	Controlled use; twice daily for one month	54	No adverse reactions	106
CADP: 10% in a hair product (diluted to 1% in water)	Kligman maximization	25	No adverse reactions; nonsensitizing	107
CADP: 5% in a cleansing cream	RIPT (occlusive)	204	Nonirritating and nonsensitizing	108
CADP: 5% in a cleansing cream	21-Day cumulative irritation (occlusive)	12	Total score = 109 (max = 1008); very mildly irritating	109
CADP: 5% in a cleansing cream	Controlled use; daily for one month	53	Nonirritating	110
CADP: 5% in a cleansing cream	Controlled use; once or twice daily for two weeks	24	No adverse reactions	111

[a]RIPT = Repeated Insult Patch Test

An eye makeup remover containing 1.1% of 70% active CADA (actual concentration of 0.77%) was evaluated for irritation and sensitization by a modified Draize RIPT. Occlusive patches containing 0.3 ml of the test material were applied for 24 h to the upper portions of the arms of 102 volunteers on alternate days for a total of 10 applications. After a two to three week nontreatment period, an occlusive challenge patch was applied for 24 h to the same test site on each volunteer. Reactions were scored upon patch removal and at 24 h. All scores were 0 (max = 4); the eye makeup remover was considered neither a primary skin irritant, sensitizer, nor fatiguing agent.[105]

Another eye makeup remover also containing 1.1% of 70% active CADA (actual concentration of 0.77%) was evaluated for irritation and sensitization by an RIPT. Occlusive patches were applied for 48 h to the same site on the back of 113 panelists on

alternate days for a total of 10 applications. Patches applied on Friday remained in place until Monday. Sites were scored 15 minutes after patch removal. After a nontreatment period, an occlusive challenge patch was applied for 48 h to a fresh site on the back. Reactions were then scored at 15 min and 24 h after patch removal. Of the 103 panelists who completed the study, only one reaction (score of 2, max = 4) was noted at challenge. However, positive irritant reactions to the product were observed during the induction phase in 28 of 113 panelists. Except for one subject, none of the irritation scores exceeded 2, even with continued application of the product. This particular subject had a score of 4+ after six applications; however, no irritation was seen when the product was reapplied under nonocclusive conditions. The irritancy level of this product would not be considered significant when applied for a short duration to normal skin although the proximity of its use to the eye should be taken into consideration. The eye makeup remover produced no evidence of sensitization but did produce some irritation.[112]

A facial cleanser containing 25% CADA (45% active) was evaluated in a controlled use study with 54 subjects. The subjects were instructed to use the cleanser twice daily for one month; 29 of the subjects used the cleanser alone and 25 used the cleanser with an antiseptic lotion. The cleanser produced no adverse reactions.[106]

A Kligman maximization test was conducted to evaluate the skin sensitization potential of a hair product containing 10% CADP. Another formulation not containing CADP was simultaneously tested. Twenty-five subjects participated in the study. The study was conducted without sodium lauryl sulfate (SLS) pretreatment, as it was determined that both test materials were mildly irritating by pretest with test solutions and SLS. The hair product was diluted with distilled water to a concentration of 1% and applied (0.3 ml) to each patch. The occlusive induction patches remained in place for 48 h, after which there was a 24-h nontreatment period. These procedures were repeated for a total of five inductions. The induction sites were scored only in the event of exacerbation or a flare. Ten days after removal of the last induction patch, occlusive challenge patches were applied to previously untreated sites for 48 h. None of the subjects had reactions to induction or challenge patches that contained samples of the hair product with 10% CADP. The investigators concluded there was no evidence of contact sensitization elicited by this product.[107]

Cleansing creams containing 5% CADP were evaluated for irritation and sensitization by an RIPT, a 21-day cumulative irritation test, and two controlled use studies. In the modified Draize-Shelanski-Jordan RIPT, a series of 10 occlusive induction patches were applied on alternate days to 204 subjects (147 males, 57 females). These patches were left in place for 24 h and results were scored (max = 4) upon removal. After a 13-day nontreatment period, challenge patches were applied for 48 h to new sites on the back. Seven days later, a second challenge patch was applied for 48 h. Challenge site reactions were scored at 48 and 72 h. Mild erythema (score of 1) was noted in 16 subjects during induction and challenge; these reactions were considered isolated and clinically insignificant. Intense erythema (score of 2) was noted in a subject after the eighth induction patch. Open patches were used thereafter and no further reactions were observed. This was considered to be an example of nonspecific irritation typical of cleansing creams. The cleansing cream was nonirritating and nonsensitizing.[108]

In the 21-day cumulative irritation test using 12 subjects, occlusive patches containing the cream were applied daily for 21 consecutive days (patches applied on Saturday remained in place until Monday). Patches were applied to the back, removed

after 24 h, and reactions were scored immediately (max = 4). Solutions of 0.5 and 2% sodium lauryl sulfate were used as markers, and had total scores of 67 and 298 (max = 1008), respectively. The cream had a total score of 109 and was considered very mildly irritating.[109]

In the first controlled use study, the cream was used by 53 subjects on a daily basis for four weeks. One subject noted a feeling of "irritation" after a few days, although no specific erythema or dermatitis was evident. This subject discontinued use. No rash, itching, burning, or irritation was noted by the other subjects.[110]

In the second controlled use study, 24 subjects used the cream once or twice daily for two weeks. No adverse reactions were noted.[111]

Photoallergenicity

The photoallergenicity of CAA, CAP, and CADA was evaluated using 5 male and 25 female subjects (18–55 years). Distilled water served as the control. Each chemical was diluted to a concentration of 10% w/v in distilled water prior to testing. During induction, a total of nine duplicate applications of each chemical were made to the back three times per week for three weeks. Each site was covered for 24 h with a gauze pad secured with surgical tape. Within 10 min after each patch removal, sites were irradiated with UVA light (4.0 J/cm^2, 22–25 s). The application sites of 13 subjects were irradiated with twice the minimal erythemal dose of UVB light (2–5 min, 2–5 mJ/cm^2) immediately after UVA irradiation. UVA (320–400 nm) and UVB (290–320 nm) radiation was emitted from a 1000 W xenon arc solar simulator with appropriate filters. Reactions were scored 48 h after applications 1, 2, 4, 5, and 8, and 72 h after applications 3, 6, and 9 according to the scale: 0 (no evidence of any reaction) to 5 (vesicular/bullous eruption). The challenge phase was initiated two weeks after the conclusion of induction. Duplicate 24-h challenge applications of each test substance were made to new sites on the back. At the conclusion of exposure, half of the challenge patches applied (one per chemical) were removed and sites were irradiated with UVA light (4.0 J/cm^2, 22–23 s). Challenge patches were then removed from the remaining nonirradiated sites. Reactions were scored at approximately 24, 48, and 72 h after patch removal. Mild to moderate erythema, at either experimental or control induction sites, was observed in a total of 11 subjects. The 11 subjects were among the 13 exposed to UVA and UVB light. The authors stated that such reactions generally result from sunburn derived from UVB exposure. CAA, CAP, and CADA did not induce photoallergic reactions or delayed contact hypersensitivity in any of the subjects tested.[101]

SUMMARY

Cocoamphoacetate (CAA), Cocoamphopropionate (CAP), Cocoamphodiacetate (CADA), and Cocoamphodipropionate (CADP) are imidazoline-derived amphoteric organic compounds. These products are prepared by reacting coconut acid with aminoethylethanolamine to produce an imidazoline, which is then reacted with monochloracetic acid or monochloropropionic acid in the presence of sodium hydroxide to form the mono- (CAA and CAP) or dicarboxylated (CADA and CADP) products.

These amphoteric compounds are supplied as amber liquids containing 40 to 50% solids. The viscosity may be increased by the addition of sodium chloride. All are soluble in water and insoluble in nonpolar organic solvents; CAP and CADP are also soluble in alcohol. The pH range for commercially available solutions of CAA, CAP, CADA, and CADP has been reported to be from 8.1 to 10.2.

CAA, CAP, CADA, and CADP can be assayed by close match to standard infrared spectra and ionization curves.

The amphoteric compounds are used in cosmetics as surfactants, mild foaming and cleansing agents, detoxifying agents, and conditioners. These ingredients are present in cosmetics at concentrations ranging from ≤ 0.1 to 50%. Product use may lead to contact of all external body surfaces, hair, eyes, and mucous membranes; frequency and duration of application could result in continuous exposure.

The amphoteric compounds are used widely in industrial and household cleaning products.

In acute oral toxicity studies, CADA and CAA were nontoxic in rats and mice, CADP was nontoxic in rats, and CAP was nontoxic in mice. CADA and CADP were also nontoxic when fed to rats for 10 days at concentrations of 0.25 and 0.50% of the diet. An oral LD_{50} of 7.8 ml/kg was reported for mice dosed with 70% CADP (as commercially supplied).

In acute dermal toxicity studies, two shampoo creams containing 4.0% CADA had LD_{50}s >10.0 ml/kg. Primary signs of systemic toxicity included depression, labored respiration, and phonation upon handling. Moderate dermal irritation also was noted.

Results of Draize ocular irritation studies in rabbits were that these ingredients, as commercially supplied, varied widely in their ocular irritancy. CADA was moderately to severely irritating when eyes were not rinsed and practically nonirritating to mildly irritating when rinsed from the eye. CADP was practically nonirritating under unrinsed conditions. CAA was minimally to severely irritating and CAP was practically nonirritating to minimally irritating under unrinsed conditions. CADA also has distinct anti-irritant activity when used in formulations.

Single insult patch tests of these ingredients in rabbits with intact or intact and abraded skin have produced varying results. As commercially supplied, CADA and CAA were nonirritating to severely irritating, CADP was nonirritating, and CAP was slightly irritating. When intradermally injected into rabbits, CADA (1%) was nonirritating while CAA (0.1%), CADP (1%), and CAP (1%) were less irritating than the control shampoo.

CAA, at a concentration of 50% active, was nonsensitizing in guinea pigs when evaluated by the Magnusson-Kligman maximization test.

The mutagenic potential of CAP, CADA, and CADP was evaluated in the standard Ames assay with and without a metabolic activation system and with positive and negative controls. The three test compounds were not mutagenic.

In a clinical ocular study, 1, 3, and 10% dilutions of a shampoo containing 28.1% CADA (32% active) were no more irritating to the human eye than sterile distilled water. CAA and CAP (concentrations = 10% in distilled water) were nonirritating and nonsensitizing in a repeated insult patch test (RIPT) involving 141 subjects; nonocclusive patches were applied. In other RIPTs, products containing CADA at concentrations of 0.61 to 28.1% were essentially nonirritating and nonsensitizing under semiocclusive conditions. These products did produce some irritation under occlusive patch conditions. A facial cleanser containing 25% CADA (45.6% active) produced no adverse

reactions in 54 subjects using the product twice daily for one month. Cleansing creams containing 5% CADP were nonirritating and nonsensitizing in 204 subjects evaluated by RIPT (occlusive), very mildly irritating in 12 subjects evaluated by a 21-day cumulative irritation test (occlusive), and nonirritating in 53 and 24 subjects using the products daily for one month or once or twice daily for two weeks, respectively. In the maximization test, a hair product (diluted to 0.1% CADP) did not induce sensitization in any of the 25 subjects tested. CAA, CAP, and CADA (concentrations = 10% in distilled water) did not induce photoallergic reactions or delayed contact hypersensitivity in a study involving 30 subjects.

DISCUSSION

The Expert Panel recognizes that Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoamphodipropionte, as commercially supplied, induced mild to severe ocular irritation in the Draize test and, also, that cosmetic products containing these ingredients are buffered.

Mutagenicity data on Cocoamphoacetate were not available. However, the Expert Panel concluded that this ingredient was not mutagenic, based on negative Ames test results for Cocoamphodiacetate.

CONCLUSION

Based upon the available data included in this report, the Expert Panel concludes that CAA, CAP, CADA, and CADP are safe as cosmetic ingredients in the present practices of use.

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Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoamphodipropionate

CONCLUSION

In a safety assessment of Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoamphodipropionate (Elder, 1990), the Cosmetic Ingredient review (CIR) Expert Panel stated these cosmetic ingredients were safe as used. The Expert Panel reviewed newly available studies since that assessment, along with updated information regarding types and concentrations of use. The Panel confirmed the safety of Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoampho-dipropionate in the practices of use and concentrations as given in Table 6, and did not reopen the safety assessment.

DISCUSSION

The Panel noted that the names for these ingredients in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2006) have changed—they are now Sodium Cocoamphoacetate, Sodium Cocoamphopropionate, Disodium Cocoamphodiacetate, and Disodium Cocoamphodipropionate, respectively.

Sodium Cocoamphoacetate was used in five cosmetic products in 1989, based on voluntary reports provided to FDA by industry with concentrations ranging from >1% to 10% (Elder 1990). In 2005, Sodium Cocoamphoacetate was reportedly used in 46 cosmetic products (FDA 2006). Data from an industry survey in 2006 indicated that Sodium Cocoamphoacetate was used at concentrations ranging from 0.9% to 18% (CTFA 2006).

Sodium Cocoamphopropionate was not in use in 1989, based on voluntary reports provided to FDA by industry (Elder 1990). In 2005, Sodium Cocoamphopropionate was reportedly used in seven cosmetic products (FDA 2006). Data from an industry survey in 2006 indicated that Sodium Cocoamphopropionate was used at concentrations ranging from 0.3% to 10% (CTFA 2006).

Disodium Cocoamphodiacetate was used in 30 cosmetic products in 1989, based on voluntary reports provided to FDA by industry with concentrations ranging from ≤0.1% to 50% (Elder 1990). In 2005, Disodium Cocoamphodiacetate was reportedly used in 194 cosmetic products (FDA 2006). Data from an industry survey in 2006 indicated that Sodium Cocoamphodiacetate was used at concentrations ranging from 0.0006% to 12% (CTFA 2006).

Disodium Cocoamphodipropionate was used in 17 cosmetic products in 1989, based on voluntary reports provided to FDA by industry with concentrations ranging from >1% to 25% (Elder 1990). In 2005, Disodium Cocoampho-dipropionate was reportedly used in 72 cosmetic products (FDA 2006). Data from an industry survey in 2006 indicated that Sodium Cocoamphodipropionate was used at concentrations ranging from 0.008% to 15% (CTFA 2006).

The CIR Expert Panel recognized that certain ingredients in this group are reportedly used in a given product category, but the concentration of use is not available. For other ingredients in this group, information regarding use concentration for specific product categories is provided, but the number of such products is not known. Although there are gaps in knowledge about product use, the overall information available on the types of products in which these ingredients are used and at what concentration indicate a pattern of use. The Panel acknowledged that uses of these ingredients in leave-on products has increased, including uses in baby products, but considered that the original safety assessment adequately addressed the safety of leave-on uses.

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Diazolidinyl Urea

CONCLUSION

In a safety assessment of Diazolidinyl Urea (Elder 1990), the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient is safe up to a maximum concentration of 0.5%. The Expert Panel reviewed newly available studies since that assessment, along with updated information regarding types and concentration of use. The Panel confirmed that Diazolidinyl Urea is safe up to a maximum concentration of 0.5%, which is consistent with the present practices of use and concentrations given in Table 7, and did not reopen the safety assessment.

DISCUSSION

Diazolidinyl Urea was used in 95 products in 1987, based on voluntary reports provided to FDA by industry, at concentrations

TABLE 6

Historical and current cosmetic product uses and concentrations for Sodium Cocoamphoacetate, Sodium Cocoamphopropionate, Disodium Cocoamphodiacetate, and Disodium Cocoamphodipropionate

Product category	1989 uses (Elder 1990)	2005 uses (FDA 2006)	1989 concentrations (Elder 1990) (%)	2006 concentrations (CTFA 2006) (%)
Sodium Cocoamphoacetate				
Baby Care				
Other baby care	—	—	—	4[b]
Bath				
Soaps and detergents	—	4	—	3–18
Bubble baths	—	4	—	0.09
Noncoloring hair care				
Conditioners	—	3	—	2
Permanent waves	—	1	—	—
Shampoos	5	11	>1–10	1–6
Tonics, dressings, etc.	—	—	—	0.1
Hair coloring				
Dyes and colors	—	—	—	0.7
Other hair coloring	—	2	—	—
Makeup				
Othermakeup	—	—	—	3
Personal hygiene				
Douches	—	—	—	0.8–2
Other personal hygiene	—	18	—	—
Skin care products				
Skin cleansing creams, lotions, liquids, and pads	—	3	—	2–5
Total uses/ranges for Sodium Cocoamphoacetate	5	46	>1–10	0.09–18
Sodium Cocomaphopropionate				
Bath				
Other bath	—	—	—	10[c]
Noncoloring hair care products				
Conditioners	—	—	—	3–5
Permanent waves	—	—	—	0.3
Shampoos	—	3	—	8
Tonics, dressings, etc.	—	2	—	—
Other	—	2	—	—
Total uses/ranges for Sodium Cocoamphopropionate	—	7	—	0.3–10
Disodium Cocoamphodiacetate				
Baby Care				
Shampoos	—	1	—	2–7
Other	—	7	—	—
Bath				
Oils, tablets, and salts	—	1	—	—
Soaps and detergents	—	7	—	2–9
Capsules	—	1	—	—
Other bath	—	6	—	4–8
Eye makeup				
Eye makeup remover	—	15	—	0.005–0.8
Mascara	—		—	0.05

(Continued on next page)

TABLE 6
Historical and current cosmetic product uses and concentrations for Sodium Cocoamphoacetate, Sodium Cocoamphopropionate, Disodium Cocoamphodiacetate, and Disodium Cocoamphodipropionate *(Continued)*

Product category	1989 uses (Elder 1990)	2005 uses (FDA 2006)	1989 concentrations (Elder 1990) (%)	2006 concentrations (CTFA 2006) (%)
Noncoloring hair care				
Straighteners	—	1	—	—
Permanent waves	—	8	—	—
Shampoos	13	82	>1–50	2–8
Hair coloring				
Dyes and colors	—	1	—	—
Rinses	—	—	—	5
Shampoos	—	4	—	—
Makeup				
Foundations	—	—	—	0.0006
Lipsticks	—	—	—	5
Personal hygiene				
Feminine deodorants	—	—	—	0.09
Other personal hygiene	—	5	—	0.05–2[d]
Shaving products				
Aftershave lotions	—	1	—	—
Shaving cream	—	1	—	—
Skin care				
Cleansing creams, lotions, etc.	10	36	≤0.1–25	0.5–12
Depilatories	—	—	—	5
Face and neck skin care	—	3	—	0.03
Foot powders and sprays	—	—	—	0.2
Moisturizers	—	2	—	—
Night skin care	—	—	—	0.06
Paste masks/mud packs	—	7	—	—
Skin fresheners	—	2	—	—
Other skin care	—	2	—	0.04—10
Suntan				
Suntan gels, creams, liquids and sprays	—	—	—	0.004
Other suntan	—	1	—	—
Miscellaneous other cosmetics[a]	7[a]	—	≤0.1–10[a]	—
Total uses/ranges for Disodium Cocoamphodiacetate	30	194	≤0.1–50	0.0006–12
Disodium Cocoamphodipropionate				
Baby care				
Other baby care	—	1	—	—
Bath				
Soaps and detergents	—	3	—	8
Noncoloring hair care products				
Conditioners	—	14	—	0.2
Sprays/aerosol fixatives	—	—	—	1
Shampoos	8	27	>1–25	15
Tonics, dressings, etc.	-	4	—	0.8
Other bath	7	15	>1–25	—

(Continued on next page)

TABLE 6
Historical and current cosmetic product uses and concentrations for Sodium Cocoamphoacetate, Sodium Cocoamphopropionate, Disodium Cocoamphodiacetate, and Disodium Cocoamphodipropionate *(Continued)*

Product category	1989 uses (Elder 1990)	2005 uses (FDA 2006)	1989 concentrations (Elder 1990) (%)	2006 concentrations (CTFA 2006) (%)
Hair coloring				
Dyes and colors	—	3	—	0.008
Personal hygiene				
Other personal hygiene	—	—	—	0.5[e]
Skin care				
Cleansing creams, lotions, etc.	2	5	>1–10	7
Total uses/ranges for Disodium Cocoamphodipropionate	17	72	>1–25	0.008–15

[a]Category previously used which does not correspond to any current categories.
[b]Baby cleansing gel.
[c]Shower gel.
[d]Perineal wipe (0.05%); feminine wash (2%).
[e]Perineal wipe.

of ≤1% to 5% (Elder 1990). Data provided to FDA in 2006 indicated that Diazolidinyl Urea was being used in 756 products (FDA 2006). Current use concentration data from a cosmetics industry survey indicated that Diazolidinyl Urea was being used in cosmetics at concentrations ranging from 0.00003% to 0.5% (CTFA 2006). Ingredient use and concentration data are included in Table 7.

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

Diazolidinyl Urea is a formaldehyde-releasing preservative, and the presence of free formaldehyde in cosmetic products preserved with this ingredient was addressed in the original discussion by noting that, due to the skin sensitivity of some individuals to formaldehyde, this ingredient should be used at the minimum effective concentration (not to exceed 0.2%) and that there was no indication that the use of Diazolidinyl Urea as used in cosmetic products would release formaldehyde at concentrations that would exceed the limits recommended for formaldehyde (Elder 1990).

In a presentation at the December 4–5, 2006, CIR Expert Panel meeting, Dr. John Merianos, with International Specialty Products, reviewed the chemistry of formaldehyde releasing preservatives. He emphasized the fundamental equilibrium that exists between these compounds and free formaldehyde itself, resulting in a steady state of availability of formaldehyde in aqueous solutions. Knowing the chemistry, he suggested, allows a calculation of the amount of free formaldehyde, which exists in a low balance. For example, at a use level of 0.6% Imidazolidinyl Urea (aq.), the steady state concentration of free formaldehyde is only 0.23 ppm, and for Diazolidinyl Urea at 0.5% (aq.), the level of free formaldhyde is only 0.40 ppm. Dr. Merianos concluded that not all formaldehyde releasing preservatives are equivalent, but, in all cases, the level of free formaldehyde is sufficiently low that maximum use levels of the preservatives cannot result in hazardous levels of formaldehyde.

The Expert Panel recognized that while earlier studies (Elder 1990) indicated that Diazolidinyl Urea was not genotoxic in bacterial or mammalian systems, but acknowledged that more recent genotoxicity data (Pfuhler and Wolf 2002) in which the authors concluded that this preservative is a weak mutagen. The Panel's review of the experimental procedure determined that the assay included a preincubation step that allowed the generation of additional free formaldehyde; this was likely the reason for the weak mutagenic effect.

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Concentration of Use by FDA Product Category – Sodium Lauroamphoacetate

Product Category	Maximum Concentration of Use
Baby shampoos	0.8%
Baby lotions, oils, and creams Not powder	1.1%
Other baby products Baby bubble bath	0.8%
Bubble bath	0.72%
Other bath preparations	1.3%
Eye makeup removers	1.3%
Hair straighteners	0.75%
Shampoos (noncoloring)	0.8-4.4%
Bath soaps and detergents	0.8-5.3%
Other personal cleanliness products	0.8-2.8%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.46-9.9%
Paste masks and mud packs	1.2%

Information collected in 2021

Table prepared September 8, 2021

Concentrations of Use by FDA Product Category – Additions (all have uses reported to the VCRP) to Sodium Lauroamphoacetate Report*

Sodium Arganamphoacetate
Sodium Cocoabutteramphoacetate
Sodium Cocoamphoacetate
Sodium Cottonseedamphoacetate
Sodium Mangoamphoacetate
Sodium Olivamphoacetate
Sodium Stearoamphoacetate
Sodium Sweetalmondamphoacetate
Disodium Cocoamphodiacetate
Disodium Lauroamphodiacetate
Disodium Soyamphodiacetate
Disodium Wheatgermamphodiacetate
Sodium Cocoamphopropionate
Sodium Isostearoamphopropionate
Disodium Cocoamphodipropionate

Ingredient	Product Category	Maximum Concentration of Use
Sodium Cocoamphoacetate	Other baby products	2.8%
Sodium Cocoamphoacetate	Hair conditioners	1%
Sodium Cocoamphoacetate	Shampoos (noncoloring)	0.03-4.5%
Sodium Cocoamphoacetate	Tonics, dressings, and other hair grooming aid	0.56%
Sodium Cocoamphoacetate	Hair shampoos (coloring)	2.1%
Sodium Cocoamphoacetate	Bath soaps and detergents	3.3%
Sodium Cocoamphoacetate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1.6-4.5%
Sodium Cocoamphoacetate	Face and neck products Not spray	 0.93%
Sodium Cocoamphoacetate	Paste masks and mud packs	1.5%
Disodium Cocoamphodiacetate	Baby shampoos	0.9-5.4%
Disodium Cocoamphodiacetate	Other baby products	0.56%
Disodium Cocoamphodiacetate	Bubble baths	1.2%
Disodium Cocoamphodiacetate	Shampoos (noncoloring)	1.4-6.9%
Disodium Cocoamphodiacetate	Tonics, dressings, and other hair grooming aids	2.3-2.7%
Disodium Cocoamphodiacetate	Bath soaps and detergents	2.1%
Disodium Cocoamphodiacetate	Other personal cleanliness products	0.1-3.3%
Disodium Cocoamphodiacetate	Shaving cream	0.99%
Disodium Cocoamphodiacetate	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.77-20%
Disodium Cocoamphodiacetate	Face products Not spray	 3.4%
Disodium Cocoamphodiacetate	Other skin care preparations	0.1%
Disodium Lauroamphodiacetate	Baby shampoos	1.3%
Disodium Lauroamphodiacetate	Other baby products	1.6%
Disodium Lauroamphodiacetate	Eye makeup removers	0.18%
Disodium Lauroamphodiacetate	Other hair preparations (noncoloring)	5.4%
Disodium Lauroamphodiacetate	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.2%

Disodium Wheatgermamphodiacetate	Hair dyes and colors	0.93%
Sodium Cocoamphopropionate	Hair conditioners	2-7.5%
Sodium Cocoamphopropionate	Permanent waves	0.84%
Sodium Cocoamphopropionate	Shampoos (noncoloring)	2.4%
Sodium Cocoamphopropionate	Hair shampoos (coloring)	2.4%
Sodium Cocoamphopropionate	Preshave lotions	2%
Disodium Cocoamphodipropionate	Preshave lotions	1.8%
Disodium Cocoamphodipropionate	Skin cleansing (cold creams, cleansing lotions, liquid and pads)	0.8%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2021
Table prepared: January 10, 2022