Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics

Status:	Revised Draft Report for Panel Review
Release Date:	May 10, 2024
Panel Meeting Date:	June 3 – 4, 2024

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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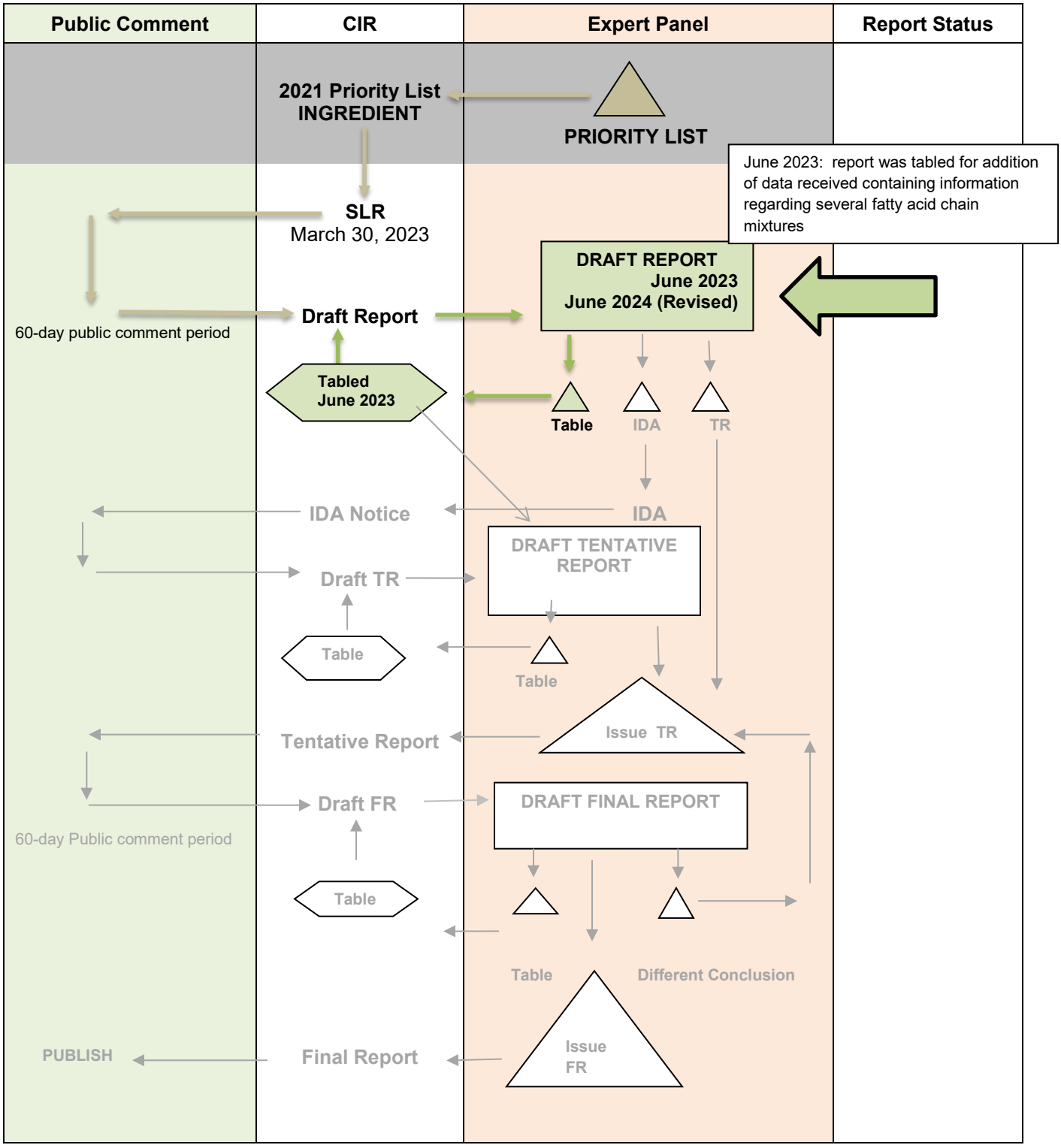
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Fatty Amphocarboxylates

MEETING June 2024



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 10, 2024
Subject: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics

Enclosed is the Revised Draft Report of the Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (*report_FattyAmphocarboxylates_062024*). This report was first reviewed at the June 2023 meeting, at which time the Panel tabled the review due to the receipt of data received in Wave 2. These data include information regarding various fatty acid chain mixtures (amphoacetates C8-C18, amphoacetates C12-14, and amphoacetates C12) that comprise ingredients reviewed in this report, and REACH dossiers for the following substances:

- reaction products of 1H-imidazole-1-ethanol, 4-5-dihydro-, 2-(C11-17 and C17 unsatd. alkyl) derivs. (equivalent to Disodium Cocoamphodiacetate; data in this dossier that weren't previously included in the report has been added, and can be found as highlighted text (please note, however, that these data are on Sodium Cocoamphopropionate and not Disodium Cocoamphodiacetate, according to CAS numbers listed under test substance names))
- sodium hydroxide and 2-propenoic acid and *N*-(2-hydroxyethl)-*N*-[2-[(1-oxooctyl)amino]ethyl]-β-alanine) (potential read-across source)

Accordingly, CIR staff has prepared read-across justification tables for representative mono- and diacetate forms of alkylamphoacetates as well as *N*-(2-hydroxyethl)-*N*-[2-[(1-oxooctyl)amino]ethyl]-β-alanine for analysis by the Read-Across Working Group (RAWG). These documents will be submitted to the Panel for the review as Wave 2, following analysis by the RAWG.

Also at the June 2023 meeting, the Panel noted that the following data (none of which has been received) are needed:

- Dermal absorption data
- DART data on Disodium Cocoamphodiacetate
- Further information regarding the composition and impurities of these ingredients as cosmetics (particularly percentage of actives in ingredients and fatty acid compositions)
- Sensitization data on Sodium Lauroamphoacetate at maximum use concentration

Data that have been incorporated since the last iteration of the report has been indicated by a highlighted X in the data profile. These data include information from the REACH dossier mentioned above and data from reports sent to the Panel via Wave 2 at the last meeting (this information is not in highlighted text as it was previously reviewed by the Panel).

It should be noted that of the 11 ingredients reviewed in this report, 4 (i.e., Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate) have previously been reviewed by the Panel in a report published in 1990 (*originalreport_FattyAmphocarboxylates_062024*); the Panel concluded that these 4 ingredients are safe as used, as described in that report. Furthermore, these ingredients were re-reviewed in 2006 (*re-review_FattyAmphocarboxylates_062024*), at which time the Panel reaffirmed the original conclusion (as published in 2008). Minutes of the deliberations from all the meetings at which these ingredients were previously reviewed have also been included herein (*originalminutes_FattyAmphocarboxylates_062024*).

The following documents are also included in this packet for your review:

- a flow chart (*flow_FattyAmphocarboxylates_062024*)
- ingredient history (*history_FattyAmphocarboxylates_062024*)
- search strategy (*search_FattyAmphocarboxylates_062024*
- data profile (*dataprofile_FattyAmphocarboxylates_062024)*
- transcripts *(transcripts_FattyAmphocarboxylates_062024)*

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 deemed insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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

- Comments received on Draft Report from PCPC
- Analogue approach received from Alkylamphoacetate Consortium suggesting inclusion of data on amphoacetates C8-18, amphoacetates C12-14, and amphoacetates C12; expert review of available DART studies on amphoacetates received
- other data received:
    - Dermal absorption data on dodecylamidopropylbetaine (potential read-across ingredient)
    - EpiOcular assay on Sodium Lauroamphoacetate (4% solids, water)
    - HET-CAM assay on Disodium Cocoamphodiacetate (4% solids, water)
    - reach dossier on Reaction products of 1H-imidazole-1-ethanol, 4-5-dihydro-, 2-(C11-17 and C17 unsatd. alkyl) derivs. and sodium hydroxide and 2-propenoic acid
    - reach dossier on *N*-(2-hydroxyethl)-*N*-[2-[(1-oxooctyl)amino]ethyl]-β-alanine
- Panel reviews Draft Report
- report tabled

April 2024

- CIR staff prepares read-across document for RAWG review
- Panel reviews Revised Draft Report

Fatty Amphocarboxylates Data Profile – June 2024 – 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	XO	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					X	XO											X	XO				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

JUNE 2023 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – June 12, 2023

DR. BELSITO: Okie doke. So, amphocarboxylates. So, I guess that the first order of business with this is are we -- sorry. Amphocarboxylates. So, the first order of business, are we okay with changing the name from amphoacetates to include the propionates? Yes.

DR. RETTIE: I think so.

DR. BELSITO: Okay. And we're happy with the name amphocarboxylates?

DR. RETTIE: Good enough for me.

DR. BELSITO: Okay. And then so basically this was a 2021 priority on how we reported frequency of use for Sodium cocamphodiacetate and then it turned out there were four other amphoacetates. Disodium cocoamphodiacetate, disodium cocoamphodipropianate, sodium cocoamphoacetate and sodium cocoamphopropionate that were up for review soon.

And so that brought it to five ingredients and then there were a bunch of others that we felt we could read across that were in the dictionary hanging out there. So, this created this group of what's now called amphocarboxylates. We had a huge, huge Wave 2 data dump, in part because it appears that the ECHA data on C12 though C14 amphoacetates, C12 amphoacetates and C8 through C18 amphoacetates may or may not have been brought into this document if I have it right.

And so, the question is do we have -- and then as part of that data dump, we were told that there is going to be some DART studies that are coming out, that we would have maybe in 2024 or 2026. There is DART data that -- one DART study that suggests cardiac defects but then this association had someone -- I forget the name of the company -- review all of the DART data and come up with the idea that this was not real and most of the DART data did not show any of those effects.

I think the bottom line is where are we going with this? Are we tabling it so that the writers can go back in and figure out what's duplicative between Wave 2 and what we saw in the original report? If we table it, are we going to wait until we get this additional repo data in 2024, or are we going to just table it to incorporate all the data we have now and see.

Because, quite honestly, from my review and I, obviously, have a huge question to Paul, is what you thought about the DART data and they thyroid effects? Those were the only issues that I really saw.

DR. SNYDER: Well, it's concerning. But, again, if there's additional data with better NOELs and things like that, I definitely want to see them. We should see them. I mean, we typically default to where we don't like to table things because otherwise they go on forever. So, I think we just need to push forward with what we want and what we need.

DR. BELSITO: I guess, but -- well, first there are some questions to us. So, why don't we go through the questions and then we can decide. These are all in Wave 2.

Do we agree that the data are directly applicable to the ingredients under review in this report? And obviously they are. This is the C8 through 18. This is that ECHA data. You didn't think so?

DR. RETTIE: I have a lot of questions about the composition of what we're looking at here, relative to the European read across REACH data. When I read that, the REACH data, in some detail, and it took me a long time. It was quite good, they provided you a synthetic scheme, I looked at the synthetic scheme. It appeared that the synthetic scheme from the European data was the same as what was being used for our ingredients in this report.

In the European data they refer to these -- it doesn't matter which group it is, C12 to 14, C10 to C18. It appeared to me that they were referring to mixtures of the monoesters with some diesters, with some ether products as well in the European set. And they provide you some structures for that. It appeared to me that that was a consequence of the synthetic methodology, and so that's all fine.

In our report there did not appear to be any mention of monoacetate and diacetate mixtures within a given ingredient. And there was no mention of ethers. So just in a very bird's eye view from this, it seemed like apples and oranges.

Are we to take from our report that the purification methodology used here are so superior to the difficulties that it seemed like our European colleagues had in making any kind of fraction, that when I look at the table structures that's a hundred percent that thing, whether it's the monoacetate, I didn't think so. But it's not here and I thought that was --

DR. BELSITO: The ECHA dossiers are coming from companies who manufacture these products, which suggested to me that these are impurities in cosmetic products.

MS. EISENMANN: I believe it's all the same information, they just provided much more information about composition in their submission.

DR. BELSITO: I agree.

MS. EISENMANN: That is in the ECHA dossier that does need to come into the report.

DR. RETTIE: Okay.

MS. EISENMANN: Because they were very specific on what that composition of each material that was tested, and it's going to be hard to determine is it this study and whatever. We're going to have to try to look up -- if they put the trade names into the dossier that might help.

MS. CHERIAN: Sometimes they did and then I -- sorry. When they provided the trade names it was easier to see what they were actually testing. Because I can go back and look at a TDS or an SDS to see what it is.

MS. EISENMANN: Well, and to their submission, too. Because they used the trade names in the submission.

DR. RETTIE: Thanks. That's helpful.

DR. BELSITO: Yeah, I mean, ECHA data is all industry. Industry is submitting it to the European commission to meet REACH documentation.

MS. EISENMANN: I think the consortium that submitted the stuff to our submission is the same group that did the ECHA dossier.

DR. BELSITO: Probably. More than likely.

DR. RETTIE: But for sure our report needs some substantial updating to reflect what we're looking at here. And the language in the document needs to describe that these are mixtures of all of these different chemical components under an ingredient. That's not clear at all from what we're looking at right now.

DR. BELSITO: Okay. So, we are going to incorporate that. Your first question as a yes. And then does the panel feel that the data in the draft report should be altered to reflect the data presented in this submission? Yes. Responses to CIR data. Oh, dermal absorption data on dodecylamidopropylbetaine potential read across ingredient. I had a question to you, Allan, for that.

DR. RETTIE: Well, I didn't feel comfortable with that. The betaine is a quaternary compound, permanently charged, going to have different distribution, I'm sure. So, for that one I would say no. And I understand that the panels looked at betaine derivatives previously in a separate report. And if that were true, I thought that was where they belonged for the betaines.

DR. BELSITO: So, the answer from us is that, no we should not be using this as a potential read across?

DR. RETTIE: Not from me for betaine.

DR. KLAASSEN: I agree with you that the quaternary is a -- that's really different chemistry.

DR. BELSITO: Okay. So, we're not doing that.

DR. RETTIE: But there's three bullet points there, Don. The Betaine's just the first one I'm looking at. There's three questions about the read across there beyond the betaine. There's another two.

DR. BELSITO: Right.

DR. RETTIE: So, the last one, the N-(2-Hydroxyethl, blah, blah, blah, ethyl beta alanine, I thought that one was okay. It's a shorter chain length than the ones we're looking at right here, but it seemed to me that was fair game for read across.

DR. BELSITO: And where are you here, Allan?

DR. RETTIE: I'm on PDF 5.

DR. BELSITO: Okay.

DR. RETTIE: Of Wave 2.

DR. BELSITO: Yeah. Can we just go through the questions in order? Because there are questions before that I thought.

DR. RETTIE: Oh, there are?

DR. BELSITO: Yes.

DR. RETTIE: Apologies.

DR. SNYDER: What page are you on?

DR. BELSITO: I'm still on PDF Page 3. So, we're not going to allow unto -- we're not going with dodecyl amino. And then PDF Page 5. Yeah, okay. Sorry. The question is does the panel agree that the amphoacetate C8 - 18, C12 - 14, and C12 directly correlate with the listed ingredients above? And I think we've settled that, correct? We agree? Um, okay. So now you're up with the read across.

DR. RETTIE: Okay. So, we've done the betaine, we've decided no. Then there's one I'd like to come back to, the second one, because I'm not sure about that one.

The third one is the hydroxyethl beta alanine. That's the one that looks like it's a good read across. It's a shorter alkyl chain length than the ones that are listed, but it looks like a decent read across. They'll be some differences but it's very close. So, I would say okay on the third one.

I'd like to hear what others say about number two. This is an unsaturated group of alkyl derivatives. Maybe it's okay. I'm sort of on the fence about it a little bit. It's a maybe for me.

DR. BELSITO: Don't look at me. I don't have a clue.

DR. RETTIE: Did you have any thoughts about that one?

DR. KLAASSEN: No. Let's see what the other group says.

DR. RETTIE: See what Dr. Ross thinks? I think it could probably be pulled in, but he might have some other comments.

DR. BELSITO: So basically, dodecylamidopropylbetaine, no. N-(2-hydroxyethl)-N-[2-[(1-oxooctyl)amino]ethyl-beta-alanine, yes. And the middle one that I won't read is basically we're going to discuss tomorrow.

Okay. Are the data in the draft report along with information provided in Wave 2 efficient for the panel to determine the safety of the ingredients? If not -- essentially, we're being asked our list. And, I mean, I guess it's always hard. I spent a lot of time -- even though repro isn't my area of expertise -- reading through that whole document that they had that company -- and I'm blanking on the company's name.

DR. SNYDER: Colonial? Was it Colonial?

DR. BELSITO: No, it wasn't Colonial. They had an outside company.

MS. FIUME: Exponent.

DR. BELSITO: Exponent -- yes. Look at all of the data and come up with a conclusion that there were no developmental or reproductive toxic effects. And that this one study where there were cardiac effects on the infants was -- I don't know -- serendipity's not the right word, but asperous. And the other where there was a 300 milligram per kilogram effect on maternal was because something was going on in the thousand milligram group and it ended up killing those dams ahead of time, which gave that NOAEL.

But this is not my area, so I was throwing it back to you because that really seemed to be the only major issue that popped up in reading these about safety. But then they turn around and say that they're doing these huge studies that aren't going to be ready until 2024-2026. And why are they doing them if they have all of -- I mean, there's a good amount of DART data already. And there's just that one study and they had an outside group review it that came up with a conclusion that there were no DART effects from these as used.

So where are we going with this? You know, I mean, are there insufficiencies? Do we want to go ahead and say sufficient as used, but flag this for 2024 and 2025? Because right now there's no opinion on these at all, right, except for the four that we previously had reviewed and said are okay. And one of those is an ingredient in question in terms of a DART effect.

I mean, I've never been faced with an issue like this where the data looks clean but then they're promising to do these two other studies that are dangling out there.

MS. FIUME: So, Don, I'm not sure if it's the same company. But if it is, it's been since 2020 that we've been told that we'd be getting the DART studies. So, it's been almost three years and we haven't received those studies yet. And I don't know if that matters in your consideration on how to handle the report, but it's been since 2020 that we first received an email saying that DART studies would be ongoing.

DR. BELSITO: But it's entirely possible, like many other studies, that they were delayed because of the pandemic.

DR. SNYDER: So those additional studies, are they DART studies? Do we know?

DR. BELSITO: Yes.

DR. SNYDER: They wouldn't be running DART studies if they didn't --

MS. EISENMANN: One's a rabbit. So, they haven't done any rabbits. All of them are in rat and then there's the one gen.

DR. SNYDER: Okay. I mean, I tried to go to that Reference 4, and they don't have it -- I can't see that study. It's that ECHA dossier, so. Do we have that actual study that is referenced to --

DR. BELSITO: With the cardiac effects?

DR. SNYDER: Yeah.

MS. FIUME: If it was an unpublished study we only have the summary information that's in the dossier.

DR. SNYDER: Yeah.

DR. BELSITO: Yeah.

DR. KLAASSEN: I mean, these DART studies don't take five years. I mean, they're relatively short studies. Why it's taken them two or three years already and they're saying another couple years.

DR. SNYDER: It can take quite a long time, I mean, to get them finalized. Yeah, because they're big datasets and it just takes time. Yeah. It doesn't take long to run the study, but to finalize it and to end up with the conclusion, particularly a NOAEL and things like that, so.

DR. BELSITO: I mean, COVID has significantly affected, obviously, human clinical studies much more than animal studies, but it's affected everything. I mean, the labs at Columbia were essentially closed for 18 months. You know, animals died because they weren't tended to.

Some of these basic researchers essentially had to restart their lab all over again. So, they lost -- they had 12 - 14 months and then it took them another 12 months to get retooled. I mean, that doesn't bother me. If we were told in 2020, and we're sitting here in 2023, then, yeah, I can accept that it was COVID that did that.

But the question is, is there enough concern that we want that data in the absence of your being able to see that one study and the Exponent review of all the other DART studies that were there? I don't know if you went through all that, Paul?

DR. SNYDER: I did not because it came in a Wave that was --

DR. BELSITO: So, maybe the best approach here then is to table this. To go in and try and sort out what data came in under the ECHA dossiers that may have been duplicated in our original. Put it all together.

You know, have that Exponent -- because I thought that was -- I mean, to me, and it may have been all BS because you could BS me in that DART data, it's not my area of expertise, so I'd like to see what other people think. Bring that response back may be helpful.

There are a few other questions before we end this. So, it -- on PDF page 13 -- again, this is all Wave 2. I just worked off of Wave 2. It says, "it should be noted that these ingredients may contain amidopropyl dimethylamine." And then they said, also known as amidoamine. And the response from the manufacturer was that this was not -- amidoamine is not amidopropyl dimethylamine but dodecylamide N12 2-hydroxyethl amino ethyl. So, Allan, is that true?

DR. RETTIE: I did not read that far into Wave 2. Unfortunately, I went through Wave 1, so I can't answer that one right now.

DR. BELSITO: Okay. So that would need to be addressed.

DR. RETTIE: Yeah.

DR. BELSITO: I have a note that the composition impurities need to be updated based on the REACH registration, which I think is probably more accurate than what we had. But it's a good point, Monice, about matching up the trade names.

On PDF Page 15 -- again, I'm working all off of Wave 2. I was fortunate enough not to do this until Wave 2. So, PDF 15 of Wave 2, Priya, it's the fourth line down where we're talking about sodium lauroamphoacetate. You have 183 rinse off's and 17. It should be leave-ons, not rinse-offs.

And of note, there are new uses for these in baby products, so as you go over that. I don't know that I had any other comments. Thanks, Curt.

Oh, Wave 2, PDF 20. The third line from the bottom. If you could just check, Priya. It says, "patch testing was performed in 40 healthy volunteers and 488 topic subjects (affected by atopic dermatitis, psoriasis, or eczema). I mean, did they mean dermatitis subjects because, otherwise, they should've all had atopic dermatitis? Yeah.

MS. CHERIAN: I'll double check.

DR. BELSITO: Yeah. And the other thing to look into when we see this again, Paul, is this thyroid effect that I didn't think was real. But, okay. So, we're going to table it and what do you think, Monice, in December we'll see this again or --

MS. FIUME: I guess it depends on if we hear back. So, I have a question before you table it. So, is DART the only data need you have? I know there's questions about it but are there other additional data needs that if once the data that we received in Wave 2 get incorporated --

DR. BELSITO: Yeah. I actually went through it, and based upon my review of the Exponent analysis, and I was hoping to hear from Paul, I thought we could go safe as used when formulated to be non-irritating. That was my opinion.

Again, because I looked at what was reported or the Exponent analysis which seemed to be independent of this manufacturing group. So, I had no other data needs assuming that everyone was fine with the DART. But that was just me.

MS. FIUME: Okay. That's what I wanted to check.

DR. KLAASSEN: Exponent is a respectable company, so.

MS. EISENMANN: And it was John DeSesso who wrote it?

DR. SNYDER: Yeah. Yeah.

DR. BELSITO: Pardon?

DR. SNYDER: Yeah, I just didn't get that deep into that 115 data dump. I mean, it was just a huge data dump and I had already moved on to other ingredients. So, I can look at that tonight and if what they're reporting in that report, if I can agree with it, I think we can basically do what you say and go safe as used when formulated to be non-irritating.

DR. BELSITO: Okay. Why don't you do that, Paul.

DR. SNYDER: I mean, I still have some concerns why they're doing additional DART studies.

MS. EISENMANN: My guess is that ECHA required them.

DR. SNYDER: Okay. So that -- okay.

DR. BELSITO: Yeah. Because of that one study. Despite all the other negative studies. I mean, Europe has gotten very tough because they are moving very rapidly towards hazard-based. And genotox and reproductive tox, endocrine disruption, it's like there's no managing that hazard. You know, it's becoming very difficult. So that's -- yeah, they probably have accepted the fact that there was something spurious with that study, but they wanted some additional studies. You're probably right, Carol.

MS. FIUME: And, Don, in answer to your question on when it will come back, we'll just look at how it balances with the rest of Priya's workload and the other reports to see which report is better --

DR. BELSITO: Yeah. You got creamed.

MS. CHERIAN: I know. Lucky me.

MS. FIUME: Sorry. So, it's whether September or December will depend on some of that. Because there's a lot to put in. But knowing that prostaglandins will probably be December, we might try and balance it that way. But we'll have to just wait and see if that's okay.

DR. BELSITO: Yeah. That's fine. I mean, I think prostaglandins are probably more critical from my point of view, because we haven't looked at it and they're coming on the market and we don't know a lot about them. Whereas, these have been on the market for a long time and the data that I've seen, I think looks fairly good with these.

MS. FIUME: So, process wise, that's why it might be able to come back in September because we have those data, we just need to incorporate it. Prostaglandins analogues, we're waiting for additional data and you could put out an IDA, so that's why it'll probably skip a meeting.

DR. BELSITO: Okay.

DR. RETTIE: Can we briefly come back to the question you had about the amidopropyl? It's just clarification so I know what I'm looking up. So, there's a lot of amidopropyl dimethylamines. There's lauro, there's dodecyl. Is this one, one of those? Because if it's the lauro dodecylamine then it's very similar to the dodecanamide and I kind of have a sense of what's going on there. But amidopropyl dimethylamine is not really telling me anything.

DR. BELSITO: I'm sorry, Allan, I'm lost. Where are you and what comment?

DR. RETTIE: I'm back to the comment on Wave 2, PDF 13, the question about the known sensitizer, amidopropyl dimethylamine and the fact that the CAS number is something different.

DR. BELSITO: Okay.

DR. RETTIE: So, I'm just trying to get my head around the question, really. Amidopropyl dimethylamine is a little compound. Dodecanamide is a big compound. But when I try to find the amidopropyl dimethylamine, up comes a lot of different fatty acid chain lengths associated with that term.

So, there's a lauro one, there's an octododecyl one, and I'm suspicious that maybe they mean one of those. And maybe the lauro makes more sense. I just need some clarification.

DR. BELSITO: Yeah. Well, what I can tell you is that amidoamine is a starting material for the production of cocamidopropyl betaine. And when we were discussing that there are skin sensitization issues related to cocamidopropyl

betaine, and the question has been raised whether it's due to residual contaminants of amidoamine or dimethylaminopropylamine, DMAPA, which is formed to a lower extent during the production of cocamidopropyl betaine or whether it's the actual molecule itself.

And that came into our discussions, and I believe that our conclusion with cocamidopropyl betaine was formulated to be non-sensitizing with QRA or some other methodology. In our discussion, the issue of the impurity, the potential amidoamine or DMAPA impurities. That's my recollection and that's why I presume this was coming into play here. So, again, it's before your time so it's sort of thrown out of context, I know.

MS. FIUME: So, I believe the original reports on one of the original ingredients mentioned that aminopropyl dimethylamine -- let me make sure. Did this come from the original report -- no this was in a data sheet. It says amidoamine is an impurity. And so we flagged it as amidopropyl dimethylamine. Do I have that right?

MS. CHERIAN: Right.

MS. FIUME: Which according to the cocamidopropyl betaine report, is a sensitizer. The comment from the reviewer that submitted comments, they said that the MSDS refers to amidoamine which is not amidopropyl dimethylamine, but dodecanamide N-22 hydroxyethyl aminoethyl based on CAS number.

And so, what they're saying is that there's no skin sensitization available so it's not appropriate to call it a sensitizing impurity. If that makes sense. I think that's what I understand from it.

DR. RETTIE: So, their question's around just removing that language.

MS. FIUME: Right. Are we flagging it correctly as a possible sensitizer, impurity?

DR. BELSITO: So, they say that amidoamine is an impurity in their product, is that it? Because it says Reference 7, MSDS, refers to amidoamine cast, dah, dah, dah, dah, dah, which is not aminopropyl dimethylamine, but dah, dah, dah, dah, dah.

For this substance, and I didn't understand what this substance was, I presumed it was dodecanamide. It says no public information on skin sensitization is available, because quite clearly public information on skin sensitization of amidoamine is available because many patch test groups, including the North American, patch test with it and we see positive results. So, I don't know what they were referring to there.

MS. FIUME: Yeah. So, the MSDS is on sodium lauroamphoacetate. But since this tabled, we will delve into it to make sure that we have the correct impurity flagged and whether or not sensitization data is available on it. We'll take a look into the comment, and then when it comes back after the table, we'll have it clarified, if that's acceptable to the panel.

DR. BELSITO: Yeah.

MS. FIUME: Since there's so much question about exactly what it is.

DR. BELSITO: Mm-hmm.

DR. RETTIE: So, it was very helpful. I don't want to beat this to death, but what was very helpful in the ECHA documents was quite a reasonably clear picture of what their fractions contained, you know, all the way down to different percentages of the different fatty acids that were present in whatever you were starting from. Whether it was this coca product or not.

What we definitely don't have here, and what I think is pertinent to what we're talking about now when you bring up dodecanamide, and we've got saturation in the side chain, and then that comes back to whether we should include the second bullet point product and read across from an earlier question.

I'd just like to know what we know about the R groups for all the ingredients listed in Table 1. Maybe to the extent we can do that relative to how the ECHA document said about it. I did read the ECHA document, I didn't read all the Wave 2 because it came in late.

MS. FIUME: So, I think what happened, and Priya please jump in in case I have the history wrong. In trying to go through this ECHA dossier when they have those different chain lengths, they'll have three dossiers that actually have often the same information in each one and it's listed as read across or supportive data to the other. But I think what was done was we were trying to identify a one-to-one match, the ingredient to the chain length given, and didn't bring in those others. Do I have that correct?

MS CHERIAN: Right.

MS. FIUME: So, when they have the different chain lengths, sometimes it's difficult to figure out do they actually correspond to one of the ingredients or is it just equal to the general chain length? And I think that's what we tried to do on the first round, was to try to find the one-to-one match. So, we will bring in the rest of the information, and it may come into the report as a general chain length rather than a link to the specific ingredient, but to provide the information for you to use in the report overall.

DR. BELSITO: But we know that in general, I think, if you go back and look at the cocamidapropyl betaine report, you know, when you're getting into the coco derivatives, the chain lengths are not going to be uniform, they're going to be C12 to C18.

And we know from other reports that there's -- I mean, when you're looking at Peg 3 there's some Peg 2 and some Peg 4. When you're looking at lauro there's going to be -- you know, lauro theoretically is C12, but there's going to be some other chain lengths in there. It's not going to be pure.

And I think that's what you were seeing with the ECHA dossier. They were reporting a product that was lauro, but it was C10 to C12 or C12 to C14. But it's what they marketed as lauro.

MS. FIUME: So, we'll go back, and we'll readjust it I think. Like I said, I think they were trying to target. Now, my other question then -- question number two, if that's okay. When we received the information it was interesting because the one dossier says -- what's it called -- rationale for read across for REACH. Because they were giving chain lengths and they wanted it to read across to the different ingredients, which we've determined are probably actually are same ingredients, so it's not read across.

That middle point in the question two in Wave 2, that is a true read across. It doesn't look like it matches to our ingredients.

DR. RETTIE: See, that's my question.

MS. FIUME: We don't know that for sure. Okay.

DR. RETTIE: I'm not sure I know that for sure because everything that we've talked about for these acyl side chains so far, has been, I understand, for saturated fatty acids. And now the notion of maybe there's some unsaturated fatty acids out there that might be relevant, I don't know that.

So I think there's -- I mean, it's not a big difference. There are differences between unsaturated fatty acids and saturated fatty acids, certainly in the way the body deals with them. So, my main question was do we have any unsaturated fatty acids in our ingredients, if we ever get a composition to that level of detail?

And if we did, then I think bullet point two would be a read across, without any chatting with Dr. Ross.

MS. FIUME: So then, if it is then read across and not a match to the ingredient, my question was going to be in the past we've said if we have information on an endpoint we don't do read across. But would it still need to be brought in because it might -- based on chain length versus the actual ingredient?

DR. BELSITO: Which specific -- I mean, because I'm, again, lost. Where are you? PDF?

MS. FIUME: Let me find out which page.

DR. BELSITO: Is this Wave 2?

MS. FIUME: Yeah. So, Wave 2 in the memo, it's PDF Page 5, Question 2.

DR. BELSITO: Okay. This is was the read across question again.

MS. FIUME: So those last two bullets, if they're truly read across but you have the exiting --

DR. RETTIE: I think the last one's read across.

MS. FIUME: Okay.

DR. RETTIE: But I think bullet point two might be a match.

MS. FIUME: Might be a match.

DR. RETTIE: Might be a match if we know whether they're saturated or unsaturated fatty acids are in our ingredients, and we don't know that.

MS. FIUME: Okay.

DR. RETTIE: I suspect they are, but.

DR. BELSITO: I mean, the question is where do they want the read across? This may be weight of evidence to support -- I don't know where this is specifically going to go in. But where normally you might be looking at a read across is this one questionable DART study, and you have a bunch of other DART studies on your products that are negative, and you want to bring in some additional weight of evidence on read across materials. So that may be what they're looking at, in which case it would be helpful.

I mean, the more negative studies we have, if we have this one study with severe cardiac effects. It didn't say mild, right, they said severe. You know it might be nice to have as many studies as we can just showing we don't know why this happened in this one study. It seems to be spurious, and we have all of these other studies that are clean.

DR. SNYDER: What's our maximum concentration of use?

DR. BELSITO: It is 20 percent in rinse off and 5.4 percent in leave ons I believe.

MS. FIUME: And that's in other hair preparations.

DR. SNYDER: Thank you.

MS. FIUME: As far as dermal --

DR. BELSITO: I think it was 5.4.

MS. FIUME: The 5.4 is a hair --

DR. BELSITO: Okay.

MS. FIUME: -- preparation. I'm trying to think of what the dermal is. Do you have that handy?

DR. BELSITO: I didn't write it down here. It's in my notes but I have so many notes on these.

MS. FIUME: Yeah, that's why I keep flipping pages.

DR. BELSITO: I've never had so many sticky notes on one.

DR. RETTIE: I've got a 1.6 for dermal contact for disodium laurodiacetate, 1.6. No, I got 9.9 for disodium lauroamphoacetate for dermal contact.

DR. BELSITO: "Use 20 percent in a cleansing product, 5.4 in hair preparations, 1.3 in an eye makeup and 5.4 in baby shampoos." That's what I tagged. So, 5.4 in other hair preparations wouldn't be considered leave on.

MS. FIUME: It's leave on. I would just not -- I always classify that as dermal.

DR. BELSITO: Right. Okay.

MS. FIUME: And I didn't know if Paul wanted to know what the actual dermal contact was or --

DR. BELSITO: Yeah. Dermal contact -- what table is this in?

DR. RETTIE: I got Table 5.

DR. BELSITO: Yeah. This was fun.

MS. FIUME: It is used in other baby products at 1.6 percent.

MS. CHERIAN: And I think that's the highest dermal.

DR. BELSITO: I think I'm getting punchy.

MS. FIUME: It's too early. Yeah, so.

MS. BENNETT: Yeah, way too early, we haven't gotten to yeast yet.

DR. BELSITO: Oh, I know.

MS. FIUME: Oh my gosh, Priya.

DR. SNYDER: Well, this is the poster child of why we can't get these data dumps late in the game. Because this one is a clear result. It's just a lot to get through.

MS. FIUME: And we knew that, that's why we wanted to throw right out front that, do you want to table it because you think it's going to be okay? Or if you had additional IDA, we'll add that in but then bring it all back, so.

DR. BELSITO: You know, we'll see what Paul says after he reads.

DR. SNYDER: I've read the summary and the conclusion exactly. I mean, they did as thorough as I could possibly do in reviewing that data.

DR. BELSITO: Came to the conclusions --

DR. SNYDER: And the doses are very high. That's why you asked what's the concentration of use because they were at very high doses. And so, I do have some level of comfort with it on my initial review.

DR. BELSITO: I think we'll come in as safe as used when formulated to be non-sensitizing.

MS. FIUME: After it comes back from the table?

DR. BELSITO: Right. I don't have any additional data needs, and there's so much data here.

DR. SNYDER: The thyroids cup is not -- it's not --

DR. BELSITO: Okay. Let me just -- so we are tabling it just for organization. Is that a good word? No data needs currently. Likely safe as used when formulated to be non-irritating.

DR. RETTIE: So, you're presenting that tomorrow?

DR. BELSITO: Pardon?

DR. RETTIE: You're presenting that one tomorrow?

DR. BELSITO: I don't know. I haven't gotten that far.

DR. RETTIE: Oh, I have. You are.

Cohen Team – June 12, 2023

DR. COHEN: Amphocarboxylates. So, this is a draft report and this assessment is for 11 derived ingredients that are used as hair conditioning agents and surfactants. These are frequently used. Cocoamphodiacetate has the highest concentration of use in a rinse off product at 20 percent. And Disodium Lauroamphodiacetate has the highest concentration of the Leave-on product at 5.4 percent in a hair product.

It was noted that four related ingredients were reviewed by the Panel in 1990 and re-reviewed in 2008. That was the Disodium Cocoamphodiacetate, the Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate and the Sodium Cocoamphopropionate. And they would soon be considered for re-review.

Even though I think this was a draft report, we got to see it twice because in Wave 2, we got a large data load and a very large report. Of note, there was a mention of amidoamine as an impurity in Disodium Lauroamphodiacetate, which is an important sensitizer.

We have some irritation at sensitization. And we have some data on guinea pig maximization tests, but there's still some data needs. And, again, we have this large Wave 2. So, why don't I open it up for comments and then we can organize our thoughts for what our needs are. Tom, you want to start?

DR. SLAGA: Yes. Four of the ingredients, as you mentioned, were reviewed before and found safe and they were up for re-review. And so, they've been added to this report. And that's where most of the data is. Very little other data for the other. So the question is, can we read across from these four to the remaining ingredients and come up with a safe that way?

DR. COHEN: Yep. That was a question, what you guys think about read across on these?

DR. ROSS: Yeah, I got to the wrong page. This can't be right.

DR. SLAGA: It looks to me that it could be used for read across.

DR. COHEN: Wasn't there a comment about excluding the amphopropionates at one point?

DR. ROSS: There was some specific questions. Does the Panel agree that the data on the amphoacetate C8-18, amphoacetate C12-14, and amphoacetate C12 directly correlate to the ingredients above.

Second, should the data on the following potential read across sources be included in the report? Dodecylamidopropylbetaine, reaction products of 1 H-imidazole-1-ethanol -- and I'll leave the rest of that. And N-(2-hydroxyethl), (1-oxooctyl)amino]ethyl]-beta-alanine. So my reads on that specific Question 2, I don't know if you can read across from dodecylamidopropylbetaine, that's a zwitterion.

I mean, these things can be zwitterionic, but they're not necessarily in resting. I think you can read across from the reaction products of the imidazole and you can probably read across from the ethyl alanine.

With respect to the first question, yes, I think you can read across from the amphoacetates C8-18 and C12-14 to the appropriate structures. The betaine I don't know about. I don't know what other people's opinions, but if you just want to -- that's speaking to the read across. It's a long list of read across here. And, you know, my comments on this document were, if we do read across, it would be really nice to see where the read across came from with respect to the data and the document. Sometimes it's really difficult to look at this data and you don't know where it's coming from. But anyway, that's my comments on the read across. Most of it can be read across, there's maybe one you can't.

DR. COHEN: So, with regard to number one, we're going to include those? The data correlate to the ingredients listed.

DR. TILTON: I think a lot of the data is already included.

DR. ROSS: It is.

DR. COHEN: Well, it -- yeah. And we're okay with it?

DR. TILTON: I agree. Yeah.

DR. COHEN: And what about, Susan, Number 2?

DR. TILTON: I primarily agree with David. And I also don't know about the betaine, but since it's specific for read across for dermal absorption, it seems like we should probably not do that.

DR. COHEN: Probably not do what?

DR. TILTON: Use it for read across for dermal absorption data, for toxicokinetics, bioavailability.

DR. COHEN: It's not okay for dermal absorption and toxicokinetics.

DR. ROSS: That's the betaine, yeah.

DR. TILTON: Yeah.

DR. COHEN: Okay, three are the data in the draft report, along with the information provided sufficient for the Panel to determine the safety of this ingredient. That's what we have to talk about now.

DR. ROSS: Yeah.

DR. COHEN: So does the group feel that there's insufficient data at this point?

DR. ROSS: Yes. For me, I don't know about anybody else?

DR. COHEN: Yeah. So what do you have as a data need?

DR. ROSS: Well, I'd love the data in this document to agree all the way through. There was a lot of conflicting data in this document. And I think that comes from the nature of these compounds. You know, they're abbreviated in the ECHA document. It's UVCB, which is Unknown Variable Composition by materials. And so, I think that's where a lot of our problems are coming from. But despite that, I felt that you needed -- well, let's just go through it.

The DART was new data, the reproductive tox. And there was one study with Disodium Cocoamphodiacetate which showed severe cardiac abnormalities, but without a dose response. It was in all test groups, but without a dose response.

The second study looked just fine. And so, it's hard to know where to go with that. That was the subject of an Exponent consulting report, which was in the document. I think we can talk about whether we need additional DART data on this compound, tested to be the highest purity possible, whether or not that's justified or not.

DR. COHEN: So DART on?

DR. ROSS: This compound would be Disodium Cocoamphodiacetate. It's the first one on the list. That's where you had the two conflicting studies, the cardiac and the visceral malformations in one study and not in the other. So that's my first issue. I thought we should discuss that, whether or not we needed it. The Sodium Lauroamphoacetate, the new compound, if you like, the DART there was just fine.

The other issue was the dermal irritation and sensitization, in particularly, the sensitization with Sodium Lauroamphoacetate. It's fine with the other original four compounds that were in the previous document. But there was no -- the only HRIPT data I could see was at 0.5 percent, the Sodium Lauroamphoacetate.

DR. COHEN: And this goes to (inaudible). And this is way below max use.

DR. ROSS: Max use is 9.9 percent. So yeah. And then, ocular I think is okay since we've got 5 percent and max is 1.3 percent. So, I guess it's HRIPT on Sodium Lauroamphoacetate and this issue of the DART. That's my summary on it.

MS. CHERIAN: We are expecting more DART data, I think by 2024, 2026. Bart, do you remember?

DR. ROSS: Yeah, that was another comment I had. It's coming, but I don't know if you want to wait that long.

DR. COHEN: Will it be within the two year window of this report? So, I don't know. Does it matter if it comes in safe?

DR. ROSS: Yeah, my dates say April 24, and then generic 2025. Oh, just while I'm talking here. Exponent, you know, in their report they did have additional rats that they -- rat citations that they considered that we didn't have in a report.

MS. CHERIAN: Okay. I'll take a look at that.

DR. ROSS: And another one did flag cardiac malformation. That was the Viends, V-I-E-N-D-S, Viends, 2022b. But it was very low incidence and I feel it should be in.

DR. TILTON: So I had also noted missing dermal absorption data and information on toxicokinetics without the read across.

DR. COHEN: Yeah, for the (inaudible)? No? Or are we talking about something else?

DR. TILTON: Well, just that there is no dermal absorption data for any of these.

DR. COHEN: Got it.

DR. TILTON: That was only going to be provided through read across. So in terms of the DART, there were severe cardiac effects noted, but they were independent of those. And I was trying to find where I made this note, but in the Wave 2 it was concluded that those were not treatment-related effects.

DR. ROSS: That was in the Exponent consulting report.

DR. TILTON: Oh, okay.

DR. COHEN: How did they come to that conclusion?

DR. ROSS: I think it was primarily because there was no dose response.

DR. COHEN: What if you're above the dose from the lowest dose?

DR. ROSS: That was their conclusion.

DR. COHEN: Okay.

DR. ROSS: And it may be a reasonable conclusion. Usually you're looking for some sort of dose response. But yeah, there are times when you may not see it.

DR. COHEN: Retinoids don't have a clear dose response to teratogenicity.

DR. ROSS: I mean, it was a flag -- it was that one study plus the additional study in the reports. And the other study was clean, so just how you interpret that.

DR. COHEN: And the control group didn't have them, right?

DR. ROSS: Correct.

DR. TILTON: That's correct.

DR. COHEN: So that's a rub. Okay. So we're going to have an IDA, right? Tom, you have a list of insufficiencies that you want to list.

DR. SLAGA: If you're talking to me, you broke up.

DR. COHEN: Yeah. Everyone here, for an IDA, has some things they want to add. Do you have anything in particular you want to enumerate? Because It's time that we just get --

DR. SLAGA: Yeah. Well it’s no problem because it's a draft report. So, IDA is fine.

DR. COHEN: Yeah. Any specifics?

DR. SLAGA: (Inaudible) some of them can stand alone.

DR. COHEN: Okay. And items in particular? Or we will run through the group and then you can add on from there. All right, Susan, let's just make sure I have it down so I can present in a coherent way. What were the data needs?

DR. TILTON: I had added that we were missing dermal absorption data. I also made a note that it would be helpful to have clarification regarding the percentage of the ingredients in the finished products.

DR. COHEN: Just point me to a specific location for that comment.

DR. ROSS: It's composition and impurities.

DR. TILTON: Yeah.

DR. SLAGA: Since the data on irritation was very mixed, we may want to address that with asking for more irritation data.

DR. COHEN: Yeah, that's on my list too. Okay.

DR. ROSS: David, I think you have to ask for the compounds at the highest purity possible. because That's one of the reasons we're getting variable data.

DR. COHEN: 30 to 60 percent of active agreements. So, how do we articulate that ask?

DR. ROSS: Very straightforwardly.

DR. BERGFELD: I think you can just ask.

DR. COHEN: No, what are we asking for?

DR. BERGFELD: You talking about irritation studies and what percentage you are asking, or?

DR. COHEN: Oh, no, no, no, no, no. That I -- so irritation and sensitization at max use, right?

DR. BERGFELD: Yep.

DR. COHEN: But the commentary on the purity.

DR. BERGFELD: You have to know the impurities then.

DR. ROSS: Well some of them you do.

DR. COHEN: We have them listed -- we have -- like amidoamine in there. The question is, are we going to comment about this issue?

DR. BERGFELD: We have to comment in the discussion about the nitrosation.

DR. COHEN: Okay, let's continue. Susan, so you want dermal absorption data. What else?

DR. TILTON: I don't know, I think David had a --

DR. COHEN: What else did you have, David?

DR. ROSS: I had the --

DR. TILTON: Sensitizing and max use.

DR. ROSS: I have DARTs. And again, as pointed out, more of that is coming. So, we know that's on the way but we don't have it right now. So, I felt we needed that at the highest purity possible. And then we needed an HRIPT with Sodium Lauroamphoacetate at max use, which is at 9.9 percent. Currently we have 0.5 percent.

DR. COHEN: Well we would take --

DR. COHEN: We would take it any of -- I mean if we're going to do some read across, right?

DR. ROSS: Well, that's the other point I was going to raise.

DR. COHEN: Right? I mean, well, I'll take max use of any of them at this point, at max use.

DR. BERGFELD: When you say highest purity, what are you talking about? Are you talking about the use?

DR. COHEN: That was the word I was trying to dig in on before.

DR. ROSS: Yeah. I was concerned that some of the issues we're seeing with variable data as related to the impurities. I don't know that for a fact.

DR. COHEN: You mean the irritation?

DR. BERGFELD: The DART you're seeing?

DR. COHEN: Or the DART?

DR. ROSS: Yeah. The DARTs. And Exponent, in their review, had a reasonable hypothesis. It didn't pan out to be correct, but they had a reasonable hypothesis that it was due to one of the impurities. That wasn't the case, actually. But, you know, given the numbers of impurities in these materials, it was a reasonable thing to consider.

DR. COHEN: What impurity would cause cardiac abnormality?

DR. ROSS: It was the EC- --

DR. COHEN: I don't remember.

DR. ROSS: Yeah, AEEA, in the Exponent report that they considered.

DR. COHEN: I guess the issue is, are the impurities present in the commercial product? And if they are, it's immaterial, it's a problem. Right?

DR. ROSS: They did some studies on the AEEA and it wasn't responsible for the cardiac malformations. At least it was higher dose than --

DR. COHEN: Okay.

DR. ROSS: At least that's my recollection of the conclusion of the Exponent report.

DR. COHEN: Okay.

DR. ROSS: And I'll just pull it up to make sure I'm quoting it correctly. Wave 2 --

DR. COHEN: All right, so I have dermal absorption data, DART, some of which is forthcoming. It's going to be hard to -- I don't know how to deal with that, specifically, except, you know, in the future we'll have that. And irritation and sensitization at max use. Anything else?

DR. BERGFELD: I know that we say that, but we accept anything.

DR. COHEN: I didn't specify which one.

DR. BERGFELD: Okay.

DR. COHEN: It's tricky when we have them all in the same report, right. We've never said that we need one of them at a very specific concentration, right?

DR. BERGFELD: I think we have.

MS. CHERIAN: We do.

DR. COHEN: We have?

MS. CHERIAN: Yeah.

DR. COHEN: So, then we'd want to use --

MS. CHERIAN: I think if we're missing a specific datapoint.

DR. ROSS: I think, you know, my read of the data here was we had HRIPT on the majority of the most frequently used compound and max concentration. I just have to read my notes here in terms of --

DR. COHEN: In the Wave 2 report?

DR. ROSS: Well, it came from the original review.

DR. COHEN: I got to go back to that.

DR. ROSS: So, Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate and Sodium Cocoamphopropionate. But, yeah, you've got sensitization there, I think, at max use. The only one that was missing for me was that Sodium Lauroamphoacetate.

DR. COHEN: What PDF are you on?

DR. ROSS: I'm on Page --

DR. TILTON: Page 19 of the Wave 2.

DR. COHEN: Page 19 of Wave 2.

DR. ROSS: Actually, I was deep in my notes, so I can't give you a PDF page.

DR. COHEN: These are clinical case reports and --

DR. TILTON: Or 18.

MS. CHERIAN: 17, I think.

DR. TILTON: Or 18.

DR. ROSS: So sensitization at max.

DR. COHEN: 10 percent.

DR. ROSS: Yeah, 10 percent on -- 5 percent on the propionate.

DR. COHEN: You know what, I read the other report, I think. Okay. Hold on a second.

DR. ROSS: I think the other report cleared those four compounds, the Sodium Lauroamphoacetate.

DR. BERGFELD: Right. A lot of stuff on that.

DR. COHEN: No, that would do it. So, should those be in the tables later on, on the dermal sensitization?

DR. ROSS: Yeah. That's all data, we don't usually put that in.

DR. HELDRETH: It can be. If the Panel is going to rely on the old data for their discussion, then we can bring it forward. Historically, we've not brought data from an old report in to it, unless the Panel relied on it for their current conclusion. So, if this is the data that will be relied on to clear sensitization and/or irritation then, yes, we can bring it forward in the other table.

DR. COHEN: Yeah, I guess I didn't take it as gospel until I got you guys to tell me that it was probably okay to use that. I'd be okay with that.

DR. HELDRETH: You know, the beauty of the Cocoamphoacetates is that as constituents, you have all the chain lengths between 8 and 18.

DR. COHEN: I thought Coco was 12 to, like, 16. You'll have lauros in there as well? Maybe not -- lauro's 12, right? Lauro is 12. But I thought Coco is like 12 to 16, not 8 all the way up.

DR. HELDRETH: I'll have to look at the table.

DR. ANSELL: That's what I remember as well. That lauro is a part of Coco, but --

DR. COHEN: Right lauro is the bottom of the coco and then it goes up to like 16. Maybe I've heard 18, but I thought it was like 16.

DR. HELDRETH: So, Table 3 on PDF page 36.

DR. COHEN: Are we on Wave 2 or wave --

DR. HELDRETH: In the report. So, it's in the draft report.

DR. COHEN: What, what --

DR. HELDRETH: PDF Page 36, Table 3.

DR. COHEN: Page 36.

DR. HELDRETH: You'll see the fatty chain lengths that come from cutting coconut -- or I should say -- not cutting it.

DR. COHEN: Chain length distribution.

DR. ANSELL: Coco is supposed to be out there?

MS. BURNETT: I don't know if it helps, but I have CAPB open and this is the fatty acid profile for CAPB.

DR. COHEN: Okay. Betaine is C8 to C18. That's a huge swath.

DR. ROSS: Big group.

DR. COHEN: It's very compelling. I'm okay with that. That really kind of swayed me.

DR. HELDRETH: Many of the single chain length names, when we're talking about cosmetic ingredients, they're derived from coconut. They take coconut and they cut out the chain lengths that they want. And so, not only is it the right length, it's probably from the same source.

DR. COHEN: And these are all saturated, right, and some of these are unsaturated, right?

DR. HELDRETH: Oleic and linoleic.

DR. COHEN: Are unsaturated, yeah.

DR. ROSS: And you know, David, we have an HRIPT for Disodium Cocoamphodiacetate.

DR. COHEN: What's that?

DR. ROSS: We have an HRIPT for Disodium Cocoamphodiacetate at 32 percent.

DR. COHEN: Where are you?

DR. ROSS: That's PDF of the reports. Page 29, right, at the top of Page 29. The end of that first paragraph on Page 29.

DR. COHEN: Yeah. Knowing that we can bring this in and it's okay. And we kind of know that the Cocamidopropyl betaine sensitization is probably coming from the amidoamine or dimethylaminopropylamine not the coca betaine itself. I'd be willing to just get rid of that need if we're going to bring this in. And then the question is, do we need the others?

DR. ROSS: Well, it's a first report I think -- well, let's not go that way. I think, yeah, you probably do need some of these requirements.

DR. COHEN: Okay, fine. So, our IDA is for dermal absorption and DART.

DR. BERGFELD: Are you going to add the caveat, and if positive, 28-day dermal?

DR. COHEN: For the dermal absorption data?

DR. BERGFELD: Yeah.

DR. COHEN: If positive. Okay. Yeah, but I think that's very compelling for the sensitization stuff.

DR. ROSS: The old data was quite strong.

DR. COHEN: And it clinically made sense to me.

DR. ROSS: And just when we -- as I said before, when we write this report, again, I don't know how easy this is to do, but if we can -- if we're bringing in read across sources, you know, I went deep into that ECHA document to figure out where this data was coming from. And then I got the Wave 2. And so, if we can identify in this new document where the read across data is coming from, that would really help me at least.

DR. HELDRETH: Do you mean within the ECHA data or do you mean just whether it came from ECHA or somewhere else?

DR. ROSS: If you've got a table which says, you know -- put a superscript there, read across from reaction product in the -- XXXX with Y. So then you know where that read across is coming from, if it is read across at all.

DR. HELDRETH: We have in the past, when there is a fair amount of read across in the report, actually created a read across table that shows, here's your read across sources and it would list the citations, where they came from and which ingredients are the read across targets in the report. And then list under there which tox endpoints.

DR. ROSS: That would help. Yeah. That would help.

DR. HELDRETH: Any directions that you can put in your Panel returns as to which ones are useful for which endpoints will help Priya a lot when she creates that table.

DR. ROSS: Yeah, I've got a few questions to it. And so, that's already in my returns, but I'm happy to help out afterwards.

DR. HELDRETH: Great.

DR. BERGFELD: Haven't we heard what you want, the DART?

DR. ROSS: Yeah. But even to clear the other data that comes in, where's the read across coming from?

DR. BERGFELD: Yeah.

DR. COHEN: Any other comments on this?

DR. BERGFELD: So you're going out for insufficient and your data needs, again, could be stated.

DR. COHEN: Dermal absorption data and if positive, further tox needs. DART, and that's it.

MS. CHERIAN: DART on a specific --

DR. BERGFELD: Okay. The amidoamine, you're putting into the discussion about nitrosation agents. The impurity, amidoamine?

DR. COHEN: In the discussion.

DR. BERGFELD: Yeah.

DR. TILTON: And then the next report will also include the Wave 2 information?

MS. CHERIAN: Yes.

DR. COHEN: Yes.

DR. TILTON: Okay.

DR. HELDRETH: So, you probably won't see this until December, so Priya has time to recuperate.

DR. COHEN: Yeah. That was a big load of info.

MS. CHERIAN: You wanted DART on a specific -- on Disodium Coco or just DART data?

DR. ROSS: The first one on the list where it was conflicting data.

MS. CHERIAN: So Disodium Coco at max concentration. Okay. And then Dr. Tilton mentioned clarification on percentage of ingredient in finished products. Do you want that as part of the IDA as well?

DR. COHEN: Can you repeat that for me?

MS. CHERIAN: Dr. Tilton mentioned it'd be helpful to have clarification on the percentage of ingredients in finished products. Do you want that to be part of the IDA?

DR. TILTON: And I think it was provided as a range, just a general range.

DR. COHEN: How do we word that insufficiency?

MS. CHERIAN: You would say percentage of ingredients as finished products in cosmetics. Because The ranges we have right now are just from TDSs or SDSs and we don't know what those ingredients are used in. So maybe specifically for cosmetics.

DR. COHEN: Wouldn't maximum concentration cover that or no?

MS. CHERIAN: We still wouldn't know the composition of the ingredient itself.

DR. BERGFELD: We never do. Formulations are not our format. We're just doing the ingredients.

DR. COHEN: That's what I'm trying to get my head around.

DR. BERGFELD: Well, you can also talk about the active concentration. If it's being broken down in any way, you'd want to know the active part of it. It's in the formulation.

DR. HELDRETH: So do you mean a concentration of components within one ingredient?

MS. CHERIAN: Right. Within the ingredient. Because this is a -- not of the product itself, but the ingredient within the product, the cosmetic ingredient. It's just an odd scenario because they're all solutions.

So, it could be labeled as Sodium Lauroamphoacetate, but the percent actives within Sodium Lauroamphoacetate kind of varies.

DR. COHEN: I see. And that, how does that influence our conclusion if we just really want to know what the maximum concentration in the final product is? So you're going in with 60 percent in the solution. Isn't that going to be adjusted for in the final concentration of the finished product?

DR. BERGFELD: It'll be diluted. And then you're going to have an active concentration. What the actual --

DR. COHEN: I'm good with the IDA ask, I just don't know how to articulate the IDA ask.

MS. CHERIAN: I understand.

DR. COHEN: Tell me if you guys have a verbiage for it. It's the concentration of the target chemical in the raw material -- in the --

DR. TILTON: Solution.

DR. HELDRETH: It's actually purity.

MS. CHERIAN: Right. It's purity.

DR. COHEN: It's purity?

DR. ANSELL: But isn't that how it's reported based on activity? I mean if it's 60 percent active and you --

MS. CHERIAN: Right. The problem is that we don't have that data for cosmetics ingredient itself, is what I'm saying. So I don't -- so the composition that I have, when it says the range of 30 to 60, I don't know if that's for cosmetic ingredients.

MR. BJERKE: That's how we handle it for Cocamidopropyl betaine.

DR. ANSELL: Yeah.

MR. BJERKE: Percent activity.

DR. ANSELL: Right.

MR. BJERKE: So, we had cosmetic grade, CAPB is supplied with 35 percent solids. CAPB activity is the percent solids minus percent sodium chloride. So then we had an example in baby shampoo. The formulation contains 13 percent CAPB raw material. CAPB activity of the raw material is 30 percent. So then the CAPB activity and the shampoo was 4 percent. So as long as we know what the activity is, then we can dial down to what the actual exposure is. So I think activity is the appropriate way to ask the question.

DR. BERGFELD: So active concentration?

MR. BJERKE: That's right.

DR. BERGFELD: Active concentration you're asking for.

MR. BJERKE: Or percent activity in --

DR. COHEN: Active concentration in cosmetic grade material?

DR. BERGFELD: Well, I don't know if you can say cosmetic grade.

DR. COHEN: No?

DR. ANSELL: No, it's not the material, it's the tested formulation. Right? Is that --

DR. COHEN: Boy, I'm all tied up here.

MS. CHERIAN: These ingredients -- products. Christina, do you remember how we asked for that specific data in CAPB?

MS. BURNETT: No, I'm looking at the report right now. I'm trying to see where it's --

MS. CHERIAN: Because we asked for the same thing for CAPB.

MS. BURNETT: Yeah. I'll have to think and see if I have it written somewhere.

DR. ROSS: I mean, aren't we just asking for more information on composition? More specific information on composition and impurities where available? Because that's what we're trying to get at. What are the impurities and what the percentages are. We've got some information here. Is there other stuff out there that we're not aware of?

DR. COHEN: So Table 4 has composition of a number of these. I guess for Disodium Lauroamphodiacetate it's 30 to 60 percent. And then we're missing 40 to 70 percent of what else is in there?

DR. ROSS: Well, it's water of salt acids.

DR. COHEN: But it doesn't say it for that one. It doesn't say it for Lauroamphodiacetate.

DR. ROSS: Yeah. And I just didn't want to be surprised by other impurities that we're not aware of.

DR. COHEN: So, Cocoamidopropyl betaine is supplied as a solution in water and with sodium chloride, the concentration of CAPB and such applied materials is described in its activity. Concentration of cosmetic grade is what is left in the supplied solution after water and sodium chloride have been accounted for.

DR. BERGFELD: That's what Don said.

DR. COHEN: Which is 30 percent of the supplied solution. Yeah.

DR. BERGFELD: What is that?

DR. HELDRETH: So, further composition and impurities data?

DR. COHEN: Yes. We definitely need to land this plane because we're running out of gas.

DR. BERGFELD: And active concentration. Put the word active in there. Let us know what is real, what it is.

DR. COHEN: Further information --

DR. BERGFELD: Can't do the arithmetic.

DR. COHEN: -- regarding what?

DR. ROSS: Composition and impurities of cosmetic grade ingredients.

DR. BERGFELD: I don't know if you can say cosmetic.

DR. COHEN: They do say it here.

DR. HELDRETH: They do.

MS. BURNETT: They use it in CAPB. It's says cosmetic grade.

MR. BJERKE: It's not a regulatory term, I think it's a supplier term.

DR. BERGFELD: Okay. And they supply other reasons too -- so it's just the name they put on it for you. Let's take it off.

DR. COHEN: Okay.

DR. SLAGA: The audio has gone extremely bad with you all.

DR. COHEN: You should thank us for that, Tom. But is that better.

DR. SLAGA: I can understand you, but several of the other people I can't.

DR. COHEN: So, we'll bring our mics in a little closer.

DR. SLAGA: You either have to be closer to the microphone or something.

DR. COHEN: Okay.

DR. SLAGA: Can you hear me now?

DR. COHEN: We can hear you beautifully. Okay, I think we got it.

DR. BERGFELD: I think we do.

DR. COHEN: Yeah.

DR. BERGFELD: I think active concentration, though, active. And I really do think, if Don is correct, that the supplier supplies it to all kinds of people and they just put the cosmetic on the one they're sending to us. It may not be any different. I don't think we should put cosmetic on it.

DR. ROSS: Okay, that's fine.

DR. COHEN: And the reason for pulling that out is why?

DR. BERGFELD: It infers that it's really a cleaned up ingredient.

DR. COHEN: And is it --

DR. BERGFELD: It may not be.

DR. ANSELL: There are trade names that we sell. But there's no cosmetic specifications.

DR. COHEN: Yeah, I got it. Like sushi grade tuna.

DR. ANSELL: Right.

MR. BJERKE: Yeah, one additional comment about the CAPB, is when we talked about the sensitizing impurities, DMAPA and amidoamine, at one point we discussed whether we want to control those impurities to a level that would cover everything. And we changed the approach to basically say, those impurities should be supported by a quantitative risk assessment for contact dermatitis.

For example, you could have higher levels of an impurity, like amidoamine in a rinse off product, and still not have a sensitization concern. But if you have higher exposure in a leave-on product, you may need a higher quality of CAPB with lower amidoamine concentrations.

DR. COHEN: Yeah, very logical. Okay.

MR. BJERKE: So, I think reporting what those impurities are and the levels are important. But then handle whether they're safe or not, based on a QRA for the particular cosmetic product used, and the level of that impurity in that raw material.

DR. COHEN: I find that very satisfying. Yeah. Okay. Can we close Amphocarboxylates?

DR. BERGFELD: Absolutely.

DR. ROSS: Please.

DR. COHEN: Move onto something simple like yeast. All right.

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DR. BELSITO: The name has been changed from Amphocarbomates to carboxylates, to include the propionate salts. We got a huge data dump in Wave 2. We're not clear whether some of that data is duplicative from data that was in the original report. Overall, we think that these are likely safe as used when formulated to be nonirritating. But we would like to table this to have the report reorganized in a uniform report.

DR. COHEN: We'll second that.

DR. BERGFELD: And that is residing on the fact that the data dump disallow for full evaluation, or timely evaluation?

DR. BELSITO: No, I think it allow for full evaluation. It's just that our team would like to see the report fully organized. Some of the team members had already reviewed the original, and didn't really have time to go through all of the data on this. So, just to give everyone time to review what was in the Wave 2.

DR. BERGFELD: It's been agreed to table. And table has no further discussion. I'll just call for the vote on tabling. All those agreed to table? Thank you. I think it's unanimous.

DR. HELDRETH: Yes, I think it's unanimous. And maybe also since so many of you went through and looked at the data that was available, if there are any known data gaps at this point, we can include that in our post-meeting announcements so that suppliers can help fill that in in the meantime.

DR. BELSITO: I went through it all. I think that when we look at it the data will be sufficient formulate to be nonirritating.

DR. COHEN: Can we go through our list with you and just, I mean, help us out.

DR. BELSITO: Sure.

DR. COHEN: We were asking for absorption data. DART, we understood some additional DART was forthcoming, particularly with the cardiac malformations for the Disodium Cocoamphoacetate.

DR. BELSITO: All of that DART information, when you look at Wave 2, was reviewed by Expedient --

DR. ROSS: Exponent.

DR. BELSITO: And, you know, it was thought that that one DART study with the cardiac effects was spurious.

DR. ROSS: There's no dose response, I would agree with that.

DR. BELSITO: No dose response.

DR. ROSS: I wouldn't necessarily agree it was spurious. It was -- you know, another study it was clean. That one was flagged. And then in the Exponent report, there was actually another reference which had a very low incidence of cardia malformations. And I gave that yesterday, I think you have that reference. And so, I felt we should have a full discussion of that.

If more DART is coming, I think that it would be prudent to look at that given those two studies. I mean, okay, one has no dose response, one has low incidences, but I think it would still be prudent to look at the additional studies if or when they arrive.

DR. BELSITO: Those aren't going to happen for another two years.

DR. ROSS: Well, I think there was one, April 24th, so it's still quite a ways out.

DR. BELSITO: Right. And the other is like late 2025.

DR. ROSS: That's 2025, yeah. But there is another one coming. I don't know what speed it'll come.

DR. SNYDER: Again, those studies were at very high doses, 300 mg/kg was the lowest dose. I mean, that's way above cosmetics. And I thought that Exponent, they did a nice job of summarizing better than I could've done spending weeks looking at the data. No individual study had a specific significance. They even combined all three studies and still didn't flag, so --

DR. ROSS: And the key is it was no dose response.

DR. COHEN: Wasn't the control negative?

DR. ROSS: Control was negative.

DR. COHEN: Control was negative.

DR. ROSS: But there was no increase as you went up in dose. But I still think at least we wanted some more clarification about that.

DR. BERGFELD: David, do you have any other needs so they can record those?

DR. COHEN: Yes, some further information regarding the composition and impurities of the cosmetic grade materials, sort of in the way that it showed up in the report for Cocamidopropyl betaine. It's a big range. And the description of what is active material and not active material was a bit complicated.

DR. BERGFELD: Yeah, go ahead if you have more.

DR. COHEN: No, I think we got everything, and maybe an organization of this irritation and sensitization, we'll review it. Do you think we have sensitization at max use, which is 9.9 percent for Sodium Lauroamphoacetate? We had that as a data need.

DR. BELSITO: I didn't flag it, so --

DR. COHEN: We'll go back to it when we see the report.

DR. BELSITO: I mean, again --

DR. BERGFELD: Well, we have all of these listed and we'll see those hopefully in the summary that precedes the new document, so that we can make sure that we have checked off all of our boxes.

I think this brings to light the fact that a large data dump two days before coming is a problem. And I want to say that we've developed a process now to table until we can fully examine materials we get comfortably. So we just put that on record, all right?

DR. COHEN: So this will be a table with additional commentary about our needs.

DR. BERGFELD: Yes.

MS. CHERIAN: I had a question about the read-across ingredients, those three extracts. Which ones do we want to see data on and which ones we don't want to see it on? I'm talking about the C08-18 or the C12, I'm talking about those three additional ingredients that were listed in the Wave 2 memo.

DR. ROSS: The Betaine, the imidazole and the beta-Alanine, right?

MS. CHERIAN: Yes.

DR. BELSITO: We discussed that, did not feel that we could use them as read-across. The Wave 2 memo. Let me go that.

DR. COHEN: Susan, you mentioned the Betaine you couldn't use for dermal absorption and tox, right?

DR. ROSS: I think we thought the additional two were okay. Allan, what was your thoughts about that?

DR. RETTIE: Yes, my notes say the Betaine, of course, no. The other two, I felt that the composition data was still vague, especially when you compared it with the very detailed explanations of what a given fraction contained from the European data.

In our data tables here, it gives the impression that each of these are pure compounds for some of them. Yet, we use the same synthetic approach to make these. And the European documents stress that these mixtures, beyond the fact that they were monoesters and di-esters, also might have ethers in them.

And so, I just felt that until we got clarification of the composition of what the ingredients we're looking at, in terms of their complexities, it was just very difficult for me to draw any conclusions about those. So, I would just reiterate that, at least from my end, I'd like to see much clearer composition data in our report. We need that so that we can evaluate read-across.

I think that number two here could be fine. But it specifies unsaturated fatty acid chains. We don't know whether we got those. I think that read-across is probably okay, but I would like to know what the composition, saturated versus unsaturated, for the fatty acid chains is in our ingredients before I would --

DR. COHEN: That was part of our ask.

DR. BERGFELD: So, that's another need that has to be clarified? Okay.

DR. ROSS: Yeah, I mean, these things are written up as UVCB, unknown variable composition biomaterials, which was probably some of the reason for the conflicting data in this report. But I think your call for more information on composition is a good one. We felt what we had, we could probably, looking at the reaction mechanism, go with read-across for the imidazole and the beta-Alanine compound, but we're certainly willing to wait until we have more composition data. I think that's a really good strategy.

DR. RETTIE: I agree with the read-across for the Beta-Alanine. I mean, it's a direct analog, It's just a shorter chain length. It's a heptane analog.

DR. BERGFELD: All right. It sounds like we have a plan here. And this particular ingredient has been tabled with all these needs being reiterated. So we're going to move on to MIBK, Dr. Cohen.

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: Revised Draft Report for Panel Review
Release Date: May 10, 2024
Panel Meeting Date: June 3 – 4, 2024

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
a.i.	active ingredient
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
Dictionary	web-based International Cosmetic Ingredient Dictionary and Handbook (wINCI)
ECHA	European Chemicals Agency
ET_{50}	effective time of exposure to reduce tissue viability to 50%
EU	European Union
FDA	Food and Drug Administration
GD	gestation days
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
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
SIDS	screening information dataset
SLS	sodium lauryl sulfate
TG	test guideline
TSH	thyroid-stimulating hormone
TUNEL	TdT-dUTP terminal nick-end labeling
US	United States
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This is a safety assessment 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 evaluated in 2006.[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* (*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 last conducted April 2024. 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://cir-reports.cir-safety.org/). 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 or active ingredient (a.i.))) 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/active ingredient 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 (common constituent of ingredients reviewed in this report) has previously been reviewed by the Panel (assess,emt 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, as published in a 2017 re-review summary.[6]

In addition, it should be noted that these ingredients may contain "amidoamine." However, one source denoting "amidoamine" as an impurity includes a CAS No. (106-09-2; and in the CAS file for this No., a chemical name *N*-[2-[(2-hydroxyethyl)amino] ethyl]-dodecanamide)[7] which does not comport with the compound more commonly known as amidoamine (i.e., fatty acid amidopropyl amine)[8,9] Fatty acid amidopropyl dimethylamine (amidoamine) is a known sensitizer.

Cocamidopropyl betaine, a surfactant that has been previously reviewed by the Panel (assessment 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.[10,11] According to the *Dictionary*, Sodium Lauroamphoacetate is an amphoteric organic compound that generally conforms to the structure:

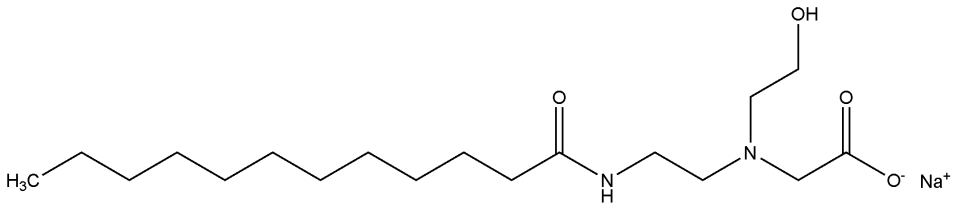


Figure 1. Sodium Lauroamphoacetate

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).[12] 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.

Disodium Cocoamphodiacetate

According to a supplier, Disodium Cocoamphodiacetate is prepared by reacting the fatty acid with amine to produce imidazoline.[13] The product then undergoes quality control, and the alkylating agent is reacted with imidazoline in water. Final processing steps involve quality control procedures.

Composition and Impurities

AEEA 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.[12] 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.[7,9,14-16] 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.[17] 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 US 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 included herein were obtained from the FDA's Voluntary Cosmetic Registration Program (VCRP) database in 2023 (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) in 2021 (maximum use concentrations). The data were provided by cosmetic product categories, based at that time 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 leave-on formulations; and 2 formulations diluted for bath use; Table 5).[18] 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 skin cleansing products.[19] Disodium Lauroampho-diacetate 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.[20]

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.[4,21] 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%.[22]

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).

The acute toxicity studies on Sodium Cocoamphopropionate and Sodium Lauroamphoacetate summarized here are described in Table 7.

A dermal LD_{50} of 2000 mg/kg bw was determined in an acute dermal toxicity assay performed in rats using Sodium Cocoamphopropionate (50.6% a.i./kg bw).[23] An LD_{50} of > 2000 mg a.i./kg bw for Sodium Cocoamphopropionate (40% a.i.; water) and > 16 ml/kg for Sodium Cocoamphopropionate (40% solids) was observed in acute oral toxicity assays. An oral LD_{50} of 6116 mg/kg for Sodium Lauroamphoacetate (% solids not stated; water and sodium chloride) was determined in mice.[4] The lowest oral 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 oral 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 (purity: 48%; 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).[4,24] 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. (A test item-related effect could not be excluded as the right-sided aortic arch incidence was above historical range; other visceral malformations observed were within historical control data range.) 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 (47.2 - 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 regarding these parameters. [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

(purity: 39.15%; 0, 100, 300, or 1000 mg/kg bw/d; in water; gavage administration). No maternal or fetal toxicity was observed in an assay in which Sodium Lauroamphoacetate was given to female Wistar Han rats (6/group) at up to 1000 mg/kg/d via gavage on gestation days (GD) 6-20. In a similar study, a maternal and developmental NOAEL was determined to be at least 1000 mg/kg bw/d in female Wistar Han rats (22/group) given up to 1000 mg/kg bw/d Sodium Lauroamphoacetate on GD 6-20.

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.[25] 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.[26] 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%).[27] 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 dermal irritation and sensitization studies summarized here can be found in Table 10. In an in vitro study, Sodium Cocoamphopropionate (40% a.i.; tested neat) was determined to be non-irritating in a reconstructed human epidermis assay.[23] No irritation was observed in a dermal irritation assay performed in rabbits using Sodium Cocoamphopropionate (40% a.i.; tested at dilution of 10%). Similarly, no dermal irritation was observed in three dermal irritation assays performed in rabbits using Sodium Lauroamphoacetate (35 – 50% solids; tested neat).[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%; tested neat).[28,29] 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.[4,21,30,31] Erythema and scaling was observed in in a 48-h occlusive patch test performed in 12 subjects using Sodium Cocoamphoacetate (10%) in citrate buffer.[32] 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.[21]

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 4% solids, water; tested at 20% dilution) reported no to slight irritation; however, a red blood cell test using 1% Disodium Cocoamphodiacetate resulted in moderate irritation.[21,33] Severe irritation potential was observed with higher concentrations. Disodium Cocoamphoacetate (4% solids, water; tested at 50% dilution) was estimated to be moderately irritating in a HET-CAM assay.[33] Severe irritation was noted in an EpiOcular™ assay evaluating the ocular irritation potential of 50% Disodium Cocoamphodiacetate.[34] Severe ocular irritation was also observed in a hen's egg test-chorioallantoic membrane (HET-CAM) assay using 40% Sodium Lauroamphoacetate.[35] 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.[36]

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).[37] 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.[38] 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).[39] 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.[40] 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.[12] 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.[41] 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.[42] 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 2006.

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.

A dermal LD_{50} of 2000 mg/kg bw was determined in an acute dermal toxicity assay performed in rats using Sodium Cocoamphopropionate (50.6% a.i./kg bw). An LD_{50} of > 2000 mg a.i./kg bw (for Sodium Cocoamphopropionate (40% a.i.; water) and > 16 ml/kg (for Sodium Cocoamphopropionate (40% solids) was observed in acute oral toxicity assays. An LD_{50} of 6116 mg/kg for Sodium Lauroamphoacetate (% solids not stated; water and sodium chloride) was determined in mice. The lowest LD_{50} in rats was reported to be > 2000 mg/kg bw (using Sodium Lauroamphoacetate (50% solids; water and sodium chloride; tested as provided) and Sodium Lauroamphoacetate (35% solids; water, sodium chloride, sodium glycolate; tested as a 20% aqueous dilution). An NOAEL of 1000 mg/kg bw/d was established in a 90-d oral subchronic toxicity assay in which Wistar Han rats (10/sex/group in main study; 5/sex/group in recovery group) were given Disodium Cocoamphodiacetate (47.2 – 48% solids), in water, via gavage, in doses of up to 1000 mg/kg bw/d.

A maternal NOAEL of 1000 mg/kg bw/d was established in a prenatal developmental toxicity study in which Disodium Cocoamphodiacetate (purity: 48%; 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 (purity: 39.15%; up to 1000 mg/kg bw/d; in water; gavage administration). No maternal or fetal toxicity was observed in an assay in which Sodium Lauroamphoacetate was given to female Wistar Han rats (6/group) at up to 1000 mg/kg/d via gavage. In a similar study, a maternal and developmental NOAEL was determined to be at least 1000 mg/kg bw/d in female Wistar Han rats (22/group) given up to 1000 mg/kg bw/d Sodium Lauroamphoacetate.

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.

In vitro, Sodium Cocoamphopropionate (40% a.i.) was determined to be non-irritating in a reconstructed human epidermis assay. Test substances were considered to be non-irritating in an irritation assay performed in rabbits using Sodium Cocoamphopropionate (40% a.i.; tested at dilution of 10%) or in three assays using Sodium Lauroamphoacetate (35-50% solids; tested neat). 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%; tested neat). Test substances (Disodium Cocoamphodiacetate (up to 5%), Disodium Cocoamphodiacetate (up to 2%), Sodium Cocoamphoacetate (up to 5%), and Sodium Lauroamphoacetate (35% solids; tested neat)) 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 4% solids, water; tested at 20% dilution) 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. Disodium Cocoamphoacetate (4% solids, water; tested at 50% dilution) was estimated to be moderately irritating in a HET-CAM assay. 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, CIR STAFF]

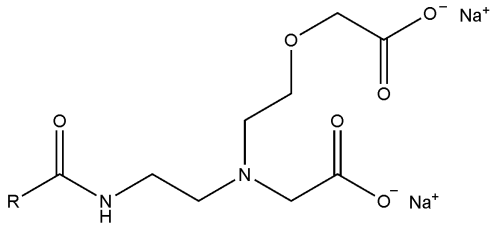
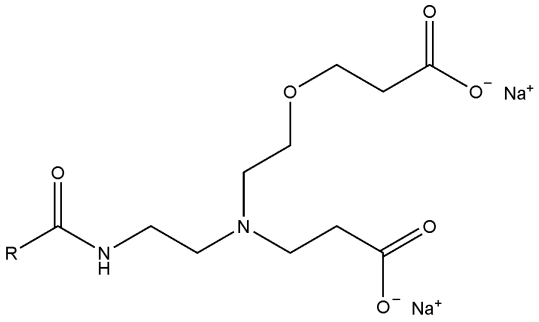
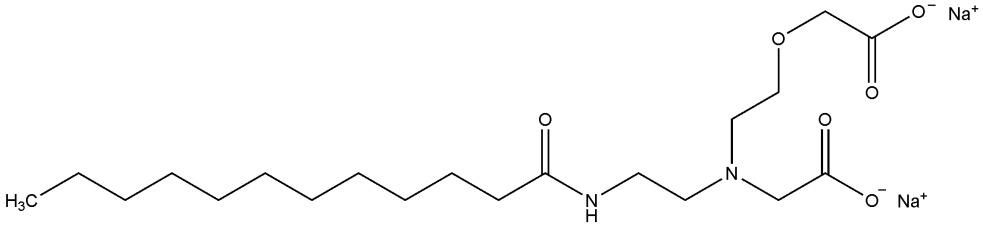
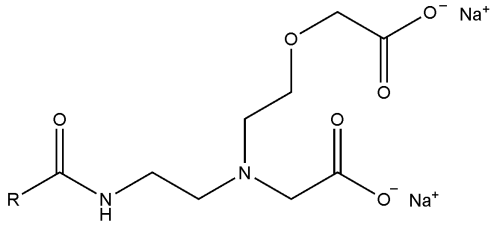
Ingredient	Definition	Function
Disodium Cocoamphodiacetate [CAS: 68650-39-5]	Disodium Cocoamphodiacetate is the amphoteric organic compound that conforms generally to the structure:  where RC(O)- represents the acyl groups derived from coconut oil.	Hair Conditioning Agents; Surfactants – Cleansing Agents;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

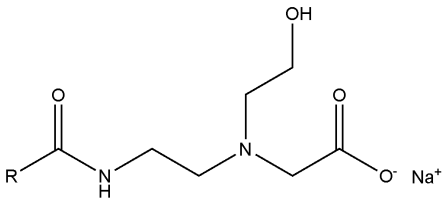
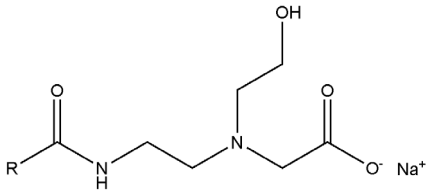
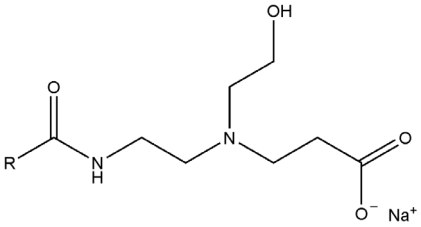
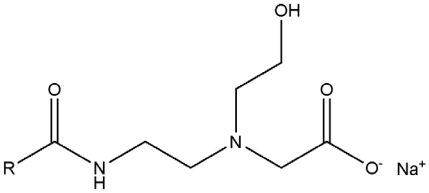
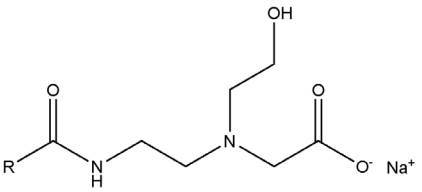
Ingredient	Definition	Function
Sodium Arganamphoacetate	Sodium Arganamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from Argania Spinosa Kernel Oil.	Surfactants - Cleansing Agents
Sodium Cocoamphoacetate [CAS: 90387-76-1;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

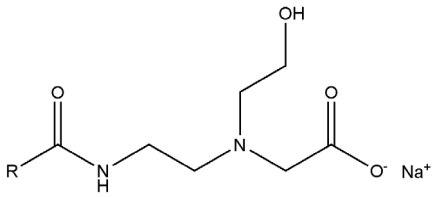
Ingredient	Definition	Function
Sodium Sweetalmondamphoacetate	Sodium Sweetalmondamphoacetate is the amphoteric organic compound that conforms generally to the formula:  where RC(O)- represents the acyl groups derived from sweet almond oil.	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants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

Table 2. Chemical properties

Property	Value	Reference
Disodium Cocoamphodiacetate		
Physical Form	liquid	1
Color	light tan	1
Odor	faintly fruity	1
Formula Weight (g/mol)	390.39 (C8 chain) – 530.66 (C18 chain)	43
Specific Gravity (@ 25ºC)	1.17	44
Melting Point (ºC)	298.94 (C8 chain; est.) - 349.84 (C18 chain; est.)	45
log K_{ow}	-5.67 (C8 chain; est.) - -0.75 (C18 chain; est.)	45
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
Formula Weight (g/mol)	404.41 (C8 chain) – 544.68 (C18; chain)	43
Specific Gravity (@ 25ºC)	1.05	46
Vapor Pressure (mmHg @ 25ºC)	0.0000225	47
Boiling Point (ºC)	≥ 100; ≤ 101	47
log K_{ow}	-7.57	47
Water Solubility	soluble	1
Alcohol Solubility	soluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Disodium Lauroamphodiacetate		
Physical Form	liquid	48
Formula Weight (g/mol)	446.5	48
log K_{ow}	-3.70	45
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	49
Color	clear – light amber	1
Odor	faintly fruity	1
Formula Weight (g/mol)	310.37 (C8 chain) – 450.64 (C18 chain)	43
Melting Point (ºC)	297.88 (C8 chain; est.) – 349.84 (C18 chain; est.)	45
log K_{ow}	-3.58 (C8 chain; est.) - 1.33 (C18 chain; est.)	45
Water Solubility	soluble	1
Alcohol Solubility	insoluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Sodium Cocoamphopropionate		
Physical Form	liquid	1
Color	light amber	1

Table 2. Chemical properties

Property	Value	Reference
Odor	faintly fruity	1
Formula Weight (g/mol)	324.40 (C8 chain) – 464.67 (C18 chain)	43
Melting Point (ºC)	303.30 (C8 chain; est.) - 349.84 (C18 chain; est.)	43
log K_{ow}	-3.09 (C8 chain; est.) - 1.82 (C18 chain; est.)	43
Water Solubility	soluble	1
Alcohol Solubility	soluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Sodium Lauroamphoacetate		
Physical Form	powder	4
Color	light yellow	4
Formula Weight (g/mol)	366.48	43
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 (%)[8,50]

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 > 33% Disodium Cocoamphodiacetates, < 55% water, < 12% sodium chloride	15,51
Disodium Cocoamphodipropionate	30 - 40% Disodium Cocoamphodipropionate, 60 - 70% water, < 0.1% other components (not specified)	14
Disodium Lauroamphodiacetate	15 - 40% Sodium Lauroamphoacetate (remaining components not stated)	52
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	9
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[18,19,53]

	# 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[18,19,53]

	# 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[18,19,53]

	# 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[18]	**2005[2]**	**2022[19]**	**2006[2]**	**2023[18]**	**2005[2]**	**2022[19]**	**2006[2]**	**2023[18]**	**2005[2]**	**2022[19]**	**2006[2]**	**2023[18]**	**2005[2]**	**2022[19]**	**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[18]	**2005[2]**	**2022[19]**	**2006[2]**	**2023[18]**	**2005[2]**	**2022[19]**	**2006[2]**	**2023[18]**	**2005[2]**	**2022[19]**	**2006[2]**	**2023[18]**	**2005[2]**	**2022[19]**	**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 toxicity studies[4]

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/ Results	References
			DERMAL			
Sodium Cocoamphopropionate (50.6% a.i.)	Water	Wistar rats (5/sex/group)	100%: 2024 mg a.i./kg bw	OECD TG 402; exposure area: 5x7 cm^2; occlusive; 24-h exposure duration	LD_{50} > 2000 mg/kg bw	[23]
			ORAL			
Sodium Cocoamphopropionate (40% a.i.; water)	No vehicle	female Wistar rats (3/group)	100%; 750 –5000 mg/ kg bw (equivalent to 300 – 2000 mg a.i./kg bw)	OECD TG 423; gavage administration; 14-d observation	LD_{50} > 2000 mg a.i./kg bw	[23]
Sodium Cocoamphopropionate (40% solids)	No vehicle	Sprague-Dawley rats (5/sex/dose)	100%; 16 ml/kg	OECD TG 401; gavage; 14-d observation	LD_{50} > 16 ml/kg bw	[23]
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, 4, and 8 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.	[4]
Sodium Lauroamphoacetate (50% solids; water and sodium chloride)	Water and 0.5% carboxymethyl-cellulose	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)	[4]
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)	[4]
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 of the 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 of the 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.	[4]
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.	[4]

a.i. = active ingredient; LD_{50} = median lethal dose; OECD = Organisation for Economic Cooperation and Development; TG = Test Guidelines

Table 8. Oral reproductive and developmental toxicity studies[4,24]

Test Article	Vehicle	Animals/Group	Dose	Procedure	Results
Disodium Cocoamphodiacetate (purity: 48%)	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 (including thyroid hormone analysis); 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. Slightly lower serum TSH levels were seen at ≥300 mg/kg/d; however, the differences from control were not statistically significant and individual values were within the historical control range. No effect on T3 or T4 (thyroid hormones) levels were observed, and thyroid organ weights and histopathology were not changed from control. 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, thyroid hormone, 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. Serum T4 (thyroid hormone) concentrations were unaffected by treatment in males; however, an increase in the incidence of minimal to slight thyroid follicular cell hypertrophy was noted at 300 and 1000 mg/kg/d. Serum T4 data were not available for parental females; however, no increased thyroid histopathology was observed in these animals at ≤ 1000 mg/kg/d. 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, thyroid hormones, spermatogenesis, and weight/ appearance/histopathology of reproductive organs evaluated	Salivation observed in animals at ≥ 300 mg/kg/d, and incidental ploughing was observed at 1000 mg/kg/d; however, these findings were considered to be due to the taste of the test material. No effects on body weight and body weight gain were observed in females; however, the terminal mean body weight for males at 1000 mg/kg/d was 88% of control (statistically-significant). No adverse effects relating to the estrous cycle were observed. TSH concentrations were significantly lower than controls in all groups of treated males, but without a dose-response. T4 was reduced in males at 1000 mg/kg/d. Qualitative assessment of spermatogenesis revealed normal progression of the spermatogenic cycle. The NOAEL for systemic toxicity was determined to be 1000 mg/kg/d.

Table 8. Oral reproductive and developmental toxicity studies[4,24]

Test Article	Vehicle	Animals/Group	Dose	Procedure	Results
Sodium Cocoamphoacetate (purity: 39.15%)	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 rats (6/group)	0, 300, 600, or 1000 mg/kg/d	OECD TG 414; dose range-finding prenatal study; animals treated via gavage; dosing GD 6-20; clinical observations performed on GD 2, 6, 15, and 21; on GD 21 dams subjected to exam of thoracic and abdominal cavities; litter indices, uterine examination, and fetus evaluation performed	A single female of the mid-dose group was found dead on GD 15 (due to gavage error). No treatment-related mortality observed. Maternal body weights in treated groups were similar to controls. Compared to the control, the mean number of implantations and the mean number of live fetuses was significantly increased and mean fetal weights were significantly reduced in the high-dose group (likely due to increased number of fetuses per litter compared to control group; the mean total litter weight was greater in the high-dose group (66.1 g) compared to the control group (50.7 g). No treatment-related effects were observed on the number of pregnant females per group, the numbers of corpora lutea, early and late resorptions, the number of dead fetuses per litter, or fetal sex ratio. No external or visceral malformations were observed in fetuses.
Sodium Lauroamphoacetate	Water	female Wistar Han (22/group)	0, 100, 300, and 1000 mg/kg bw/d	OECD TG 414; animals treated from GD 6- 20 post-coitum, via gavage; animals killed on GD 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 NOAELs were both determined to at least 1000 mg/kg bw/d.

GD – gestation days; NOAEL = no-observed-adverse-effect-level; OECD = Organisation for Economic Cooperation and Development; TG = test guideline; TSH = thyroid-stimulating hormone

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						
IN VITRO						
Sodium Cocoamphopropionate (40% a.i.; water)	No vehicle	100%: 10 µl	EpiSkin™ tissues (3 replicates)	Reconstructed human epidermis assay; OECD TG 439; negative control: deionized water; positive control: sodium lauryl sulfate; 15 min exposure period	Non-irritating (mean tissue viability of test substance: 102.1%) tissue viability of negative control: 100% tissue viability of positive control: 13.9 %	[23]
Animal						
Sodium Cocoamphopropionate (40% a.i.)	Water	10%; 0.5 ml	6 New Zealand white rabbits (sex not stated)	OECD TG 404; occlusive conditions; test substance applied to intact and abraded skin for 24 h; observations 24, 48, and 72 h after patch removal	Non-irritating	[23]
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]

Table 10. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
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)	[28]
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)	[29]
			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	[31]
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)	[21]
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)	[21]
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.	[30]
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)	[21]
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)	[21]

Table 10. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
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.	30
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.	32
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)	21
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)	21
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
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

Table 10. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
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]

a.i. = active ingredient; HRIPT = human repeated-insult patch test; NR = not reported; OECD = Organisation for Economic Cooperation and Development; SLS = sodium lauryl sulfate; TG = test guideline

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	[21]
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)	[21]
Disodium Cocoamphodiacetate (4% solids, water)	Water	50%	4	HET-CAM assay	Moderately irritating (estimated that undiluted test substance (4% solids) would have moderate ocular irritation potential)	[33]
Disodium Cocoamphodiacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient = 0.63 (quotient ≤ 0.8 indicates slightly irritating)	[21]
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)	[34]
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	[21]
Sodium Cocoamphoacetate	Water	1%	3	Red blood cell test	Non-irritating; H_{50}/DI = 102.40 (score > 100 indicates non-irritating)	[21]
Sodium Cocoamphoacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient = 0.42 (quotient ≤ 0.8 indicates slightly irritating)	[21]
Sodium Lauroamphoacetate (4% solids: water)	Water	20%	NR	EpiOcular™ MTT ET_{50}	Minimally irritating; ET_{50} = 87.6 min (at tested concentration); Draize ocular irritation score was estimated to be approximately 6.1 (minimally irritating) for undiluted test substance (4% solids)	[33]
Sodium Lauroamphoacetate	Water	1%	3	Red blood cell test	Non-irritating; H_{50}/DI = 222.13 (score > 100 indicates non-irritating)	[21]
Sodium Lauroamphoacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient: 0.79 (quotient ≤ 0.8 indicates slightly irritating)	[21]
Sodium Lauroamphoacetate	Water	40%	6	HET-CAM assay	Severely irritating; irritation quotient: 3.41 (quotient ≥ 2 indicates severely irritating)	[35]
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]

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	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]
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.	[36]
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.	[36]

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; NR = not reported; OECD = Organisation for Economic Cooperation and Development; TG = 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.

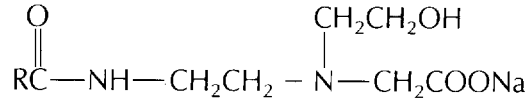
INTRODUCTION

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]

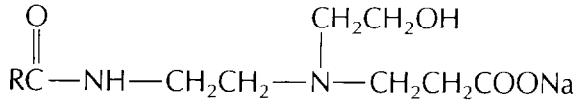
CHEMICAL AND PHYSICAL PROPERTIES

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



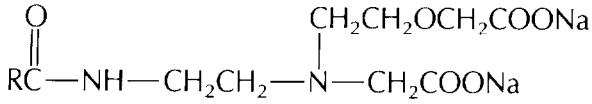
Cocoamphoacetate

I

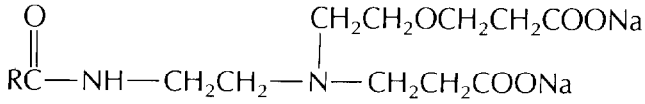


Cocoamphopropionate

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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