Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 22, 2026
Panel Meeting Date:	June 15-16, 2026

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D., Donald V. Belsito, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: David E. Cohen, M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Priya Ferguson, M.S., Associate Toxicologist/Senior Scientific Analyst/Writer, CIR.

555 13th Street, NW, Suite 300W, Washington, DC 20004
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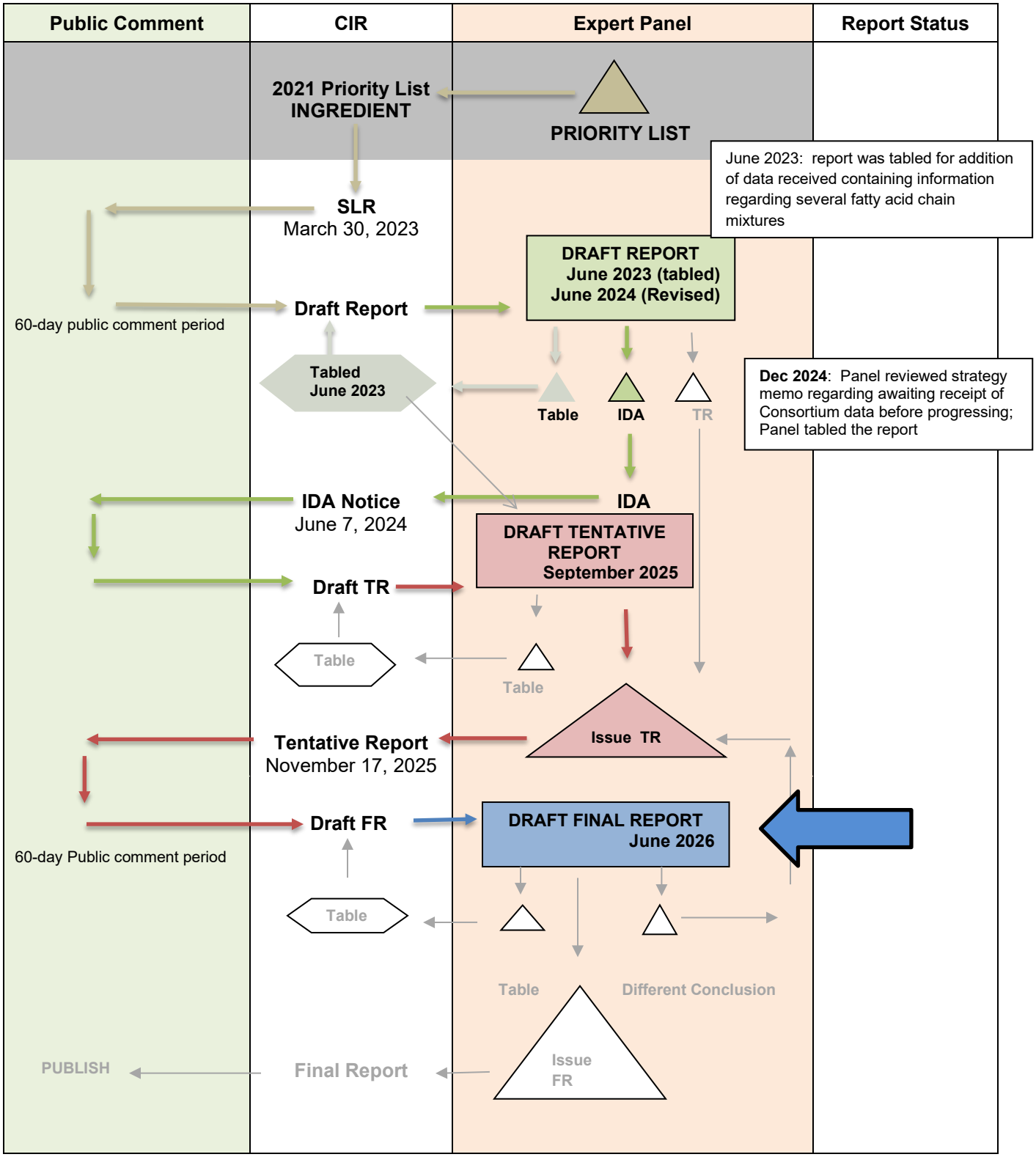
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Fatty Amphocarboxylates

MEETING June 2026



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Ferguson, M.S.
Associate Toxicologist/Senior Scientific Analyst/Writer, CIR
Date: May 22, 2026
Subject: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (*report_FattyAmphocarboxylates_062026*). At the September 2025 meeting, the Panel issued a Tentative Report with the conclusion that the 11 fatty amphocarboxylates are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing, based on a quantitative risk assessment (QRA) or other appropriate methodology.

Since the September 2025 meeting, an HRIPT on a product containing 2.04% Disodium Lauroamphodiacetate (final test concentration: 0.02% Disodium Lauroamphodiacetate) was received and incorporated into the report in highlighted text (*data_FattyAmphocarboxylates_062026*). In addition, a study was found in published literature assessing the ocular irritation potential of Disodium Cocoamphodiacetate, Sodium Cocoamphoacetate, and Sodium Lauroamphoacetate in rabbits. These data have been incorporated into the report in highlighted text.

Comments received from the Council prior to the September 2025 meeting and on the Tentative Report have been addressed (*PCPCcomments1_FattyAmphocarboxylates_062026*; *PCPCcomments2_ FattyAmphocarboxylates_062026* and *response-PCPCcomments1_ FattyAmphocarboxylates_062026*; *response-PCPCcomments2_FattyAmphocarboxylates_062026*). In addition, comments on the Tentative Report from the EU Reach Consortium (*ConsortiumComments_FattyAmphocarboxylates_062026*) were received and addressed (*response-ConsortiumComments_FattyAmphocarboxylates_062026*).

Also, since the September meeting, CIR has updated the use data with RLD obtained from the FDA in 2025. According to these data, Disodium Cocoamphodiacetate has the highest frequency of use (it is reported to be used in 3010 formulations). The results of the concentration of use survey conducted by Council in 2025 indicate that Sodium Cocoamphoacetate has the highest concentration of use in leave-on products (it is used at up to 3% in leave-on face and neck (not spray) and body and hand products (not spray)) and Disodium Cocoamphodipropionate has the highest concentration of use overall, in rinse-off products (it is used at up to 14.8% in rinse-off non-coloring shampoos).

Disodium Cocoamphodiacetate, Sodium Cocoamphoacetate, and Sodium Lauroamphoacetate were reported to have uses under 'category (17) Other preparations (i.e., those preparations that do not fit another category)' in 2025 RLD. Twelve products for Disodium Cocoamphodiacetate were co-categorized as either bath preparations, manicuring preparations, skincare preparations, or hair preparations (coloring and non-coloring). One product for Sodium Cocoamphoacetate was co-categorized as a non-coloring hair preparation, and one product for Sodium Lauroamphoacetate was co-categorized as a personal cleanliness product. In addition, in several instances, products were only categorized in RLD with a categorization of '(17) Other preparations;' however, the product names were useful in determining product type. For Disodium Cocoamphodiacetate, these products include makeup remover wipes, facial cleansers, cleansing pads, micellar waters, makeup brush cleaning wipes, face masks, and beard and face scrubs. For Sodium Cocoamphoacetate, these product types include face wash and shampoo bars. For one product containing Disodium Cocoamphodiacetate, neither the product type nor the area/route of exposure is obvious from the information submitted to the RLD. Lastly, information reported for some of the '(17) Other preparations' suggests that those submitted products might not be considered cosmetic products in the US. We have sent a request to our colleagues in the FDA's OCAC for clarification.

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

- original 1990 report on Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate (*originalreport1990_FattyAmphocarboxylates_062026*)
- 2008 re-review on Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate (*re-review2008_FattyAmphocarboxylates_062026*)
- minutes from deliberations from the meetings at which the original report and re-review on Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate were discussed (*originalminutes_FattyAmphocarboxylates_062026)*
- a flow chart (*flow_FattyAmphocarboxylates_062026*)
- ingredient history (*history_FattyAmphocarboxylates_062026*)
- search strategy (*search_FattyAmphocarboxylates_062026*)
- data profile (*dataprofile_FattyAmphocarboxylates_062026)*
- transcripts *(transcripts_FattyAmphocarboxylates_062026)*

The Panel should carefully review the Abstract, Discussion, and Conclusion, and issue a Final Report.

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

June 2024

- CIR staff prepares read-across document for RAWG review
- Panel reviews Revised Draft Report
- Comments received from PCPC and Amphoacetates Consortium
- RAWG reviews ingredients – determines to re-review ingredients at an upcoming mtg
- Panel issued an IDA with the following insufficiencies:
- 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, fatty acid compositions, and degrees of esterifications (e.g., how much of Sodium Cocoamphoacetate has 0, 1, or 2 acetate substitutions)
- Sensitization data on Sodium Lauroamphoacetate at maximum use concentration
- Sensitization data on Disodium Lauroamphodiacetate at maximum use concentration

- Any information (e.g., clarification on compositions) to support the use of the read-across sources previously suggested to Panel

December 2024

- Panel reviewed strategy memo; tabled report for receipt of upcoming DART data

December 2024 – August 2025

- Ample data received including HRIPTs, DART data on Amphoacetates C8-18), expert opinions on DART data, composition information on Disodium Lauroamphodiacetate, use assay, updated concentration of use data, prediction reports on RA ingredients, analogue approach information, conference proceedings

September 2025

- Panel reviews Draft Tentative Amended Report and issues Tentative Report for public comment conclusion of safe was used when formulated to be non-sensitizing, based on a QRA
- RAWG mtg on ingredient group
- Comments received from Council on Draft Amended Tentative Report

January 2026

- comments received on Tentative Report from EU REACH Consortium

May 2026

- HRIPT on product containing 2.04% Disodium Lauroamphodiacetate received from Council

June 2026

- Panel reviews Draft Final Amended Report

Fatty Amphocarboxylates Data Profile – June 2026 – Writer, Priya Ferguson

				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	XO	X		
Disodium Cocomphodipropionate	XO	O		X				O							O					O	O			O			O			X
Disodium Lauroamphodiacetate	X																							X						X
Disodium Wheatgermamphodiacetate	X		X	X																										
Sodium Arganamphoacetate	X																													
Sodium Cocoamphoacetate	XO	O	X					O						X	O					O	X		X	XO	O	X	XO			X
Sodium Cocoamphopropionate	XO	O					X	XO											X	XO				O	O		O			X
Sodium Cottonseedamphoacetate																														
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 Ferguson

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 PubMed along with INCI names and CAS numbers
Searches on INCI name and CAS numbers also performed on websites list below

Search Terms

- metabolism
- dermal
- inhalation
- skin
- toxicity
- drugs
- medicine
- irritation
- ocular
- eye
- sensitization
- allergy
- manufacture
- cancer

Searched Websites/Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- 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

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Kimberly Norman, Ph.D., DABT, ERT
Industry Liaison to the CIR Expert Panel

DATE: September 2, 2025

SUBJECT: Draft Tentative Report: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (draft prepared for the September 8-9, 2025, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics.

Key Issues

The Cosmetic Use section says: "Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting)." Based on this statement, the memo should not describe the RLD uses as "higher" than VCRP uses (there are many more products reported to the RLD – comparative terms should not be used), nor should the Cosmetic Use section say: "For comparison".

Abstract – It is not appropriate to refer to the FDA and the EPA for limits on amidoamines. Although the FDA and EPA have limits for heavy metals, do they really have limits for "amidoamines"? If the FDA and/or EPA have limits for amidoamines, they should be noted elsewhere in the CIR report.

Rather than using the term "amidoamines" for impurities for the amphocarboxylates, Table 2 of the document titled "Analogue Approach for REACH Registration of ALKYLAMPHOACETATES" indicates that an impurity is: amido hydroxyethyl ethylenediamines (which seems to be consistent with the impurity reported in reference 7 cited in the Introduction). The Composition and Impurities section should explain that although the impurities are sometimes called amidoamines, they are amido hydroxyethyl ethylenediamines. The concentrations of these impurities are stated in Table 2 of the Analogue Approach document and should be added to the CIR report. All of the composition information included in Table 2 of Analogue Approach report should be added to the CIR report.

Toxicokinetics – It is not correct to state that no unpublished information was submitted. The REACH Consortium for the amphocarboxylates provided information on the penetration assumptions they are using to support these ingredients. Based on physical chemical properties of these complex mixtures (charge, Kow, MW) low dermal penetration (10%) is being used. They support this assumption with a dermal rat study of another amphoteric compound Cocamidopropyl Betaine which had low <10% dermal penetration.

Developmental and Reproductive Toxicity – It is not clear why the new rabbit developmental toxicity study and the new rat extended one generation study were not included in the CIR report. Both studies were on amphoacetates C8-18 (diacetate) which is essentially the same mixture that was tested in other developmental studies already included in the CIR report. Appendix 5 of the REACH Read-Across document provides information on the approximate concentrations of the mono and diacetates in the materials tested. It would be helpful if this information was added with the appropriate studies in the CIR report.

Additional Considerations

Cosmetic Use; Summary – The Cosmetic Use section should make it clear that the 2022 concentration of use survey was completed using the VCRP product categories, while the 2025 survey was completed using the new MoCRA product categories.

When stating a use concentration, the product category in which it was reported should always be stated.

Developmental and Reproductive Toxicity – Since the DeSesso, Lavin Williams report is being used as a source for details of the developmental and reproductive toxicity studies, please include their conclusions regarding the potential of these mixtures to cause developmental and reproductive toxicity.

Co-Reactivity of Surfactant Allergens; Reactivity to Irritants in Atopic and Non-Atopic Patients – It is not clear why separate sections are needed for these studies. They belong in the Dermal Irritation and Sensitization Section.

Dermal Irritation and Sensitization – If available, please state the EC_3 value for the LLNA. It would also be helpful to state the authors conclusion which is noted in Table 10 “The result was considered to be inconclusive as surfactants have clear irritating effects and may lead to false positives.”

Photosensitization/Phototoxicity, old report summary – If available, please provide information about the light exposure.

Ocular Irritation – Please change: “were reported to use” to “were used”

Case Reports, Sodium Cocoamphoacetate – Please correct: “It was not stated whether control subjects elicited a response to the eye makeup remover formulation.” It would be clearer as: “It was not stated whether the eye makeup remover formulation elicited a response in the control subjects.”

Summary – Please correct: “Results of recent concentration of use surveys (2022-2025) indicate that Disodium Cocamphodiacetate and Disodium Lauroamphodiacetate have the highest frequency of use in leave-on products (both are used at up to 5.4%).” There were 2 surveys so it should say (2022 VCRP product categories; 2025 MoCRA product categories). These surveys did not provide any information about frequency of use, this should be “concentration of use”. Please state the product categories for which the 5.4% use concentration was reported (Bath soaps for Disodium Cocamphodiacetate; Other hair preparations Disodium Lauroamphodiacetate).

The Summary should note that only a few fetuses had cardiac defects and all but the right-sided aortic arch defects were within historical control values. The conclusion of DeSesso and Lavin Williams should also be added to the Summary.

Please include the gestation days the rats were treated in the rat study of Sodium Lauroamphoacetate.

Reference 21 – Although it was provided by PCPC, reference 21, the article from the Proceedings of the 5th World Surfactants Conference is not “Unpublished”.

Fatty Amphocarboxylates – June 2026 – Priya Ferguson	
Comment Submitter: Kimberly Norman, Ph.D., DABT, ERT; Personal Care Products Council **Subject:** Draft Tentative Report: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (draft prepared for the September 8-9, 2025, meeting) **Date of Submission:** September 2, 2025	
Comment	**Response/Action**
The Cosmetic Use section says: "Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting)." Based on this statement, the memo should not describe the RLD uses as "higher" than VCRP uses (there are many more products reported to the RLD – comparative terms should not be used), nor should the Cosmetic Use section say: "For comparison".	Addressed
Abstract – It is not appropriate to refer to the FDA and the EPA for limits on amidoamines. Although the FDA and EPA have limits for heavy metals, do they really have limits for "amidoamines"? If the FDA and/or EPA have limits for amidoamines, they should be noted elsewhere in the CIR report.	Addressed
Rather than using the term "amidoamines" for impurities for the amphocarboxylates, Table 2 of the document titled "Analogue Approach for REACH Registration of ALKYLAMPHOACETATES" indicates that an impurity is: amido hydroxyethyl ethylenediamines (which seems to be consistent with the impurity reported in reference 7 cited in the Introduction). The Composition and Impurities section should explain that although the impurities are sometimes called amidoamines, they are amido hydroxyethyl ethylenediamines. The concentrations of these impurities are stated in Table 2 of the Analogue Approach document and should be added to the CIR report. All of the composition information included in Table 2 of Analogue Approach report should be added to the CIR report.	Addressed
Toxicokinetics – It is not correct to state that no unpublished information was submitted. The REACH Consortium for the ampho-carboxylates provided information on the penetration assumptions they are using to support these ingredients. Based on physical chemical properties of these complex mixtures (charge, Kow, MW) low dermal penetration (10%) is being used. They support this assumption with a dermal rat study of another amphoteric compound Cocamidopropyl Betaine which had low <10% dermal penetration	Addressed
Developmental and Reproductive Toxicity – It is not clear why the new rabbit developmental toxicity study and the new rat extended one generation study were not included in the CIR report. Both studies were on amphoacetates C8-18 (diacetate) which is essentially the same mixture that was tested in other developmental studies already included in the CIR report. Appendix 5 of the REACH Read-Across document provides information on the approximate concentrations of the mono and diacetates in the materials tested. It would be helpful if this information was added with the appropriate studies in the CIR report.	These studies were not added prior to Discussion with RAWG. They are now incorporated into the report.
Cosmetic Use; Summary – The Cosmetic Use section should make it clear that the 2022 concentration of use survey was completed using the VCRP product categories, while the 2025 survey was completed using the new MoCRA product categories.	Addressed
When stating a use concentration, the product category in which it was reported should always be stated.	Addressed

Fatty Amphocarboxylates – June 2026 – Priya Ferguson	
Comment Submitter: Kimberly Norman, Ph.D., DABT, ERT; Personal Care Products Council **Subject:** Draft Tentative Report: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (draft prepared for the September 8-9, 2025, meeting) **Date of Submission:** September 2, 2025	
Comment	**Response/Action**
Developmental and Reproductive Toxicity – Since the DeSesso, Lavin Williams report is being used as a source for details of the developmental and reproductive toxicity studies, please include their conclusions regarding the potential of these mixtures to cause developmental and reproductive toxicity.	Council discussion at the September 2025 meeting indicate that outside discussions will not be incorporated into the reports. Experimental data from these studies have been included, and the Panel's interpretation of the data have been included in the Discussion.
Co-Reactivity of Surfactant Allergens; Reactivity to Irritants in Atopic and Non-Atopic Patients – It is not clear why separate sections are needed for these studies. They belong in the Dermal Irritation and Sensitization Section	This study was not included in the dermal irritation and sensitization section because it included atopic patients.
Dermal Irritation and Sensitization – If available, please state the EC3 value for the LLNA. It would also be helpful to state the authors conclusion which is noted in Table 10 "The result was considered to be inconclusive as surfactants have clear irritating effects and may lead to false positives."	EC_3 value not available; the results section already states that the result was considered to be inconclusive
Photosensitization/Phototoxicity, old report summary – If available, please provide information about the light exposure.	Addressed
Ocular Irritation – Please change: "were reported to use" to "were used"	Addressed
Case Reports, Sodium Cocoamphoacetate – Please correct: "It was not stated whether control subjects elicited a response to the eye makeup remover formulation." It would be clearer as: "It was not stated whether the eye makeup remover formulation elicited a response in the control subjects."	Addressed
Summary – Please correct: "Results of recent concentration of use surveys (2022-2025) indicate that Disodium Cocamphodiacetate and Disodium Lauroamphodiacetate have the highest frequency of use in leave-on products (both are used at up to 5.4%)." There were 2 surveys so it should say (2022 VCRP product categories; 2025 MoCRA product categories). These surveys did not provide any information about frequency of use, this should be "concentration of use". Please state the product categories for which the 5.4% use concentration was reported (Bath soaps for Disodium Cocamphodiacetate; Other hair preparations Disodium Lauroamphodiacetate).	Addressed
The Summary should note that only a few fetuses had cardiac defects and all but the right-sided aortic arch defects were within historical control values. The conclusion of DeSesso and Lavin Williams should also be added to the Summary.	Addressed
Please include the gestation days the rats were treated in the rat study of Sodium Lauroamphoacetate.	Addressed
Reference 21 – Although it was provided by PCPC, reference 21, the article from the Proceedings of the 5th World Surfactants Conference is not "Unpublished".	Addressed

Personal Care Products Council
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Memorandum

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

FROM: Jaap Venema, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: December 4, 2025

SUBJECT: Tentative Report: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (release date: November 17, 2025)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics.

Key Issues

Cosmetic Use; Summary; Tables 5 and 6 – How this CIR report presents concentration of use information is not consistent with other CIR reports. Generally, only the most recent concentration information is included in a CIR report rather than information from older surveys. If information from all the surveys is left in the report, the PCPC references need to be cited correctly. Only reference 35 (the 2025 survey) included all the ingredients in the report. Reference 34 only included Sodium Lauroamphoacetate, while references 33 and 36 included some of the ingredients added to the report on Sodium Lauroamphoacetate.

The product categories with the highest use concentration in leave-on products needs to be corrected. The use section says "5.4% in face and neck products (not spray) [Disodium Cocoamphodiacetate] and other hair preparations [Disodium Lauroamphodiacetate]". The Summary says: "use in leave-on products (both are used at up to 5.4% in bath soaps for Disodium Cocoamphodiacetate and in other hair preparations for Disodium Lauroamphodiacetate)". In Table 5, the face and neck product that contains 5.4% Disodium Cocoamphodiacetate is listed as a rinse-off product, not a leave-on product. Bath soaps and detergents are not considered leave-on products.

Based solely on the 2025 concentration of use survey, the maximum use concentration for Disodium Cocoamphodiacetate in a leave-on product is 2.8% in a leave-on face and neck product.

Please consider a careful recheck of Table 5. Another error is that the summary "Baby Products" category gives a concentration range of 0.56-5.4%, while the concentrations listed by specific

baby product categories are 0.9% for Baby Shampoo and 0.56% for Other Baby Products. There is no 5.4% listed for a baby product.

Dermal Irritation and Sensitization; Summary - Regarding the LLNA, Table 10 states: "The result was considered to be inconclusive as surfactants have clear irritating effects and may lead to false positives." This statement should be included in the text of the Dermal Irritation and Sensitization, and Summary sections.

Discussion – Does the Expert Panel really want to say that the findings in the developmental and reproductive toxicity study were "spurious"? Perhaps these findings should be called chance, and non-treatment-related (as indicated in Table 8).

Additional Considerations

Introduction – For the final report, the following sentence should be deleted from the Introduction: "Clarification is needed regarding the composition of these ingredients/percentages of these ingredients in finished solutions as used in cosmetics."

Composition and Impurities – The structure of the "amidoamine" (amidodipropyl dimethylamines) impurity is shown in the CIR report on Cocamidopropyl Betaine. It would also be helpful to show the structure of the amido hydroxyethyl ethylenediamine impurity in this CIR report.

It would be helpful to note that: "The majority of these ingredients consist of [aqueous] mixtures…" (please add the word aqueous).

Acute – Please complete the following: "An oral LD_{50} of 6116 mg/kg for"

Dermal Irritation and Sensitization – Please correct: "observed in in a 48-h occlusive patch test" (delete the second "in")

Ocular Irritation; Summary – As the test in red blood cells is not actually measuring irritation, rather than "resulted in moderate irritation" it would be better to state that it "predicted moderate irritation".

Summary – The second paragraph does not need to state twice that the concentration of use surveys completed before 2025 were done by VCRP categories, while the 2025 survey was done by MoCRA product categories.

Table 1 – The definition of Disodium Wheatgermamphodiacetate has been revised in the PCPC database ("amphoteric" added before organic) to make it consistent with the definitions of the other ingredients in this report. Please include this change in Table 1.

Table 2 – Please present the Water Solubility values for Sodium Lauroamphoacetate together (there are currently 3 rows between the 2 values).

If the composition information on the second page of Table 2 is left in this table titled Chemical Properties, please change the title of this table to also indicate that it includes composition information.

Table 7 – The study of Sodium Lauroamphoacetate in Charles River rats appeared to use a diluted solution for all doses. Rather than saying "and 3422 mg/kg for the undiluted test substance", it would be clearer if it said: "and 3422 mg/kg for the a.i."

Table 8, last study – As there was no dose of 100 mg/kg bw/day tested (according to the Dose column), in the Results column, please correct, or clarify what is meant by the "100 mg/kg/day group".

Table 10 – Please correct: "contaminating" (should be "containing")

Please state the duration of the rest period used in the third HRIPT.

Fatty Amphocarboxylates – June 2026 Meeting – Priya Ferguson	
Comment Submitter: Jaap Venema, Ph.D.; Personal Care Products Council **Subject:** Tentative Report: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (release date: November 17, 2025) **Date of Submission:** December 4, 2025	
Comment	**Response/Action**
Cosmetic Use; Summary; Tables 5 and 6 – How this CIR report presents concentration of use information is not consistent with other CIR reports. Generally, only the most recent concentration information is included in a CIR report rather than information from older surveys. If information from all the surveys is left in the report, the PCPC references need to be cited correctly. Only reference 35 (the 2025 survey) included all the ingredients in the report. Reference 34 only included Sodium Lauroamphoacetate, while references 33 and 36 included some of the ingredients added to the report on Sodium Lauroamphoacetate.	Addressed – only 2025 concentration of use is provided in this iteration of the report
The product categories with the highest use concentration in leave-on products needs to be corrected. The use section says "5.4% in face and neck products (not spray) [Disodium Cocoamphodiacetate] and other hair preparations [Disodium Lauroamphodiacetate]". The Summary says: "use in leave-on products (both are used at up to 5.4% in bath soaps for Disodium Cocoamphodiacetate and in other hair preparations for Disodium Lauroamphodiacetate)". In Table 5, the face and neck product that contains 5.4% Disodium Cocoamphodiacetate is listed as a rinse-off product, not a leave-on product. Bath soaps and detergents are not considered leave-on products.	Addressed
Based solely on the 2025 concentration of use survey, the maximum use concentration for Disodium Cocoamphodiacetate in a leave-on product is 2.8% in a leave-on face and neck product	Addressed
Please consider a careful recheck of Table 5. Another error is that the summary "Baby Products" category gives a concentration range of 0.56-5.4%, while the concentrations listed by specific 2 baby product categories are 0.9% for Baby Shampoo and 0.56% for Other Baby Products. There is no 5.4% listed for a baby product.	Addressed
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Discussion – Does the Expert Panel really want to say that the findings in the developmental and reproductive toxicity study were "spurious"? Perhaps these findings should be called chance, and non-treatment-related (as indicated in Table 8).	Addressed; Panel should determine if edited language is appropriate
Introduction – For the final report, the following sentence should be deleted from the Introduction: "Clarification is needed regarding the composition of these ingredients/percentages of these ingredients in finished solutions as used in cosmetics."	Addressed
Composition and Impurities – The structure of the "amidoamine" (amidodipropyl dimethylamines) impurity is shown in the CIR report on Cocamidopropyl Betaine. It would also be helpful to show the structure of the amido hydroxyethyl ethylenediamine impurity in this CIR report	no changes made unless Panel requests addition of structure
It would be helpful to note that: "The majority of these ingredients consist of [aqueous] mixtures…" (please add the word aqueous)	Addressed
Acute – Please complete the following: "An oral LD50 of 6116 mg/kg for"	Addressed
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Table 7 – The study of Sodium Lauroamphoacetate in Charles River rats appeared to use a diluted solution for all doses. Rather than saying "and 3422 mg/kg for the undiluted test substance", it would be clearer if it said: "and 3422 mg/kg for the a.i."	Addressed
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Please state the duration of the rest period used in the third HRIPT	Addressed

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: EU REACH Consortium

DATE: January 16, 2026

SUBJECT: Tentative Report: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (release date: November 17, 2025)

Composition and Impurities – "amidodipropyl dimethylamines" should be "amidopropyl dimethylamines".

Table 8; Reproductive and Developmental Toxicity – The EU REACH Consortium commissioned the OECD guideline studies 414 (rat), 422, 408 as well as the 442 and the rabbit 414 studies. All these studies were completed on the same material, which should be called the same thing throughout the CIR report. In Table 8, it is called Disodium Cocoamphodiacetate for the 414 (rat), 422 and 408 studies and Amphoacetates C8 –C18 diacetate form (read-across for Disodium Cocoamphodiacetate) for the 442 and 414 (rabbit) studies. If two names are used in the CIR report, it should be made clear that they are two names for the same material.

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Comment Submitter: EU Reach Consortium **Subject:** Tentative Report: Safety Assessment of Fatty Amphocarboxylates as Used in Cosmetics (release date: November 17, 2025) **Date of Submission:** January 16. 2026	
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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.

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

DR. BELSITO: I agree.

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

DR. RETTIE: Okay.

DR. 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.

DR. 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.

DR. 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 --

DR. 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.

DR. 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.

DR. 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.

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

DR. ANSELL: Yeah.

DR. BJERKE: Percent activity.

DR. ANSELL: Right.

DR. 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?

DR. BJERKE: That's right.

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

DR. 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.

DR. 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.

DR. 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.

DR. 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.

Full Panel – June 13, 2023

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.

JUNE 2024 PANEL MEETING – SECOND REVIEW/REVISED DRAFT REPORT

Belsito Team – June 3, 2024

DR. BELSITO: Then we're moving on to the fatty amphocarboxylates. So, again, before we start that report, Allan, do you want to update us on the Read-Across Working Group?

DR. RETTIE: Sure. So, going back to the general summary comments that I read earlier, we had all the issues we've been talking about with regard to very potent receptor-based interactions. Now, these don't apply here, but what does apply is read-across when mixtures may be involved. Clarification of the composition of the -- is it 11 ingredients that we have here? -- 11, I think, is something we'll get to.

So, this is where the betaine example, which I tried to bring up earlier and shouldn't have done, applies. Much of the arguments seemed, to me at least, to rely on read-across from the betaine. As I mentioned earlier, the group, all of us, even before we had the Read-Across Working Group together, did not accept the notion that using the permanently quaternary ammonium charged compound was appropriate.

DR. EISENMANN: I thought they're only proposing that compound for dermal penetration, period, is my understanding. And, to me, it's just getting them into the ballpark.

DR. RETTIE: Okay. Well, we'll take that under consideration. I think you're right. But while I'm still on the betaines, an argument made for potential read-across to the amphocarboxylates for dermal penetration for both surfactant groups are ionized at all pHs, and we acknowledge that that's true. But it's a different circumstance when we move away from the betaines. Amphocarboxylates do not have a charge nitrogen under alkaline conditions, and they're uncharged, of course, at the isoelectric point or largely uncharged in the isoelectric range. We considered that these distinctive features might affect tissue distribution. So, we started in with that because we had begun with discussion of the betaines before, and alkyl betaines have been through this group and reviewed positively in the past. What else do we have here?

Once again, we came to the tentative conclusion that read-across for highly-sensitive toxic endpoints are not appropriate. And in this case here, we have concerning tox signals such as cardiac abnormalities, just another complicating feature. We were worried about that especially since we have no mechanistic underpinning for that observation.

DR. BELSITO: So, the Exponent analysis of that DART and -- we have one study of several.

DR. RETTIE: Did we disregard it because it was --

DR. BELSITO: Yeah.

DR. RETTIE: I had the impression there were three separate studies that brought up the same cardiac malformation.

DR. BELSITO: Think it was only one, no?

DR. RETTIE: Paul, did you get into that, the number of studies that brought up cardiac malformations?

DR. SNYDER: I did not. I did not.

DR. BELSITO: Well, Table 8 summarizes all the repro studies we saw. So, if we look at Table 8. Okay. Gavage. No treatment-related effects. Another gavage. No external or visceral malformations. OECD TG 414 was again a gavage. No adverse effects related to developmental parameters were observed in the fetus. So --

DR. SNYDER: In that study, it was positive. They couldn't determine an NOAEL for that effect either.

DR. BELSITO: Right. There was no dose response, right?

DR. KLAASSEN: That's what they said.

DR. BELSITO: So, we have studies with NOAELs above a gram per kilogram. Gavage studies, by the way, which people criticize for overwhelming defense systems.

DR. RETTIE: So, are we centering around that single cardiac abnormality study here then?

DR. EISENMANN: I thought that John DeSesso's report that was provided at the last meeting was useful in that he took all the studies together and combined them.

DR. BELSITO: Right. That's the Exponent report.

DR. EISENMANN: Right.

DR. BELSITO: Yeah. I mean, I found that very helpful as well, and we've agreed to take in outside expert opinion on an ad hoc basis. I think this is one opinion we should take in. And I'm not really concerned about the DART effect. I mean, I think that it is spurious. There was no dose response, and it's inconsistent with everything else we have, the gavage studies we have, wasn't seen. But it's not my area of expertise, so I'll see to other people.

Paul, I usually go to you for repro. What did you think?

DR. SNYDER: Yeah. I mean, I thought in June of 2023 we asked for more DART, and we have not received any more data since then, right. So, are we saying we're not concerned anymore about DART, my notes say?

DR. BELSITO: Well, I think we asked for it because David Ross wanted it, not because we wanted it.

DR. SNYDER: Okay. All right.

DR. BELSITO: If you go back with the original, I think we're willing to start with safe as used for this group.

DR. RETTIE: Yeah, I know from what I recall, the reading work across group, Dave is the main proponent for additional DART studies for that. Not my area of expertise either.

DR. EISENMANN: In their update, they've said there's a rabbit study underway, and there's a one-gen underway for ECHA. But the one-gen's going to take a while for it to be completed.

DR. RETTIE: So, to consider additional DART data, we're likely looking at a long time.

MS. CHERIAN: September-October.

DR. RETTIE: Oh, that soon?

DR. EISENMANN: That's when they give a report. So, however long it'll take them to finalize a report after they get it, so it might be a while yet.

DR. KLAASSEN: Yeah, they say that there's no dose response, and we have to kind of take their word for it. What might be interesting is that if we can get the number 24 report, which this comes from, what does the actual data look like? Instead of concluding there's no dose response --

DR. EISENMANN: Some of the actual data is in the Exponent report.

DR. KLAASSEN: That's in the Exponent report?

DR. BELSITO: Yeah.

DR. KLAASSEN: Okay.

DR. BELSITO: Reference 24 is the Exponent report.

DR. KLAASSEN: Oh, that is it.

DR. BELSITO: Yeah. DeSesso is the Exponent report looking at all the data.

DR. KLAASSEN: Okay. We had that the last time but not this time.

DR. SNYDER: (Inaudible) data to clear all the other IDAs, the dermal absorption, composition, impurity, sensitization?

DR. BELSITO: Not sure of your question. Did he clear read-across for those, or what was your question?

DR. SNYDER: No, before, we came out with an insufficient data announcement for four items in addition to the DART. So, I just wanted to be clear. Did we get data, because my notes say we received no new data?

DR. RETTIE: I mean, that report went into some detail about the AEEA effects or lack thereof, and they excluded the AEEA as being a contributor to the toxicity observed. But that leaves us with no working hypothesis or any kind of clues about what might underlie this serious toxicity. And so, if we can get anymore clarification on that, I think the Working Group would appreciate it.

DR. KLAASSEN: Monice or Bart, could you send me that DeSesso review that we saw the last time. I could read it tonight again. I know we talked about it three months. It looked pretty good then, but I'd like to read it again.

DR. RETTIE: Could you CC me too, Monice? Save me digging out.

DR. BELSITO: Just send it to everyone.

DR. KLAASSEN: If I recall right, the quality of the products in this class were not great. Am I remembering correctly?

DR. BELSITO: Well, none of them are pure. They all have active ingredient probably as much as 50 percent if you're lucky, and then they have other material. But the other material is reportedly things like water and other inactive, quote-unquote, for lack of a better word. You see that -- it's in Table 1 or 2.

DR. KLAASSEN: I remember.

DR. RETTIE: It's in Table 4, composition of tradename mixtures. We have compositions for -- one, two, three, four, five -- five of them. And as you said, large component of the preps, as listed here, are water, up to 70 percent. What's not listed here but which I wondered about at least having a declaration that when we were talking about an acetate we did not have the diacetate, when we were talking about a propionate, a declaration that we don't have the dipropionate because this mono-, di- piece is missing from here. And from what I read of documents that came from Europe, it was common that mixtures of the mono- and di- constituents were being used. I felt that was a little problematic and made it a little difficult for the Read-Across Group to know how to deal with that.

I kind of feel that monoacetate to monopropionate -- this is just me -- is probably okay. I have more concern about monoacetate to diacetate, monopropionate to dipropionate just because you got a bigger molecular weight. It's farther away. Maybe it's okay to accept it as read-across, but I just didn't know what we were dealing with composition-wise in the current report.

DR. BELSITO: Why would the greater molecular weight bother you?

DR. RETTIE: Well, again, it's read-across, and mostly when you're thinking about read-across and applying simple rules, you want to go as close as you can to the chemical structure. And so, it's less of a distance from the monopropionate to the monoacetate, as compared from the monoacetate to the diacetate or the dipropionate here.

DR. BELSITO: But we're also looking at something that first has to be dermally absorbed.

DR. RETTIE: Yep.

DR. BELSITO: And would you expect a diacetate to be more or less absorbed than a monoacetate?

DR. RETTIE: I felt it should have a higher log P, and I thought it should be probably more absorbed than less absorbed. The log Ps that were reported in the document here weren't that clear to me. The ranges that we're reporting make an awful lot of sense. Now, the log Ps in our tables here for chemical properties, Table 2, go from minus-8 all the way up to 0.5. Seems very wide, so I was just questioning what the compositions were.

DR. KLAASSEN: I thought if there was one thing that in silico could do for us was to give us the pKa in these physical properties, and apparently, it can't even do that.

DR. RETTIE: Well, it might because I have a note here that we're using three different programs to estimate.

DR. KLAASSEN: Yeah, I know. Maybe I was naïve --

DR. RETTIE: No, no.

DR. KLAASSEN: -- because I thought, man. I took those numbers as rock solid until I saw this. And being so different, I don't know what to believe anymore from in silico.

DR. RETTIE: I mean, it gives us some information about the range of log Ps that you'd estimate for really the part of the molecule I wasn't that concerned about, which was the acyl side chain variation all the way from C8 up to C18. I would've like to have seen information on the log Ps, which should be easy to get, as you say, for the monoacetates and diacetates, but maybe I'm completely wrong here and the composition of these compounds that we're looking is absolutely as described. But like I said, it's quite a bit different from what I was reading in the ECHA documents, so I was just suspicious.

DR. EISENMANN: The wheatgerm one came from a NICNAS document, was not estimated by us. I wonder if it would be good if you guys did an estimate. I think they picked a specific structure that's predominantly in the wheatgerm oil. I don't remember what fatty acid they picked. That's the real outlier, that 0.5 percent.

DR. RETTIE: Zero-point-five. Yeah, that's right.

DR. EISENMANN: Oh-point-five (inaudible) percent. So, it might be good if you guys did the -- I don't know if you did the calculations for the other ones or not, or if they came from references. But that one might be good for you guys to do an estimate.

DR. HELDRETH: Yeah, we just used EPA's EPI Suite and just plugged in the SMILES codes for the two ends of the possible chain links. Since we're talking about coco-derived C8 up to C18, we get both of those ends of the range.

DR. EISENMANN: So, to be consistent, put in the wheatgerm just out of curiosity because that came from a different source.

DR. HELDRETH: Okay.

DR. RETTIE: Thanks. I would just like to reiterate that my concerns fall out if we accept the purities of the mono- versus diacetates as stated here. But just would like somebody to tell me why they're so different from the ECHA compositions. Seems like a disconnect. Are these call them purified, HPLC-purified, in the U.S.?

DR. EISENMANN: I don't know. I have to look back and see where that data is coming from. But the people that are providing data is the ECHA Consortium. They're the ones that have the data ongoing.

DR. RETTIE: Okay.

DR. EISENMANN: I mean, they're testing their mixtures, I think.

DR. RETTIE: And in that document somewhere, there's up to 25 percent of the diacetate in one of these, or more, because it's here. That was my concern. Why don't we see 25 percent of the diacetate? I mean, it should be fairly innocuous. I don't want to make a big deal about it. It's just the lack of consistency between the ECHA document and what we're looking at in Table 2, I guess -- no, Table 1.

DR. HELDRETH: Yeah. So, in Table 1, we presented exactly what you would find in the dictionary monographs. But document folks that actually make these sorts of materials where it's like they took coconut acid. They took a cut of coconut acid, has a range of like C8 to C18. And then they're reacting it to make the amphoacetate or to make it diacetate.

DR. RETTIE: Sure, I understand.

DR. HELDRETH: And even though you might call it disodium cocoamphodiacetate, both the ingredient itself and any source materials that we were reading from, they're probably all mixtures of monoacetates and diacetates to some extent but with a peak that's higher, for example, the diacetate when it's named diacetate, and a peak that's higher for the monopropionate when it's named monopropionate. But I think it's always a mixture. And you see the same kinds of mixtures from the source materials and the ingredient.

DR. RETTIE: So, you'd say that it's always a mixture, not only at the level of the acyl side chains, which we kind of all understand, but given the synthetic methodology making the imidazoline and then opening it up, it's always a mixture of the monoacetate or the diacetate.

DR. HELDRETH: That's my understanding of it. Sitting and talking with the folks on the INCI Committee who actually have experience making these sorts of things, you take even a mixture of the fatty acid side chains and try to do acetylation of that, you're going to get mixtures because you're starting with mixtures, and it's just a challenge. You can push the majority to be one or the other, but to get exclusive and then to do separations on it -- I mean, you can do separations like that in a lab, but on the large scale, probably not worth the effort. And why? What are you excluding in a --

DR. RETTIE: So, the level of the Read-Across Working Group's deliberations about this one, we were kind of stymied because I don't know that we had that amount of clarity at the Read-Across Working Group. And so, we honed in on the idea that, when you've got mixtures in your ingredient, mixtures of these analogues basically, we weren't really sure how to deal with that. So, we stopped short.

My feeling is the read-across to the diacetates -- the diacetates are going to have bigger differences I think in terms of physical chemical properties. But maybe it's all awash if they're all a mixture of monoacetates and diacetates or monopropionates and dipropionates. Certainly something we should talk about again in the Read-Across Group.

DR. BELSITO: Does the method of manufacturer on PDF 41 that's given for these help you understand in any way the fact that they would like -- I mean, I'm assuming that this is a generic method of manufacture for both the mono- and the diacetates, is that correct?

MS. CHERIAN: First paragraph?

DR. BELSITO: Pardon?

MS. CHERIAN: The first paragraph?

DR. BELSITO: Yeah.

MS. CHERIAN: Yes.

DR. RETTIE: So, we're on PDF 41, first paragraph, Method of Manufacture?

DR. BELSITO: Yeah.

DR. RETTIE: Yeah. So, as I mentioned earlier, yeah, it tells us we get a substitute, imidazoline, which then gets reacted and splits. As I understand it, it's the same method of manufacture as is outlined in a figure in the ECHA documents, and it shows both monoacetates and diacetates being made from the same method of manufacture, which is where I started with this and wondered why we didn't have the di-, just had the mono-. But based on Bart's comments, I can understand that a little bit better now. I'm just wondering if we have more detailed information for the tradename mixes. Do they give more detail, and is that what we should be including?

DR. HELDRETH: My understanding with the tradename mixtures is these aren't the ingredients themselves that we're talking about purity. These are essentially like pre-formulations. So, it's the ingredient plus this and this and this, so that when someone at a finishing house includes one of these ingredients, it meshes well with the rest of the formulation.

DR. RETTIE: But it therefore doesn't shed any light on whether it's 15 percent of the dye or 25 percent of the dye.

DR. HELDRETH: Right. Right.

DR. RETTIE: That's just an unknown, and we can't get that info, it sounds like. Well, it may simplify read-across if we can, as the Read-Across Working Group, accept the fact that the mixtures are going to be heterogenous, as we're discussing here. And it's not a huge jump from the diacetate from the monoacetate. It's further than I would like, but can I say it precludes read-across? Maybe not. I'd like to have a chat with the rest for the members of the Working Group to decide that.

What do you think, Curt? Do you have strong feelings?

DR. KLAASSEN: I have no strong feelings.

DR. BELSITO: Paul?

DR. SNYDER: No. That chemistry's a little bit not in my (inaudible). One of my concerns too, Don, is that -- not to change the subject or anything -- but we now that we know there's a rabbit repro study and a one-generation repro study that's forthcoming, are we going to wait until we see that data? Or are going to go ahead and -- because this is a, yeah, draft report. So, maybe it'll be done by the time we get to final.

DR. BELSITO: Yeah, I mean, that was one of my comments in a note from on the developmental and repro tox study. Do we want a table for the data promised on those studies and also for final decision on read-across?

DR. HELDRETH: Yeah, you could either go that way or, since it wouldn't come back till this December panel meeting at the soonest anyway, you could just put out an insufficient data announcement that includes those pieces. Either way will work. It's the Panel's prerogative.

DR. BELSITO: I mean, again, the one positive DART study, there was no dose response. We have an LLNA which is negative at 30 percent, negative guinea pig maximization test. I mean, I really thought that we could go with safe as used when formulated to be nonirritant. And if you were concerned about the amidoamine impurities, deal with it the same we deal with the betaines and say formulate to be non-sensitizing. But I guess we want to await the further DART studies and decisions from the Read-Across Working Group. Is that what I'm hearing from my team?

DR. SNYDER: Yeah, I was getting the same message from Allan there regarding the research -- or the Read-Across Working Group. I mean, I still think they haven't kind of got their guidance for how they're going to approach these things. So, in addition to that, I mean, why would somebody be doing a rabbit repro study and a one-generation study if everything was this clean as we're saying? So, I don't quite understand the basis for that.

DR. EISENMANN: Because ECHA is making them do it based on volume of use. They had a response in their comments on why they're being made to do it. It wasn't a concern; it was just because of the volume.

DR. SNYDER: All right. So, they're just checking a box. Okay, thank you, Carol, for that clarification.

DR. KLAASSEN: I guess, it seemed --

DR. SNYDER: So, if Allan's okay with the read-across, Don, I'm okay with what you propose. We can put it back out there as a safe as used when formulated to be nonirritating and let the other group drive the discussion.

DR. BELSITO: Well, Cohen is actually -- their team is starting the discussion.

DR. RETTIE: Perhaps the last point of clarification from the Wave 2 the first time around, there was some confusion about what amidoamine was. Do we still care about that? You asked me a question, and I didn't know the answer. But turns out that both of the compounds that were being described, amidopropyl dimethylamine and this dodecyl compound -- well, they're both amidoamines, but one's a C16. One's a C12. I don't know that we need to keep going on this, but I just wondered if it was still an outstanding question for the group.

DR. BELSITO: The amidoamine becomes an issue if it's a residual -- the starting material is a residual and what's marketed because it's a sensitizer. So, we had this issue with a group of compounds called betaines that we reviewed before you joined the Panel where there were questions about sensitization to betaines and whether they were due to dimethylaminopropylamine or to amidoamine. We went back and forth, and there were some positive sensitization data, negative sensitization data. Anyway, the long and short of it was that it was resolved by saying that they were safe as used when formulated to be non-sensitizing based upon a QRA or other similar methodologies. Which we could do here as well if we were concerned about potential sensitizing starting materials that remained in the final product.

So, to answer your question, Allan, no, it doesn't matter whether it's C12 or C16.

DR. RETTIE: They're both known sensitizers. Okay.

DR. BELSITO: I had a question for you, Carol. When we're getting these concentrations of use, are we getting the concentration of the mixture, or we're getting the concentration of the, quote-unquote, active ingredient, the amphoacetate that we're looking at in the final product?

DR. EISENMANN: (Inaudible) I'm asking (inaudible) concentration of the active.

DR. BELSITO: You're asking.

DR. EISENMANN: Yeah.

DR. HELDRETH: Good answer.

DR. EISENMANN: So, that's what I want them to give me. I don't have access to their files, so that's what I'm asking them.

DR. BELSITO: So, we have to operate under the assumption that they have told you the concentration of the active.

DR. EISENMANN: And I do my best if something seems out of place to go back and say, is this real? Or is this correct? Though, sometimes, if I do right away, the person -- they just looked at it, so they assume that it's correct. But if I go back a few months later, somebody else might be looking at their database, and I sometimes get a different answer. But, yeah, it is (inaudible). They change their formulations too a fair amount, so it is moving. Concentrations of use are moving targets, I've decided.

DR. HELDRETH: Part of the reason we have the caveat as described in this report.

DR. BELSITO: Right. Okay.

DR. KLAASSEN: The name can stay the same, but the ingredients can change. The first time I came across this was with Tide soap. Tide soap used to have a lot of phosphate in it, and then they got all this fungal growth and what have you in the rivers and stuff. So, they took it completely out and reformulated about 98 percent, and it was still called Tide. Is that right?

UNIDENTIFIED MALE: Yeah.

DR. KLAASSEN: So, the name can stay the same, but the ingredients can change.

DR. BELSITO: Okay. And just Allan and Curt, since you're in the Read-Across Working Group, the lamidopropylbetaine is being asked for a read-across for absorption only, not for other endpoints, if you remain concerned about absorption. So, it's --

DR. RETTIE: Yeah. And I felt the C12 was the most prominent constituent, so probably is the best candidate for selection there.

DR. KLAASSEN: I'm okay with that.

DR. BELSITO: Okay. So, just going through the documents. I mean, I know we're going to table this, but again for -- Priya, this is your document as well? Boy, you're a lucky lady, aren't you?

MS. CHERIAN: I know.

DR. HELDRETH: She gets all the fun ones.

DR. BELSITO: Yeah. Okay. I don't have any additional -- oh.

On table -- well, PDF Page 65, it's Table 10. For the LLNA on the top one, the sodium lauroamphoacetate, we described the ear thickness increases. You didn't give values for the stimulation indexes because the ear swelling could simply be secondary to the irritation that we know these have. So, it would be helpful, at least for me, in terms of sensitization if you put the SIs for the different concentrations for the EC3s, if they were given.

Okay. Then we had a Wave 2 on this. Let's just discuss. We received comments from the Council, which I thought were all fine. Curt, Allan, Paul, did you have any?

DR. RETTIE: I did not.

DR. SNYDER: I did not either.

DR. BELSITO: Okay. And then we received comments from the REACH Amphoacetate's Consortium asking us to, again, look at the Exponent analysis. But since they're already doing a rabbit study and other DART studies, my hearing from you all is that we're going to table this and wait for those DART studies before reopening it again or looking at it again.

DR. SNYDER: No, I probably retracked that based on Carol because, if it's just to meet data needs based on volume of product, not based on any concern. I think there's certainly sufficient studies that are under that table. So, I would be okay with going back to the safe as used when formulated to be non-sensitizing.

DR. BELSITO: And non-irritating.

DR. SNYDER: And non-irritating. Sorry, yes.

DR. BELSITO: Okay. So, now we're coming full circle. We don't need read-across. So --

DR. SNYDER: But that's based on if Allan's okay with that.

DR. BELSITO: Pardon?

DR. SNYDER: Pending Allan's input on that.

DR. BELSITO: Well, Allan's input on what, read-across? Because if we're going safe as used, what we're saying is we don't need additional read-across data at this point, right?

DR. SNYDER: Yes.

DR. KLAASSEN: By definition.

DR. BELSITO: Right. So, Curt and Allan, what do you think of that approach, which was our initial recommendation? I mean, these data needs all came from the Cohen team, not from our team.

DR. RETTIE: Again, I feel a little naked talking about the Read-Across Working Group without the other members.

DR. BELSITO: We're not talking about reading. We're talking about not having read-across at all based upon the information that you're seeing in this document. And Wave 2, do you feel they're sufficient, or do you feel that we still need read-across? And for what endpoints, do we need read-across for?

DR. KLAASSEN: I think it's sufficient if I can read this document tonight, that Exponent sent, and to make sure I remember that correctly. And if I do, I think we can go as Paul said.

DR. BELSITO: Sufficient when formulated to be non-irritating, and we can talk about the sensitizing endpoint that whether it's non-sensitizing or not. I don't think we need it for this one. I'm not that concerned about the level of residual amidoamines. But I don't think the other team is going to go safe as used, by the way, but that doesn't matter. Allan, your thoughts?

DR. RETTIE: I can go along with it.

DR. BELSITO: Okay.

DR. RETTIE: We don't need for read-across.

DR. BELSITO: So, Curt, you're going to give me a heads up at some point before the meeting?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay.

DR. KLAASSEN: As long as someone sends that article to me.

MS. FIUME: It should be in your inbox.

DR. KLAASSEN: Okay, great.

DR. BELSITO: Okay. Is there anything else? Wave 2 was the fall of the various, looking at the in silico predictions for potential read-acrosses. So, I think we've covered the comments in Wave 2. Okay. Anything else on the amphoacetates?

Priya, have we completely confused you as to where we are?

MS. CHERIAN: I'm okay right now.

DR. BELSITO: Ask you again tomorrow morning?

MS. CHERIAN: Yes.

DR. BELSITO: Okay.

Cohen Team – June 3, 2024

DR. COHEN: Okay. We're going to move on to fatty amphocarboxylates. It's like we're doing a lot of the heavy lifting early today. So, this is a revised draft safety report for fatty amphocarboxylates who was first reviewed in June of 2023 at which time the panel tabled the review due to receipt of a large amount of information in Wave 2. It included various fatty chain mixtures that are listed and reach dossiers for the following substances that are listed here as well.

The CIR prepared a read across justification table and the Read Across Working Group met to adjudicate that. Also, in June, the panel noted that the following data points were needed. Dermal absorption/DART on disodium cocoamphodiacetate and further information regarding composition and impurities of these ingredients as cosmetics, particularly percentage of actives in ingredients in fatty composition. And we wanted sensitization data on sodium lauroamphoacetate at max use concentration and I don't believe we've received that.

DR. ROSS: We didn't.

DR. COHEN: Yeah. So, again, just as a reminder of the 11 ingredients, disodium cocoamphodiacetate, disodium cocoamphodipropionate, sodium cocoamphoacetate, and sodium cocoamphopropionate have previously been reviewed as safe as used in a 1990 report which was rereviewed and reaffirmed in 2006. So, we needed feedback from the Read Across Group on this.

DR. ROSS: Yeah. So, I gave the last one so Susan, you want me to do this one or do you want to do this one?

DR. TILTON: We talked about some of the general read across concerns earlier already and with this group one of the primary concerns was doing read across for mixtures and the differences in composition across the different mixture groups. And then, also doing read across for certain sensitive endpoints. And in this case, that involved in some of the DART data that I'm sure we'll discuss.

DR. ROSS: There was a specific question on this betaine read across and there was a specific request that came in to reconsider that. I think that came from the consortium.

DR. TILTON: Specifically, for --

DR. ROSS: The betaine.

DR. TILTON: -- absorption.

DR. ROSS: Yeah. And so, the RAWG -- should we call it the RAWG or the Read Across Group? Anyway, the Read Across Group didn't support that so the betaine was not supported for read across. So basically, we hadn't changed our position on read across for two reasons. One being the mixtures that Susan pointed out and secondly the betaine was not supported. It's bitter ionic compound whereas the other ones, they're ionized also physiological ph. That's true, but only the betaines have a charged quaternary nitrogen in all PH values.

DR. COHEN: So, you couldn't take the betaine read across.

DR. ROSS: Correct.

DR. COHEN: Okay.

DR. ROSS: So that was that. You know, I think there are still concerns with the amphocarboxylates in general. The DART data and cardiac malformations. A new developmental toxicity study has been completed. We saw this document a few times, I believe, and the new DART data was always coming. Well, I think it's been completed now.

DR. COHEN: Didn't it say it was coming in September or October?

DR. ROSS: Yeah. And so, it'll be -- it's right now, I think, it's with Exponent, the consultants, and it'll be released to us in September/October as David comments. And I would just make the statement, which I do feel strongly about, you know, I wasn't strong on the yeast issues, but I do feel strongly about this one, that I think it's very unwise, in my opinion, to move ahead until we've seen that new DART data. So, I would support tabling this as well until December until we have a chance to look at that new DART data.

DR. COHEN: I had the same conclusion was to table until the December meeting because it said it would be available September/October which won't give us time.

DR. ROSS: Yeah. And I just think it would be very wise to do if we haven't seen that data.

MS. FIUME: Can I make a request? So, procedurally this is only a revised draft report and insufficient data announcement has never been issued yet. So, it is the Panel's prerogative to weigh on those data but also identify any other additional data needs to avoid that having to be the next step. And rather than table, if there are additional data needs, you can go out with an insufficient data announcement, then it would probably come back in December anyway and hopefully you would have those new data as well instead of having to wait and ask for additional data at that point if more is needed.

DR. COHEN: So, when -- I thought we had -- so, at June, we noted the following data are needed. I viewed that as an IDA. But maybe it wasn't an IDA.

MS. FIUME: Because it was tabled, there could be no true action. So, at times we'll know in the post/in the announcement as hey, industry, this hasn't been formally requested yet but this is what we're looking for. Just know that the Panel is also interested in this information.

DR. ROSS: Are you sure we can? Well, you know because you wrote it. But, I mean, did we not make that request?

MS. FIUME: It may have been asked for informally, but it hasn't been a formal --

DR. COHEN: So, it wasn't an IDA?

MS. FIUME: It wasn't an IDA. It was tabled which is why it came back as a revised draft report and not as a draft tentative report.

DR. COHEN: I think that makes a lot of sense. Otherwise, it's going to slow this process down a lot if we table to December, pick it up as a draft report -- well, it would be a draft --

MS. FIUME: Then it would be a revised draft report.

DR. COHEN: Revised draft report and it's going to take another year to get through.

DR. TILTON: So, this wouldn't be a tabling, this would be --

DR. COHEN: This would be an IDA.

DR. TILTON: -- an IDA and one of those requests would be for this data set that's coming forward.

DR. COHEN: So, let's line up our IDA then.

DR. ROSS: Yeah.

DR. BERGFELD: But you have a list already that you informally -- would you want to change that list? I mean --

DR. COHEN: I was just going to go through that with the group.

DR. ROSS: What's the PDF of that? I'm sorry, I'm just --

DR. COHEN: Well, it would be in the beginning.

DR. ROSS: Right in the beginning of the report, right.

DR. COHEN: Just look at the previous memo.

DR. ROSS: It should be there, right?

DR. COHEN: It's right on the first page. These memos are great.

DR. ROSS: Yeah, yeah. They're good. Yeah, yeah, yeah, yeah. I've got it. Got it, got it, got it. Yeah. Thanks. Yeah, there's the sensitization data on sodium lauroamphoacetate at max. We didn't get that. I would also like to see the, and we may not get this, but I'd like to see the ocular concentrations of use of the compounds that are used for that indication. We don't have concentrations of use in our use tables for those.

DR. COHEN: Okay. So, we still want dermal absorption data on what?

DR. BERGFELD: Sodium cocoamphopropionate.

DR. COHEN: We get to the table.

DR. ROSS: I think that's whether we're using read across to the betaine and --

DR. TILTON: Because we really don't have any data.

DR. ROSS: Yeah. So, I think you can just note that as dermal absorption data.

DR. COHEN: Say that again.

DR. ROSS: You could ask generically for dermal absorption data.

DR. COHEN: On the whole group?

DR. ROSS: Yeah. And then see what we get because I think it depends on the read across with -- if you're going to read across this point -- we're not.

DR. COHEN: So, none of these in this group are reading across to the others?

DR. ROSS: That's correct at this point.

DR. COHEN: That's pretty heavy.

DR. ROSS: Yeah. I think we have tox endpoints for most of the major compounds apart from DART. For most of the major compounds we have -- I think there's a way forward on many of these compounds that are used, at least the major ones -- and that, I think, we'd have to address when this comes up again. But I think all is not lost on this, I think there are potentially ways forward.

DR. COHEN: Okay. So dermal absorption data and we want DART.

DR. BERGFELD: Do you want the results of the DART? I mean, if they said they're doing it and it'll be ready, I mean, what --

DR. COHEN: This is for disodium cocoampho- --

DR. ROSS: Acetate, yeah.

DR. COHEN: -- -diacetate, right?

DR. TILTON: Diacetate, yes.

DR. ROSS: That's the compound where we had the cardiac malformation data. I think you could just leave it as is. DART data on disodium.

DR. COHEN: We'll keep that. We'll keep that. Further information regarding the composition and impurities of these ingredients.

DR. ROSS: Well, remember these things are listed as VC -- variable com- -- no, I've got that wrong. Anyway, their materials are listed at variable composition. I forget the actual definition. But that's what we were getting at with that comment. We wanted more definition around what's in them, but I think that we're going to get that because that's how they are. That's how they're made and that's how it's going to be. So, that was our request.

DR. COHEN: So, what's the disposition of the IDA for that?

DR. ROSS: I think we ask for it and if we can get it, that's great, because we need to know what's in there. I suspect we won't get it but that doesn't necessarily preclude a way forward. But it would be very good if we could point out what was actually in this study.

DR. COHEN: The sensitization at max use for sodium lauroamphoacetate.

DR. ROSS: I think that was 9.9 percent as I recall.

DR. COHEN: It was -- I thought it was 5.4 percent.

DR. ROSS: Ah, right. Max concentrations probably would be a safer way to go.

MS. FIUME: That's what we typically try to put into the post meeting announcement is just stating max concentration of use.

DR. COHEN: Yeah, max concentration.

MS. FIUME: Yeah.

DR. COHEN: There's a cocoamphoacetate at 20 percent in a rinse off product. The disodium lauroamphodiacetate has the highest concentration of use in a leave on product. So, I have one, two, three, four of the original plus ocular concentration of use in products used near the eye.

DR. ROSS: Yeah. That would be great, David, thank you.

DR. COHEN: Did I capture --

DR. ROSS: Yeah.

DR. COHEN: I like that idea of that we're not tabling it. This is just going to keep coming back around. So, this could come back anyway in December with that data anyway. That would be the course anyway and then we'd go to a draft tentative.

MS. FIUME: It would come in as a draft tentative report and go out as a tentative.

DR. COHEN: Yeah.

MS. FIUME: Yes.

DR. COHEN: Yeah.

DR. BERGFELD: What did you say about the eye? You wanted further documentation on this one, the concentrations in the eye? I note that there are some concentrations up to three percent.

DR. ROSS: Yeah, there are but there's --

DR. BERGFELD: That's up to 20 percent.

DR. ROSS: -- but in the eye a lot of them are not reported that are used around the eye.

MS. FIUME: Yeah, I believe it's those that -- the four that had been reviewed before have eye use, but no concentration given for them.

DR. ROSS: Yeah. So that was the only thing I needed, Wilma, just to --

DR. COHEN: Do we have a specific one for that, though? I'm trying to find it.

DR. ROSS: Well, there are -- I abbreviated these two numbers so -- in my report.

MS. FIUME: For those that are missing the concentration?

DR. ROSS: Yeah. For the eye area.

MS. FIUME: It's disodium cocoamphodiacetate, disodium cocoamphodipropionate, and sodium cocoamphoacetate. I have frequency of use for eye area products but not concentration. Did I miss any, Priya?

DR. ROSS: Which one --

DR. COHEN: Which PDF is that? Well, let me try to get to that PDF.

DR. ROSS: I have four compounds. Compounds one to four, but I'll have to get to my definitions.

DR. COHEN: Because you had a -- that chart is pretty useful.

DR. BERGFELD: So, if you had eye at 0.18 in one report and eye in another report of 1.3, are there other particular ingredients that's noted there is not reported would you not assume that they couldn't exceed what has been reported?

MS. FIUME: That is typically what happens, yeah.

DR. BERGFELD: So, the highest would be 1.3.

DR. COHEN: But if we can't read across does that still hold? That's a real bonified question. If you can't read across, does it matter that you've tagged a concentration of one, but you can't pull that data over to the other.

DR. BERGFELD: Well, that's a valid suggestion but that's all you have, so it probably shouldn't exceed that.

DR. COHEN: But how do we know that one's toxic at that concentration and not at the other if you're not reading across?

DR. ROSS: But you have, of the five most commonly used compounds there you've got three of them -- just provide notation here, one -- compounds one, three, and five we have in vitro ocular data at three percent. Compound five we have animals that meet compound one, we have humans at 1.2 percent and the maximum ocular concentration is 0.11 and 1.3 percent. It's already closed on one, three, five. So, three of the five compounds. So --

DR. COHEN: You're building, at least, a body of data to --

DR. ROSS: Yeah.

DR. COHEN: -- it's not a read across but it's culminating to safety.

DR. ROSS: So, it's like here we've got quite a few of these tox endpoints and many of them were frequently used compounds.

DR. COHEN: You still want the IDA?

DR. ROSS: Oh, yeah.

DR. COHEN: Okay.

MS. CHERIAN: So, for sensitization you want to just put sodium lauro?

DR. ROSS: Yeah.

DR. COHEN: For sodium lauroampho- --

MS. CHERIAN: Do you want specifically an HRIPT because we have LLNA data right now.

DR. COHEN: We have --

DR. BERGFELD: I don't think you ask specifically, you just ask for the sensitization data.

DR. COHEN: Can you just repeat what you just said?

MS. CHERIAN: If you wanted specifically an HRIPT because we have an LLNA and our maximum for leave on for that one I think is 1.1, but maximum for rinse off is 9.9.

DR. COHEN: Wait. I thought the maximum leave on for that was 5.4.

MS. CHERIAN: That's disodium lauroamphodiacetate.

DR. ROSS: It's 9.9.

MS. CHERIAN: For rinse off.

DR. COHEN: For rinse off.

MS. CHERIAN: The maximum leave on for all of these is 5.4 in disodium lauroamphodiacetate.

DR. COHEN: Disodium lauroamphodiacetate.

MS. CHERIAN: Mm-hmm.

DR. COHEN: So why is it? Let me just see something here. So why is our requested data different? You see in the memo? It's a sensitization data on sodium lauroamphoacetate at max use.

MS. CHERIAN: Well, we have data for disodium --

DR. ROSS: Isn't the max use 9.9? That's what I have in my notes. May be different.

DR. COHEN: Let me go back in my notes.

DR. ROSS: Let's go back to the table.

MS. FIUME: The highest leave on is 5.4. I think the 9.9 might be the rinse off.

DR. ROSS: Let's take a quick look, shall we?

MS. FIUME: Actually, I think -- I'm sorry -- the rinse off is 20 percent.

DR. COHEN: Yeah. I had it as 20 percent for cocoamphodiacetate. And the highest leave on was 5.4 percent for disodium lauroamphodiacetate. Is that wrong or is that old?

DR. ROSS: I just kept my dermal --

DR. COHEN: That's correct, what'd I just said? And our sensitization is way below that, right?

DR. ROSS: For sodium lauroampho, yeah.

DR. COHEN: Well, I'm looking at human.

DR. ROSS: For -- okay, so what I've got here, okay, for human with respect to the older data which I'm guessing this comes from previous reports, compound one which is the most common which is cocoamphodiacetate, for example, irritation in humans is okay to 25 percent and sensitization is okay at 35 percent.

DR. COHEN: But where are you?

DR. ROSS: This came from the old data.

DR. COHEN: I know, but what PDF are you in?

DR. ROSS: I don't have that in my notes.

DR. COHEN: I have human irritation, we have five percent for disodium cocoamphoacetate, right, for irritation in eight subjects.

DR. ROSS: Compare --

DR. COHEN: And then ten percent for sodium cocoamphoacetate.

DR. ROSS: Well, the old data I have summarized here.

DR. COHEN: I think these were a little irritated.

DR. BERGFELD: And they're detergents.

DR. COHEN: Yeah, they were moderate -- that's right, they're irritating. But for sensitization --

DR. BERGFELD: You have a guinea pig.

DR. COHEN: I see a guinea pig at --

DR. BERGFELD: You have irritations in humans.

DR. ROSS: You've got irritation/sensitization in humans.

DR. BERGFELD: Yeah.

DR. COHEN: Where's the sensitization? It's sodium lauroamphoacetate at 0.15. That's the only HRIPT I see.

DR. ROSS: Correct. Which is why we asked for that data. But the older data, Priya, tell me where that is on the PDF.

MS. CHERIAN: The summarized version is in italicized text.

DR. ROSS: Yeah. So that said -- at least I've got it in my notes and maybe I noted it incorrectly, but we were up at --

MS. FIUME: PDF Page 45.

DR. ROSS: Okay. Let's take a look because I've got it as high as 35 percent. PDF Page 45.

DR. COHEN: PDF 45.

DR. ROSS: Okay. And it should be italicized, correct?

MS. FIUME: HRIPTs are the second paragraph.

DR. COHEN: Ten percent. Is that not in the table?

MS. CHERIAN: No, because it's old data.

DR. ROSS: You don't put the older data in the table --

DR. TILTON: It's from when the first four were grouped so it doesn't include --

DR. COHEN: But we're not reading across, right? Again, what am I supposed to do with this if we're not reading across?

DR. ROSS: Well, you've got a list of --

DR. COHEN: Just reminded me, do we have this report in there?

MS. CHERIAN: (Inaudible).

DR. ROSS: I didn't have --

MS. FIUME: (Inaudible) sodium cocoamphodiacetate. That HRIPT; the last sentence.

DR. COHEN: Give me that again.

MS. FIUME: The last sentence with the italicized text with the HRIPTs it says in addition the sensitization was observed in an HRIPT using disodium cocoamphodiacetate, 32 percent solids, under semi occlusive conditions. However, some irritation was noted under occlusive conditions.

DR. COHEN: That's good.

DR. ROSS: The maximum use, I believe, is 20 percent. So --

DR. COHEN: So, that's the disodium cocoamphodiacetate and we asked for sodium lauroamphoacetate, right?

MS. FIUME: Yeah.

DR. ROSS: Yeah.

MS. FIUME: Yeah. So --

DR. COHEN: And there's a report of disodium lauroamphodiacetate allergy in the literature at one and two percent patch testing.

DR. ROSS: So, you definitely need that.

DR. COHEN: I'd like to have it.

DR. ROSS: I think -- it looks to me --

DR. COHEN: Let me see if I can find it again.

MS. CHERIAN: If you look on 26.

DR. ROSS: So, the cocoamphodiacitates, I have the maximum use at 20 percent. Irritation was okay from the older data at 25 percent. Sensitization was okay at 32 percent. So that one I thought was okay.

DR. COHEN: So, are we continuing the IDA with what we had?

DR. ROSS: I think so and then we work through these issues of what we need with respect to when it comes in. If we assume no read across, I mean, I think you can clear, at least by my notes, disodium cocoamphodiacetate on the dermal and sodium cocoamphoacetate on the dermal based on all the data we have and the concentrations that are used. We still have data gaps with some of the other compounds including the sodium lauroamphoacetate which you are asking for specifically in the IDA.

DR. COHEN: Okay. Hold on a second. So, were you clearing the original four that were cleared?

DR. ROSS: What were the original four that were cleared?

DR. COHEN: Disodium cocoamphoacetate, disodium cocoamphodipropionate, sodium cocoamphoacetate, and sodium cocoamphopropionate.

DR. ROSS: Clearing in what respect? Just on the ocular end?

DR. COHEN: No, just for everything.

DR. ROSS: No, I wasn't clearing anything.

DR. COHEN: Okay.

MS. CHERIAN: That was in there.

DR. COHEN: That was in there.

MS. CHERIAN: It's 38.

DR. COHEN: It's number 38. Okay.

MS. FIUME: So, I can prepare you for Don tomorrow?

DR. COHEN: What's that again.

MS. FIUME: I said I can prepare you for Don tomorrow. It's PDF Page 65. So those --

DR. COHEN: PDF 65.

MS. FIUME: Right, because you're asking for sodium lauroamphoacetate. So those sensitization studies are not sufficient.

DR. COHEN: Hold on. Let me clear this because I'm not getting the page numbers. Okay. Here?

MS. FIUME: Yes.

DR. COHEN: Sodium lauroamphoacetate is at 0.15 percent for humans as opposed to 5.4 percent. So, and then let me look at the others. Are you going to --

MS. FIUME: There's -- the animal studies in there.

DR. COHEN: Yeah, I know he's going to -- I know that -- I know it --

MS. FIUME: As I said, I'm preparing you for tomorrow.

DR. COHEN: Positive reactions were observed in 5 in 20 test animals during challenge. Positive.

MS. FIUME: But the study was deemed unsensitive and I don't remember why. The substance was classified to be non-sensitive

DR. ROSS: Non-sensitizing, yeah. But 5 of 20 test animals.

MS. FIUME: I know. Yeah. I read the last part first.

DR. ROSS: But the induction was only done with half percent, and the challenge was 20 percent.

DR. COHEN: Right. Yeah. It's, yeah. So, we can have that discussion tomorrow. It's definitely coming. I saw the launch before it happened, but we'll see.

DR. ROSS: So, the IDA basically stands.

DR. COHEN: Yeah.

DR. ROSS: Okay.

MS. CHERIAN: But would you like the addition of the disodium lauroamphodiacetate at 5.4 percent for sensitization because of that liquid hand soap study?

DR. COHEN: So, the liquid soap study is disodium lauroamphodiacetate.

MS. CHERIAN: Mm-hmm.

DR. COHEN: What's its max use?

MS. CHERIAN: 5.4.

DR. COHEN: That was 5.4?

DR. ROSS: I thought it was 9.9.

MS. CHERIAN: Oh, 5.4 for disodium lauroamphodiacetate for leave on.

MS. FIUME: Rinse off because that's not typically used at max concentration in HRIPTs.

DR. COHEN: So, what's the sodium -- what's the max use of sodium lauroamphoacetate?

MS. FIUME: It's usually the leave ons has been what the Panel has typically done.

DR. COHEN: Okay.

MS. CHERIAN: I think 1.1 in leave on and 9.9 in rinse off.

DR. COHEN: This one's 9.9 --

MS. CHERIAN: Rinse off.

DR. COHEN: Rinse off -- and what?

MS. CHERIAN: 1.1 from what I remember, I think. Yes, 1.1.

DR. COHEN: Leave on. And then we're amending the IDA for disodium, right?

MS. CHERIAN: You can still ask for sodium lauroamphoacetate too.

DR. COHEN: Yeah. We still will.

MS. CHERIAN: Okay. But I think you want sodium lauroamphodiacetate at max use of 5.4.

MS. FIUME: 5.4 is the disodium lauroamphodiacetate. It's a leave on hair product.

DR. ROSS: Oh, okay.

DR. COHEN: Acetate at 5.4 percent.

MS. FIUME: Mm-hmm.

DR. COHEN: Yep, okay. Good. That extra discussion helped. Any other further comments on the amphocarboxylates?

DR. BERGFELD: I'm sorry, I'm going to just ask you to summarize what you're going to say.

DR. COHEN: No, that's perfectly fine. So, we're going to come out with an IDA for dermal absorption data on the whole group. DART on disodium cocoamphodiacetate. Further information on composition and impurities of these ingredients in cosmetics. Sensitization data on sodium lauroamphoacetate at max use, which is 9.9 in rinse off, 1.1 in leave on. Sensitization data on disodium laurodiacetate up to 5.4 percent. Ocular concentrations of use of products used near the eye that don't have them listed now.

DR. BERGFELD: So, you're actually on the sensitization on sodium lauro, going to give a concentration of 5.4 or a max --

DR. COHEN: No. I'm just going to say max use.

DR. BERGFELD: Okay.

DR. COHEN: That was just for our -- because we might have a discussion tomorrow and the need for the concentrations at hand may be necessary. Okay. Let me just check that one off. I don't know if we're a third of the way through.

DR. ROSS: Downhill from here.

DR. COHEN: I'd like to think so.

Full Panel – June 4, 2023

DR. COHEN: This is a Revised Draft Report on the safety assessment of Fatty Amphocarboxylates. This report was reviewed at the June 2023 meeting at which time the Panel tabled the review due to receipt of data received in Wave 2. These data include information regarding various fatty acid chain mixtures that comprised ingredients reviewed in this report and REACH dossiers for some of the substances.

The read-across coterie members on this team expressed apprehension regarding some of the following. The apprehension on the read-across was problems reading across for mixtures, reading across for certain endpoints like DART which they found concerning, and read-across for the betaines which was not supported.

So our motion, given these read-across headwinds, is an Insufficient Data Announcement with the following needs: dermal absorption data for the whole group, DART data on Disodium Cocoamphodiacetate which we understand is due to be completed in September-October, further information regarding the composition and impurities of these ingredients in cosmetics particularly percentage of actives in ingredients and fatty acid compositions, sensitization data on Sodium Lauroamphoacetate at max use and Disodium Lauroamphoacetate which is the highest concentration of use reported in leave-on products, and ocular concentration of use in products used around the eye. That's my motion. I'm sure there will be some discussion.

DR. BELSITO: Well, you had a lot more insufficiencies than we did, number one. Number two, I think, again, the read-across needs to go to the Read-Across Working Group. Concerning the betaine, I think it's important that read-across is endpoints specific and they were looking at that just for absorption, and not for other endpoints. And that the use of the betaine for the absorption was approved by ECHA, so there are other authorities who have accepted that as a read-across for absorption.

I'm not sure that we need sensitization data. We have data in the report I think that clears that. It can be irritating, and of course that would end up in our conclusion. If we found these safe as used they'd be formulated to be nonirritating. You said you want absorption on all of them?

DR. COHEN: I don't think we have absorption on any of them.

DR. BELSITO: But, you're asking for absorption on each and every one in the group?

DR. COHEN: Well, so, Don, if there's no read-across on these --

DR. BELSITO: But we don't know that yet.

DR. COHEN: I was under the impression that we couldn't do much read-across.

DR. RETTIE: For the betaines initial meeting of the working group, we're really not in favor of that at all for the betaines for arguments related to differing ionization across the pH range. Which is not an issue for the betaines, but they do vary for the other compounds. So we need to go back and take a closer look at that.

I had a comment about read-across as it relates to mixtures. In the working group we had a strong feeling that that was a complication. And I still think for two mixtures it's a complication that we have to acknowledge exists. But for this particular group of compounds that we're looking at here, just over the last day I've seen my attention has been drawn to citations that abrogate a lot of my concerns about heterogeneity. My concerns about heterogeneity were at the level of monoacetates and diacetates being in the same preparation.

It would appear that there is another view on this, that in fact the compounds at the level of monoacetates, diacetates, monopropionates, dipropionates, is pretty pure. The confusion as I had in my head seems to exist at the level of a wrong hypothesis being proposed for how these things were synthesized.

Now, in the exponent report there's a reference to a foreign book chapter, which my team have now to take a look at in detail. And that really lays out another view of those impurities, vis-à-vis, no impurities at the level of the monoacetate versus diacetate, etcetera.

I still think we have some level of heterogeneity, of course, the level of the different e-cell site chains that comes from the oils that are being use. But that's just inherent in there, and this group has seen that in the alcohol betaines and probably other reports in the past. And given that by far the major constituent there is the C12, we know a quite a bit about it. And so a lot of these impurities concerns that I was raising yesterday have fallen away for me. And I think we're dealing with a more homogenous group than I originally thought.

DR. ROSS: If I can just make a comment that we haven't seen that paper or papers you're referring to, Allan.

DR. RETTIE: I emailed it to you at 12:02 last night.

DR. ROSS: Oh, I stand corrected. But, I think the RAW Group needs to consider that again. I think it wasn't just you that was "confused" on the composition and impurities of these things. I think that was a joint RAWG decision. And it appeared to us these were variable composition biomaterials that basically have -- and the components of these mixtures had very different physical properties. So you're looking at solubility and LogPs. It's an order of magnitude different. And so a lot of the conclusion was predicated on that analysis. Now, if that's different, then I think the RAW Group needs to look at that again.

DR. RETTIE: Absolutely. I feel it's different, and you'll be able to assess that with this foreign document that you now have.

DR. ROSS: I look forward to reading it on the plane at 12:02 -- no, okay.

DR. BELSITO: Don, on PDF 65, in animal sensitization, there seems in the results to be signals there. And, there's a case report on contact sensitization to Disodium Lauroamphoacetate where they patch tested it at one and two percent it was positive. So I think this early in the game with the animal, right, you see in Table 10?

DR. BELSITO: Yes.

DR. COHEN: So, I thought having some more sensitization, whether that be animal in silco, or HRIPT, getting this dossier a little bit more beefed up in sensitization would be helpful.

DR. BELSITO: Well, we have to be careful. I mean, we can't ask for new animal data, right.

DR. COHEN: No, no, they just may be out there, right, and we don't need to ask for new animal data.

DR. BELSITO: I mean, we think it's insufficient based upon definitely the genotox. Curt looked at the exponent report and it actually were two of three studies showing some cardiac abnormalities. So we look forward to the report that's promised. So we have no problem going out with insufficiencies. If you want to add your insufficiencies, we've done this before. We can eliminate them when we look at them later on, so I'm fine.

DR. COHEN: Did you want to add your geno? I don't know if I'm -- I mentioned DART.

DR. BELSITO: I think you mentioned the study that has been promised on the DART endpoints, but if not, yeah, I think that's the biggest data point that we need.

DR. COHEN: It's in there.

DR. ROSS: There is another paper as Don points out. There are at least two or three of those studies. I think I pointed this out last time that that should be added to our Discussion. I think that reference was Greens, et al 2022, with the cardiac malformations and the DART data.

DR. COHEN: Okay.

DR. BERGFELD: So we have a motion and a second that we're going out for an IDA. Do we have a list of things that are needed, David?

DR. COHEN: Yeah.

DR. BERGFELD: Great discussion. I call the question, all those in favor of this conclusion? Thank you, very much. And, Paul, I'm assuming you agree?

DR. SNYDER: I concur.

DR. BERGFELD: Okay, thank you. Okay, moving on to Inositol, Dr. Belsito.

JUNE 2024 PANEL MEETING – REVISED DRAFT AMENDED REPORT REVIEW

Belsito Team – June 03, 2024

DR. BELSITO: Then we're moving on to the fatty amphocarboxylates. So, again, before we start that report, Allan, do you want to update us on the Read-Across Working Group?

DR. RETTIE: Sure. So, going back to the general summary comments that I read earlier, we had all the issues we've been talking about with regard to very potent receptor-based interactions. Now, these don't apply here, but what does apply is read-across when mixtures may be involved. Clarification of the composition of the -- is it 11 ingredients that we have here? -- 11, I think, is something we'll get to.

So, this is where the betaine example, which I tried to bring up earlier and shouldn't have done, applies. Much of the arguments seemed, to me at least, to rely on read-across from the betaine. As I mentioned earlier, the group, all of us, even before we had the Read-Across Working Group together, did not accept the notion that using the permanently quaternary ammonium charged compound was appropriate.

DR. EISENMANN: I thought they're only proposing that compound for dermal penetration, period, is my understanding. And, to me, it's just getting them into the ballpark.

DR. RETTIE: Okay. Well, we'll take that under consideration. I think you're right. But while I'm still on the betaines, an argument made for potential read-across to the amphocarboxylates for dermal penetration for both surfactant groups are ionized at all pHs, and we acknowledge that that's true. But it's a different circumstance when we move away from the betaines. Amphocarboxylates do not have a charge nitrogen under alkaline conditions, and they're uncharged, of course, at the isoelectric point or largely uncharged in the isoelectric range. We considered that these distinctive features might affect tissue distribution. So, we started in with that because we had begun with discussion of the betaines before, and alkyl betaines have been through this group and reviewed positively in the past. What else do we have here?

Once again, we came to the tentative conclusion that read-across for highly-sensitive toxic endpoints are not appropriate. And in this case here, we have concerning tox signals such as cardiac abnormalities, just another complicating feature. We were worried about that especially since we have no mechanistic underpinning for that observation.

DR. BELSITO: So, the Exponent analysis of that DART and -- we have one study of several.

DR. RETTIE: Did we disregard it because it was --

DR. BELSITO: Yeah.

DR. RETTIE: I had the impression there were three separate studies that brought up the same cardiac malformation.

DR. BELSITO: Think it was only one, no?

DR. RETTIE: Paul, did you get into that, the number of studies that brought up cardiac malformations?

DR. SNYDER: I did not. I did not.

DR. BELSITO: Well, Table 8 summarizes all the repro studies we saw. So, if we look at Table 8. Okay. Gavage. No treatment-related effects. Another gavage. No external or visceral malformations. OECD TG 414 was again a gavage. No adverse effects related to developmental parameters were observed in the fetus. So --

DR. SNYDER: In that study, it was positive. They couldn't determine an NOAEL for that effect either.

DR. BELSITO: Right. There was no dose response, right?

DR. KLAASSEN: That's what they said.

DR. BELSITO: So, we have studies with NOAELs above a gram per kilogram. Gavage studies, by the way, which people criticize for overwhelming defense systems.

DR. RETTIE: So, are we centering around that single cardiac abnormality study here then?

DR. EISENMANN: I thought that John DeSesso's report that was provided at the last meeting was useful in that he took all the studies together and combined them.

DR. BELSITO: Right. That's the Exponent report.

DR. EISENMANN: Right.

DR. BELSITO: Yeah. I mean, I found that very helpful as well, and we've agreed to take in outside expert opinion on an ad hoc basis. I think this is one opinion we should take in. And I'm not really concerned about the DART effect. I mean, I think that it is spurious. There was no dose response, and it's inconsistent with everything else we have, the gavage studies we have, wasn't seen. But it's not my area of expertise, so I'll see to other people.

Paul, I usually go to you for repro. What did you think?

DR. SNYDER: Yeah. I mean, I thought in June of 2023 we asked for more DART, and we have not received any more data since then, right. So, are we saying we're not concerned anymore about DART, my notes say?

DR. BELSITO: Well, I think we asked for it because David Ross wanted it, not because we wanted it.

DR. SNYDER: Okay. All right.

DR. BELSITO: If you go back with the original, I think we're willing to start with safe as used for this group.

DR. RETTIE: Yeah, I know from what I recall, the reading work across group, Dave is the main proponent for additional DART studies for that. Not my area of expertise either.

DR. EISENMANN: In their update, they've said there's a rabbit study underway, and there's a one-gen underway for ECHA. But the one-gen's going to take a while for it to be completed.

DR. RETTIE: So, to consider additional DART data, we're likely looking at a long time.

MS. CHERIAN: September-October.

DR. RETTIE: Oh, that soon?

DR. EISENMANN: That's when they give a report. So, however long it'll take them to finalize a report after they get it, so it might be a while yet.

DR. KLAASSEN: Yeah, they say that there's no dose response, and we have to kind of take their word for it. What might be interesting is that if we can get the number 24 report, which this comes from, what does the actual data look like? Instead of concluding there's no dose response --

DR. EISENMANN: Some of the actual data is in the Exponent report.

DR. KLAASSEN: That's in the Exponent report?

DR. BELSITO: Yeah.

DR. KLAASSEN: Okay.

DR. BELSITO: Reference 24 is the Exponent report.

DR. KLAASSEN: Oh, that is it.

DR. BELSITO: Yeah. DeSesso is the Exponent report looking at all the data.

DR. KLAASSEN: Okay. We had that the last time but not this time.

DR. SNYDER: (Inaudible) data to clear all the other IDAs, the dermal absorption, composition, impurity, sensitization?

DR. BELSITO: Not sure of your question. Did he clear read-across for those, or what was your question?

DR. SNYDER: No, before, we came out with an insufficient data announcement for four items in addition to the DART. So, I just wanted to be clear. Did we get data, because my notes say we received no new data?

DR. RETTIE: I mean, that report went into some detail about the AEEA effects or lack thereof, and they excluded the AEEA as being a contributor to the toxicity observed. But that leaves us with no working hypothesis or any kind of clues about what might underlie this serious toxicity. And so, if we can get anymore clarification on that, I think the Working Group would appreciate it.

DR. KLAASSEN: Monice or Bart, could you send me that DeSesso review that we saw the last time. I could read it tonight again. I know we talked about it three months. It looked pretty good then, but I'd like to read it again.

DR. RETTIE: Could you CC me too, Monice? Save me digging out.

DR. BELSITO: Just send it to everyone.

DR. KLAASSEN: If I recall right, the quality of the products in this class were not great. Am I remembering correctly?

DR. BELSITO: Well, none of them are pure. They all have active ingredient probably as much as 50 percent if you're lucky, and then they have other material. But the other material is reportedly things like water and other inactive, quote-unquote, for lack of a better word. You see that -- it's in Table 1 or 2.

DR. KLAASSEN: I remember.

DR. RETTIE: It's in Table 4, composition of tradename mixtures. We have compositions for -- one, two, three, four, five -- five of them. And as you said, large component of the preps, as listed here, are water, up to 70 percent. What's not listed here but which I wondered about at least having a declaration that when we were talking about an acetate we did not have the diacetate, when we were talking about a propionate, a declaration that we don't have the dipropionate because this mono-, di- piece is missing from here. And from what I read of documents that came from Europe, it was common that mixtures of the mono- and di- constituents were being used. I felt that was a little problematic and made it a little difficult for the Read-Across Group to know how to deal with that.

I kind of feel that monoacetate to monopropionate -- this is just me -- is probably okay. I have more concern about monoacetate to diacetate, monopropionate to dipropionate just because you got a bigger molecular weight. It's farther away. Maybe it's okay to accept it as read-across, but I just didn't know what we were dealing with composition-wise in the current report.

DR. BELSITO: Why would the greater molecular weight bother you?

DR. RETTIE: Well, again, it's read-across, and mostly when you're thinking about read-across and applying simple rules, you want to go as close as you can to the chemical structure. And so, it's less of a distance from the monopropionate to the monoacetate, as compared from the monoacetate to the diacetate or the dipropionate here.

DR. BELSITO: But we're also looking at something that first has to be dermally absorbed.

DR. RETTIE: Yep.

DR. BELSITO: And would you expect a diacetate to be more or less absorbed than a monoacetate?

DR. RETTIE: I felt it should have a higher log P, and I thought it should be probably more absorbed than less absorbed. The log Ps that were reported in the document here weren't that clear to me. The ranges that we're reporting make an awful lot of sense. Now, the log Ps in our tables here for chemical properties, Table 2, go from minus-8 all the way up to 0.5. Seems very wide, so I was just questioning what the compositions were.

DR. KLAASSEN: I thought if there was one thing that in silico could do for us was to give us the pKa in these physical properties, and apparently, it can't even do that.

DR. RETTIE: Well, it might because I have a note here that we're using three different programs to estimate.

DR. KLAASSEN: Yeah, I know. Maybe I was naïve --

DR. RETTIE: No, no.

DR. KLAASSEN: -- because I thought, man. I took those numbers as rock solid until I saw this. And being so different, I don't know what to believe anymore from in silico.

DR. RETTIE: I mean, it gives us some information about the range of log Ps that you'd estimate for really the part of the molecule I wasn't that concerned about, which was the acyl side chain variation all the way from C8 up to C18. I would've like to have seen information on the log Ps, which should be easy to get, as you say, for the monoacetates and diacetates, but maybe I'm completely wrong here and the composition of these compounds that we're looking is absolutely as described. But like I said, it's quite a bit different from what I was reading in the ECHA documents, so I was just suspicious.

DR. EISENMANN: The wheatgerm one came from a NICNAS document, was not estimated by us. I wonder if it would be good if you guys did an estimate. I think they picked a specific structure that's predominantly in the wheatgerm oil. I don't remember what fatty acid they picked. That's the real outlier, that 0.5 percent.

DR. RETTIE: Zero-point-five. Yeah, that's right.

DR. EISENMANN: Oh-point-five (inaudible) percent. So, it might be good if you guys did the -- I don't know if you did the calculations for the other ones or not, or if they came from references. But that one might be good for you guys to do an estimate.

DR. HELDRETH: Yeah, we just used EPA's EPI Suite and just plugged in the SMILES codes for the two ends of the possible chain links. Since we're talking about coco-derived C8 up to C18, we get both of those ends of the range.

DR. EISENMANN: So, to be consistent, put in the wheatgerm just out of curiosity because that came from a different source.

DR. HELDRETH: Okay.

DR. RETTIE: Thanks. I would just like to reiterate that my concerns fall out if we accept the purities of the mono- versus diacetates as stated here. But just would like somebody to tell me why they're so different from the ECHA compositions. Seems like a disconnect. Are these call them purified, HPLC-purified, in the U.S.?

DR. EISENMANN: I don't know. I have to look back and see where that data is coming from. But the people that are providing data is the ECHA Consortium. They're the ones that have the data ongoing.

DR. RETTIE: Okay.

DR. EISENMANN: I mean, they're testing their mixtures, I think.

DR. RETTIE: And in that document somewhere, there's up to 25 percent of the diacetate in one of these, or more, because it's here. That was my concern. Why don't we see 25 percent of the diacetate? I mean, it should be fairly innocuous. I don't want to make a big deal about it. It's just the lack of consistency between the ECHA document and what we're looking at in Table 2, I guess -- no, Table 1.

DR. HELDRETH: Yeah. So, in Table 1, we presented exactly what you would find in the dictionary monographs. But document folks that actually make these sorts of materials where it's like they took coconut acid. They took a cut of coconut acid, has a range of like C8 to C18. And then they're reacting it to make the amphoacetate or to make it diacetate.

DR. RETTIE: Sure, I understand.

DR. HELDRETH: And even though you might call it disodium cocoamphodiacetate, both the ingredient itself and any source materials that we were reading from, they're probably all mixtures of monoacetates and diacetates to some extent but with a peak that's higher, for example, the diacetate when it's named diacetate, and a peak that's higher for the monopropionate when it's named monopropionate. But I think it's always a mixture. And you see the same kinds of mixtures from the source materials and the ingredient.

DR. RETTIE: So, you'd say that it's always a mixture, not only at the level of the acyl side chains, which we kind of all understand, but given the synthetic methodology making the imidazoline and then opening it up, it's always a mixture of the monoacetate or the diacetate.

DR. HELDRETH: That's my understanding of it. Sitting and talking with the folks on the INCI Committee who actually have experience making these sorts of things, you take even a mixture of the fatty acid side chains and try to do acetylation of that, you're going to get mixtures because you're starting with mixtures, and it's just a challenge. You can push the majority to be one or the other, but to get exclusive and then to do separations on it -- I mean, you can do separations like that in a lab, but on the large scale, probably not worth the effort. And why? What are you excluding in a --

DR. RETTIE: So, the level of the Read-Across Working Group's deliberations about this one, we were kind of stymied because I don't know that we had that amount of clarity at the Read-Across Working Group. And so, we honed in on the idea that, when you've got mixtures in your ingredient, mixtures of these analogues basically, we weren't really sure how to deal with that. So, we stopped short.

My feeling is the read-across to the diacetates -- the diacetates are going to have bigger differences I think in terms of physical chemical properties. But maybe it's all awash if they're all a mixture of monoacetates and diacetates or monopropionates and dipropionates. Certainly something we should talk about again in the Read-Across Group.

DR. BELSITO: Does the method of manufacturer on PDF 41 that's given for these help you understand in any way the fact that they would like -- I mean, I'm assuming that this is a generic method of manufacture for both the mono- and the diacetates, is that correct?

MS. CHERIAN: First paragraph?

DR. BELSITO: Pardon?

MS. CHERIAN: The first paragraph?

DR. BELSITO: Yeah.

MS. CHERIAN: Yes.

DR. RETTIE: So, we're on PDF 41, first paragraph, Method of Manufacture?

DR. BELSITO: Yeah.

DR. RETTIE: Yeah. So, as I mentioned earlier, yeah, it tells us we get a substitute, imidazoline, which then gets reacted and splits. As I understand it, it's the same method of manufacture as is outlined in a figure in the ECHA documents, and it shows both monoacetates and diacetates being made from the same method of manufacture, which is where I started with this and wondered why we didn't have the di-, just had the mono-. But based on Bart's comments, I can understand that a little bit better now. I'm just wondering if we have more detailed information for the tradename mixes. Do they give more detail, and is that what we should be including?

DR. HELDRETH: My understanding with the tradename mixtures is these aren't the ingredients themselves that we're talking about purity. These are essentially like pre-formulations. So, it's the ingredient plus this and this and this, so that when someone at a finishing house includes one of these ingredients, it meshes well with the rest of the formulation.

DR. RETTIE: But it therefore doesn't shed any light on whether it's 15 percent of the dye or 25 percent of the dye.

DR. HELDRETH: Right. Right.

DR. RETTIE: That's just an unknown, and we can't get that info, it sounds like. Well, it may simplify read-across if we can, as the Read-Across Working Group, accept the fact that the mixtures are going to be heterogenous, as we're discussing here. And it's not a huge jump from the diacetate from the monoacetate. It's further than I would like, but can I say it precludes read-across? Maybe not. I'd like to have a chat with the rest for the members of the Working Group to decide that.

What do you think, Curt? Do you have strong feelings?

DR. KLAASSEN: I have no strong feelings.

DR. BELSITO: Paul?

DR. SNYDER: No. That chemistry's a little bit not in my (inaudible). One of my concerns too, Don, is that -- not to change the subject or anything -- but we now that we know there's a rabbit repro study and a one-generation repro study that's forthcoming, are we going to wait until we see that data? Or are going to go ahead and -- because this is a, yeah, draft report. So, maybe it'll be done by the time we get to final.

DR. BELSITO: Yeah, I mean, that was one of my comments in a note from on the developmental and repro tox study. Do we want a table for the data promised on those studies and also for final decision on read-across?

DR. HELDRETH: Yeah, you could either go that way or, since it wouldn't come back till this December panel meeting at the soonest anyway, you could just put out an insufficient data announcement that includes those pieces. Either way will work. It's the Panel's prerogative.

DR. BELSITO: I mean, again, the one positive DART study, there was no dose response. We have an LLNA which is negative at 30 percent, negative guinea pig maximization test. I mean, I really thought that we could go with safe as used when formulated to be nonirritant. And if you were concerned about the amidoamine impurities, deal with it the same we deal with the betaines and say formulate to be non-sensitizing. But I guess we want to await the further DART studies and decisions from the Read-Across Working Group. Is that what I'm hearing from my team?

DR. SNYDER: Yeah, I was getting the same message from Allan there regarding the research -- or the Read-Across Working Group. I mean, I still think they haven't kind of got their guidance for how they're going to approach these things. So, in addition to that, I mean, why would somebody be doing a rabbit repro study and a one-generation study if everything was this clean as we're saying? So, I don't quite understand the basis for that.

DR. EISENMANN: Because ECHA is making them do it based on volume of use. They had a response in their comments on why they're being made to do it. It wasn't a concern; it was just because of the volume.

DR. SNYDER: All right. So, they're just checking a box. Okay, thank you, Carol, for that clarification.

DR. KLAASSEN: I guess, it seemed --

DR. SNYDER: So, if Allan's okay with the read-across, Don, I'm okay with what you propose. We can put it back out there as a safe as used when formulated to be nonirritating and let the other group drive the discussion.

DR. BELSITO: Well, Cohen is actually -- their team is starting the discussion.

DR. RETTIE: Perhaps the last point of clarification from the Wave 2 the first time around, there was some confusion about what amidoamine was. Do we still care about that? You asked me a question, and I didn't know the answer. But turns out that both of the compounds that were being described, amidopropyl dimethylamine and this dodecyl compound -- well, they're both amidoamines, but one's a C16. One's a C12. I don't know that we need to keep going on this, but I just wondered if it was still an outstanding question for the group.

DR. BELSITO: The amidoamine becomes an issue if it's a residual -- the starting material is a residual and what's marketed because it's a sensitizer. So, we had this issue with a group of compounds called betaines that we reviewed before you joined the Panel where there were questions about sensitization to betaines and whether they were due to dimethylaminopropylamine or to amidoamine. We went back and forth, and there were some positive sensitization data, negative sensitization data. Anyway, the long and short of it was that it was resolved by saying that they were safe as used when formulated to be non-sensitizing based upon a QRA or other similar methodologies. Which we could do here as well if we were concerned about potential sensitizing starting materials that remained in the final product.

So, to answer your question, Allan, no, it doesn't matter whether it's C12 or C16.

DR. RETTIE: They're both known sensitizers. Okay.

DR. BELSITO: I had a question for you, Carol. When we're getting these concentrations of use, are we getting the concentration of the mixture, or we're getting the concentration of the, quote-unquote, active ingredient, the amphoacetate that we're looking at in the final product?

DR. EISENMANN: (Inaudible) I'm asking (inaudible) concentration of the active.

DR. BELSITO: You're asking.

DR. EISENMANN: Yeah.

DR. HELDRETH: Good answer.

DR. EISENMANN: So, that's what I want them to give me. I don't have access to their files, so that's what I'm asking them.

DR. BELSITO: So, we have to operate under the assumption that they have told you the concentration of the active.

DR. EISENMANN: And I do my best if something seems out of place to go back and say, is this real? Or is this correct? Though, sometimes, if I do right away, the person -- they just looked at it, so they assume that it's correct. But if I go back a few months later, somebody else might be looking at their database, and I sometimes get a different answer. But, yeah, it is (inaudible). They change their formulations too a fair amount, so it is moving. Concentrations of use are moving targets, I've decided.

DR. HELDRETH: Part of the reason we have the caveat as described in this report.

DR. BELSITO: Right. Okay.

DR. KLAASSEN: The name can stay the same, but the ingredients can change. The first time I came across this was with Tide soap. Tide soap used to have a lot of phosphate in it, and then they got all this fungal growth and what have you in the rivers and stuff. So, they took it completely out and reformulated about 98 percent, and it was still called Tide. Is that right?

UNIDENTIFIED MALE: Yeah.

DR. KLAASSEN: So, the name can stay the same, but the ingredients can change.

DR. BELSITO: Okay. And just Allan and Curt, since you're in the Read-Across Working Group, the lamidopropylbetaine is being asked for a read-across for absorption only, not for other endpoints, if you remain concerned about absorption. So, it's --

DR. RETTIE: Yeah. And I felt the C12 was the most prominent constituent, so probably is the best candidate for selection there.

DR. KLAASSEN: I'm okay with that.

DR. BELSITO: Okay. So, just going through the documents. I mean, I know we're going to table this, but again for -- Priya, this is your document as well? Boy, you're a lucky lady, aren't you?

MS. CHERIAN: I know.

DR. HELDRETH: She gets all the fun ones.

DR. BELSITO: Yeah. Okay. I don't have any additional -- oh.

On table -- well, PDF Page 65, it's Table 10. For the LLNA on the top one, the sodium lauroamphoacetate, we described the ear thickness increases. You didn't give values for the stimulation indexes because the ear swelling could simply be secondary to the irritation that we know these have. So, it would be helpful, at least for me, in terms of sensitization if you put the SIs for the different concentrations for the EC3s, if they were given.

Okay. Then we had a Wave 2 on this. Let's just discuss. We received comments from the Council, which I thought were all fine. Curt, Allan, Paul, did you have any?

DR. RETTIE: I did not.

DR. SNYDER: I did not either.

DR. BELSITO: Okay. And then we received comments from the REACH Amphoacetate's Consortium asking us to, again, look at the Exponent analysis. But since they're already doing a rabbit study and other DART studies, my hearing from you all is that we're going to table this and wait for those DART studies before reopening it again or looking at it again.

DR. SNYDER: No, I probably retracked that based on Carol because, if it's just to meet data needs based on volume of product, not based on any concern. I think there's certainly sufficient studies that are under that table. So, I would be okay with going back to the safe as used when formulated to be non-sensitizing.

DR. BELSITO: And non-irritating.

DR. SNYDER: And non-irritating. Sorry, yes.

DR. BELSITO: Okay. So, now we're coming full circle. We don't need read-across. So --

DR. SNYDER: But that's based on if Allan's okay with that.

DR. BELSITO: Pardon?

DR. SNYDER: Pending Allan's input on that.

DR. BELSITO: Well, Allan's input on what, read-across? Because if we're going safe as used, what we're saying is we don't need additional read-across data at this point, right?

DR. SNYDER: Yes.

DR. KLAASSEN: By definition.

DR. BELSITO: Right. So, Curt and Allan, what do you think of that approach, which was our initial recommendation? I mean, these data needs all came from the Cohen team, not from our team.

DR. RETTIE: Again, I feel a little naked talking about the Read-Across Working Group without the other members.

DR. BELSITO: We're not talking about reading. We're talking about not having read-across at all based upon the information that you're seeing in this document. And Wave 2, do you feel they're sufficient, or do you feel that we still need read-across? And for what endpoints, do we need read-across for?

DR. KLAASSEN: I think it's sufficient if I can read this document tonight, that Exponent sent, and to make sure I remember that correctly. And if I do, I think we can go as Paul said.

DR. BELSITO: Sufficient when formulated to be non-irritating, and we can talk about the sensitizing endpoint that whether it's non-sensitizing or not. I don't think we need it for this one. I'm not that concerned about the level of residual

amidoamines. But I don't think the other team is going to go safe as used, by the way, but that doesn't matter. Allan, your thoughts?

DR. RETTIE: I can go along with it.

DR. BELSITO: Okay.

DR. RETTIE: We don't need for read-across.

DR. BELSITO: So, Curt, you're going to give me a heads up at some point before the meeting?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay.

DR. KLAASSEN: As long as someone sends that article to me.

MS. FIUME: It should be in your inbox.

DR. KLAASSEN: Okay, great.

DR. BELSITO: Okay. Is there anything else? Wave 2 was the fall of the various, looking at the in silico predictions for potential read-acrosses. So, I think we've covered the comments in Wave 2. Okay. Anything else on the amphoacetates?

Priya, have we completely confused you as to where we are?

MS. CHERIAN: I'm okay right now.

DR. BELSITO: Ask you again tomorrow morning?

MS. CHERIAN: Yes.

DR. BELSITO: Okay.

Cohen Team – June 03, 2024

DR. COHEN: Okay. We're going to move on to fatty amphocarboxylates. It's like we're doing a lot of the heavy lifting early today. So, this is a revised draft safety report for fatty amphocarboxylates who was first reviewed in June of 2023 at which time the panel tabled the review due to receipt of a large amount of information in Wave 2. It included various fatty chain mixtures that are listed and reach dossiers for the following substances that are listed here as well.

The CIR prepared a read across justification table and the Read Across Working Group met to adjudicate that. Also, in June, the panel noted that the following data points were needed. Dermal absorption/DART on disodium cocoamphodiacetate and further information regarding composition and impurities of these ingredients as cosmetics, particularly percentage of actives in ingredients in fatty composition. And we wanted sensitization data on sodium lauroamphoacetate at max use concentration and I don't believe we've received that.

DR. ROSS: We didn't.

DR. COHEN: Yeah. So, again, just as a reminder of the 11 ingredients, disodium cocoamphodiacetate, disodium cocoamphodipropionate, sodium cocoamphoacetate, and sodium cocoamphopropionate have previously been reviewed as safe as used in a 1990 report which was rereviewed and reaffirmed in 2006. So, we needed feedback from the Read Across Group on this.

DR. ROSS: Yeah. So, I gave the last one so Susan, you want me to do this one or do you want to do this one?

DR. TILTON: We talked about some of the general read across concerns earlier already and with this group one of the primary concerns was doing read across for mixtures and the differences in composition across the different mixture groups. And then, also doing read across for certain sensitive endpoints. And in this case, that involved in some of the DART data that I'm sure we'll discuss.

DR. ROSS: There was a specific question on this betaine read across and there was a specific request that came in to reconsider that. I think that came from the consortium.

DR. TILTON: Specifically, for --

DR. ROSS: The betaine.

DR. TILTON: -- absorption.

DR. ROSS: Yeah. And so, the RAWG -- should we call it the RAWG or the Read Across Group? Anyway, the Read Across Group didn't support that so the betaine was not supported for read across. So basically, we hadn't changed our position on read across for two reasons. One being the mixtures that Susan pointed out and secondly the betaine was not supported. It's

bitter ionic compound whereas the other ones, they're ionized also physiological ph. That's true, but only the betaines have a charged quaternary nitrogen in all PH values.

DR. COHEN: So, you couldn't take the betaine read across.

DR. ROSS: Correct.

DR. COHEN: Okay.

DR. ROSS: So that was that. You know, I think there are still concerns with the amphocarboxylates in general. The DART data and cardiac malformations. A new developmental toxicity study has been completed. We saw this document a few times, I believe, and the new DART data was always coming. Well, I think it's been completed now.

DR. COHEN: Didn't it say it was coming in September or October?

DR. ROSS: Yeah. And so, it'll be -- it's right now, I think, it's with Exponent, the consultants, and it'll be released to us in September/October as David comments. And I would just make the statement, which I do feel strongly about, you know, I wasn't strong on the yeast issues, but I do feel strongly about this one, that I think it's very unwise, in my opinion, to move ahead until we've seen that new DART data. So, I would support tabling this as well until December until we have a chance to look at that new DART data.

DR. COHEN: I had the same conclusion was to table until the December meeting because it said it would be available September/October which won't give us time.

DR. ROSS: Yeah. And I just think it would be very wise to do if we haven't seen that data.

MS. FIUME: Can I make a request? So, procedurally this is only a revised draft report and insufficient data announcement has never been issued yet. So, it is the Panel's prerogative to weigh on those data but also identify any other additional data needs to avoid that having to be the next step. And rather than table, if there are additional data needs, you can go out with an insufficient data announcement, then it would probably come back in December anyway and hopefully you would have those new data as well instead of having to wait and ask for additional data at that point if more is needed.

DR. COHEN: So, when -- I thought we had -- so, at June, we noted the following data are needed. I viewed that as an IDA. But maybe it wasn't an IDA.

MS. FIUME: Because it was tabled, there could be no true action. So, at times we'll know in the post/in the announcement as hey, industry, this hasn't been formally requested yet but this is what we're looking for. Just know that the Panel is also interested in this information.

DR. ROSS: Are you sure we can? Well, you know because you wrote it. But, I mean, did we not make that request?

MS. FIUME: It may have been asked for informally, but it hasn't been a formal --

DR. COHEN: So, it wasn't an IDA?

MS. FIUME: It wasn't an IDA. It was tabled which is why it came back as a revised draft report and not as a draft tentative report.

DR. COHEN: I think that makes a lot of sense. Otherwise, it's going to slow this process down a lot if we table to December, pick it up as a draft report -- well, it would be a draft --

MS. FIUME: Then it would be a revised draft report.

DR. COHEN: Revised draft report and it's going to take another year to get through.

DR. TILTON: So, this wouldn't be a tabling, this would be --

DR. COHEN: This would be an IDA.

DR. TILTON: -- an IDA and one of those requests would be for this data set that's coming forward.

DR. COHEN: So, let's line up our IDA then.

DR. ROSS: Yeah.

DR. BERGFELD: But you have a list already that you informally -- would you want to change that list? I mean --

DR. COHEN: I was just going to go through that with the group.

DR. ROSS: What's the PDF of that? I'm sorry, I'm just --

DR. COHEN: Well, it would be in the beginning.

DR. ROSS: Right in the beginning of the report, right.

DR. COHEN: Just look at the previous memo.

DR. ROSS: It should be there, right?

DR. COHEN: It's right on the first page. These memos are great.

DR. ROSS: Yeah, yeah. They're good. Yeah, yeah, yeah, yeah. I've got it. Got it, got it, got it. Yeah. Thanks. Yeah, there's the sensitization data on sodium lauroamphoacetate at max. We didn't get that. I would also like to see the, and we may not get this, but I'd like to see the ocular concentrations of use of the compounds that are used for that indication. We don't have concentrations of use in our use tables for those.

DR. COHEN: Okay. So, we still want dermal absorption data on what?

DR. BERGFELD: Sodium cocoamphopropionate.

DR. COHEN: We get to the table.

DR. ROSS: I think that's whether we're using read across to the betaine and --

DR. TILTON: Because we really don't have any data.

DR. ROSS: Yeah. So, I think you can just note that as dermal absorption data.

DR. COHEN: Say that again.

DR. ROSS: You could ask generically for dermal absorption data.

DR. COHEN: On the whole group?

DR. ROSS: Yeah. And then see what we get because I think it depends on the read across with -- if you're going to read across this point -- we're not.

DR. COHEN: So, none of these in this group are reading across to the others?

DR. ROSS: That's correct at this point.

DR. COHEN: That's pretty heavy.

DR. ROSS: Yeah. I think we have tox endpoints for most of the major compounds apart from DART. For most of the major compounds we have -- I think there's a way forward on many of these compounds that are used, at least the major ones -- and that, I think, we'd have to address when this comes up again. But I think all is not lost on this, I think there are potentially ways forward.

DR. COHEN: Okay. So dermal absorption data and we want DART.

DR. BERGFELD: Do you want the results of the DART? I mean, if they said they're doing it and it'll be ready, I mean, what --

DR. COHEN: This is for disodium cocoampho- --

DR. ROSS: Acetate, yeah.

DR. COHEN: -- -diacetate, right?

DR. TILTON: Diacetate, yes.

DR. ROSS: That's the compound where we had the cardiac malformation data. I think you could just leave it as is. DART data on disodium.

DR. COHEN: We'll keep that. We'll keep that. Further information regarding the composition and impurities of these ingredients.

DR. ROSS: Well, remember these things are listed as VC -- variable com- -- no, I've got that wrong. Anyway, their materials are listed at variable composition. I forget the actual definition. But that's what we were getting at with that comment. We wanted more definition around what's in them, but I think that we're going to get that because that's how they are. That's how they're made and that's how it's going to be. So, that was our request.

DR. COHEN: So, what's the disposition of the IDA for that?

DR. ROSS: I think we ask for it and if we can get it, that's great, because we need to know what's in there. I suspect we won't get it but that doesn't necessarily preclude a way forward. But it would be very good if we could point out what was actually in this study.

DR. COHEN: The sensitization at max use for sodium lauroamphoacetate.

DR. ROSS: I think that was 9.9 percent as I recall.

DR. COHEN: It was -- I thought it was 5.4 percent.

DR. ROSS: Ah, right. Max concentrations probably would be a safer way to go.

MS. FIUME: That's what we typically try to put into the post meeting announcement is just stating max concentration of use.

DR. COHEN: Yeah, max concentration.

MS. FIUME: Yeah.

DR. COHEN: There's a cocoamphoacetate at 20 percent in a rinse off product. The disodium lauroamphodiacetate has the highest concentration of use in a leave on product. So, I have one, two, three, four of the original plus ocular concentration of use in products used near the eye.

DR. ROSS: Yeah. That would be great, David, thank you.

DR. COHEN: Did I capture --

DR. ROSS: Yeah.

DR. COHEN: I like that idea of that we're not tabling it. This is just going to keep coming back around. So, this could come back anyway in December with that data anyway. That would be the course anyway and then we'd go to a draft tentative.

MS. FIUME: It would come in as a draft tentative report and go out as a tentative.

DR. COHEN: Yeah.

MS. FIUME: Yes.

DR. COHEN: Yeah.

DR. BERGFELD: What did you say about the eye? You wanted further documentation on this one, the concentrations in the eye? I note that there are some concentrations up to three percent.

DR. ROSS: Yeah, there are but there's --

DR. BERGFELD: That's up to 20 percent.

DR. ROSS: -- but in the eye a lot of them are not reported that are used around the eye.

MS. FIUME: Yeah, I believe it's those that -- the four that had been reviewed before have eye use, but no concentration given for them.

DR. ROSS: Yeah. So that was the only thing I needed, Wilma, just to --

DR. COHEN: Do we have a specific one for that, though? I'm trying to find it.

DR. ROSS: Well, there are -- I abbreviated these two numbers so -- in my report.

MS. FIUME: For those that are missing the concentration?

DR. ROSS: Yeah. For the eye area.

MS. FIUME: It's disodium cocoamphodiacetate, disodium cocoamphodipropionate, and sodium cocoamphoacetate. I have frequency of use for eye area products but not concentration. Did I miss any, Priya?

DR. ROSS: Which one --

DR. COHEN: Which PDF is that? Well, let me try to get to that PDF.

DR. ROSS: I have four compounds. Compounds one to four, but I'll have to get to my definitions.

DR. COHEN: Because you had a -- that chart is pretty useful.

DR. BERGFELD: So, if you had eye at 0.18 in one report and eye in another report of 1.3, are there other particular ingredients that's noted there is not reported would you not assume that they couldn't exceed what has been reported?

MS. FIUME: That is typically what happens, yeah.

DR. BERGFELD: So, the highest would be 1.3.

DR. COHEN: But if we can't read across does that still hold? That's a real bonified question. If you can't read across, does it matter that you've tagged a concentration of one, but you can't pull that data over to the other.

DR. BERGFELD: Well, that's a valid suggestion but that's all you have, so it probably shouldn't exceed that.

DR. COHEN: But how do we know that one's toxic at that concentration and not at the other if you're not reading across?

DR. ROSS: But you have, of the five most commonly used compounds there you've got three of them -- just provide notation here, one -- compounds one, three, and five we have in vitro ocular data at three percent. Compound five we have animals that meet compound one, we have humans at 1.2 percent and the maximum ocular concentration is 0.11 and 1.3 percent. It's already closed on one, three, five. So, three of the five compounds. So --

DR. COHEN: You're building, at least, a body of data to --

DR. ROSS: Yeah.

DR. COHEN: -- it's not a read across but it's culminating to safety.

DR. ROSS: So, it's like here we've got quite a few of these tox endpoints and many of them were frequently used compounds.

DR. COHEN: You still want the IDA?

DR. ROSS: Oh, yeah.

DR. COHEN: Okay.

MS. CHERIAN: So, for sensitization you want to just put sodium lauro?

DR. ROSS: Yeah.

DR. COHEN: For sodium lauroampho- --

MS. CHERIAN: Do you want specifically an HRIPT because we have LLNA data right now.

DR. COHEN: We have --

DR. BERGFELD: I don't think you ask specifically, you just ask for the sensitization data.

DR. COHEN: Can you just repeat what you just said?

MS. CHERIAN: If you wanted specifically an HRIPT because we have an LLNA and our maximum for leave on for that one I think is 1.1, but maximum for rinse off is 9.9.

DR. COHEN: Wait. I thought the maximum leave on for that was 5.4.

MS. CHERIAN: That's disodium lauroamphodiacetate.

DR. ROSS: It's 9.9.

MS. CHERIAN: For rinse off.

DR. COHEN: For rinse off.

MS. CHERIAN: The maximum leave on for all of these is 5.4 in disodium lauroamphodiacetate.

DR. COHEN: Disodium lauroamphodiacetate.

MS. CHERIAN: Mm-hmm.

DR. COHEN: So why is it? Let me just see something here. So why is our requested data different? You see in the memo? It's a sensitization data on sodium lauroamphoacetate at max use.

MS. CHERIAN: Well, we have data for disodium --

DR. ROSS: Isn't the max use 9.9? That's what I have in my notes. May be different.

DR. COHEN: Let me go back in my notes.

DR. ROSS: Let's go back to the table.

MS. FIUME: The highest leave on is 5.4. I think the 9.9 might be the rinse off.

DR. ROSS: Let's take a quick look, shall we?

MS. FIUME: Actually, I think -- I'm sorry -- the rinse off is 20 percent.

DR. COHEN: Yeah. I had it as 20 percent for cocoamphodiacetate. And the highest leave on was 5.4 percent for disodium lauroamphodiacetate. Is that wrong or is that old?

DR. ROSS: I just kept my dermal --

DR. COHEN: That's correct, what'd I just said? And our sensitization is way below that, right?

DR. ROSS: For sodium lauroampho, yeah.

DR. COHEN: Well, I'm looking at human.

DR. ROSS: For -- okay, so what I've got here, okay, for human with respect to the older data which I'm guessing this comes from previous reports, compound one which is the most common which is cocoamphodiacetate, for example, irritation in humans is okay to 25 percent and sensitization is okay at 35 percent.

DR. COHEN: But where are you?

DR. ROSS: This came from the old data.

DR. COHEN: I know, but what PDF are you in?

DR. ROSS: I don't have that in my notes.

DR. COHEN: I have human irritation, we have five percent for disodium cocoamphoacetate, right, for irritation in eight subjects.

DR. ROSS: Compare --

DR. COHEN: And then ten percent for sodium cocoamphoacetate.

DR. ROSS: Well, the old data I have summarized here.

DR. COHEN: I think these were a little irritated.

DR. BERGFELD: And they're detergents.

DR. COHEN: Yeah, they were moderate -- that's right, they're irritating. But for sensitization --

DR. BERGFELD: You have a guinea pig.

DR. COHEN: I see a guinea pig at --

DR. BERGFELD: You have irritations in humans.

DR. ROSS: You've got irritation/sensitization in humans.

DR. BERGFELD: Yeah.

DR. COHEN: Where's the sensitization? It's sodium lauroamphoacetate at 0.15. That's the only HRIPT I see.

DR. ROSS: Correct. Which is why we asked for that data. But the older data, Priya, tell me where that is on the PDF.

MS. CHERIAN: The summarized version is in italicized text.

DR. ROSS: Yeah. So that said -- at least I've got it in my notes and maybe I noted it incorrectly, but we were up at --

MS. FIUME: PDF Page 45.

DR. ROSS: Okay. Let's take a look because I've got it as high as 35 percent. PDF Page 45.

DR. COHEN: PDF 45.

DR. ROSS: Okay. And it should be italicized, correct?

MS. FIUME: HRIPTs are the second paragraph.

DR. COHEN: Ten percent. Is that not in the table?

MS. CHERIAN: No, because it's old data.

DR. ROSS: You don't put the older data in the table --

DR. TILTON: It's from when the first four were grouped so it doesn't include --

DR. COHEN: But we're not reading across, right? Again, what am I supposed to do with this if we're not reading across?

DR. ROSS: Well, you've got a list of --

DR. COHEN: Just reminded me, do we have this report in there?

MS. CHERIAN: (Inaudible).

DR. ROSS: I didn't have --

MS. FIUME: (Inaudible) sodium cocoamphodiacetate. That HRIPT; the last sentence.

DR. COHEN: Give me that again.

MS. FIUME: The last sentence with the italicized text with the HRIPTs it says in addition the sensitization was observed in an HRIPT using disodium cocoamphodiacetate, 32 percent solids, under semi occlusive conditions. However, some irritation was noted under occlusive conditions.

DR. COHEN: That's good.

DR. ROSS: The maximum use, I believe, is 20 percent. So --

DR. COHEN: So, that's the disodium cocoamphodiacetate and we asked for sodium lauroamphoacetate, right?

MS. FIUME: Yeah.

DR. ROSS: Yeah.

MS. FIUME: Yeah. So --

DR. COHEN: And there's a report of disodium lauroamphodiacetate allergy in the literature at one and two percent patch testing.

DR. ROSS: So, you definitely need that.

DR. COHEN: I'd like to have it.

DR. ROSS: I think -- it looks to me --

DR. COHEN: Let me see if I can find it again.

MS. CHERIAN: If you look on 26.

DR. ROSS: So, the cocoamphodiacitates, I have the maximum use at 20 percent. Irritation was okay from the older data at 25 percent. Sensitization was okay at 32 percent. So that one I thought was okay.

DR. COHEN: So, are we continuing the IDA with what we had?

DR. ROSS: I think so and then we work through these issues of what we need with respect to when it comes in. If we assume no read across, I mean, I think you can clear, at least by my notes, disodium cocoamphodiacetate on the dermal and sodium cocoamphoacetate on the dermal based on all the data we have and the concentrations that are used. We still have data gaps with some of the other compounds including the sodium lauroamphoacetate which you are asking for specifically in the IDA.

DR. COHEN: Okay. Hold on a second. So, were you clearing the original four that were cleared?

DR. ROSS: What were the original four that were cleared?

DR. COHEN: Disodium cocoamphoacetate, disodium cocoamphodipropionate, sodium cocoamphoacetate, and sodium cocoamphopropionate.

DR. ROSS: Clearing in what respect? Just on the ocular end?

DR. COHEN: No, just for everything.

DR. ROSS: No, I wasn't clearing anything.

DR. COHEN: Okay.

MS. CHERIAN: That was in there.

DR. COHEN: That was in there.

MS. CHERIAN: It's 38.

DR. COHEN: It's number 38. Okay.

MS. FIUME: So, I can prepare you for Don tomorrow?

DR. COHEN: What's that again.

MS. FIUME: I said I can prepare you for Don tomorrow. It's PDF Page 65. So those --

DR. COHEN: PDF 65.

MS. FIUME: Right, because you're asking for sodium lauroamphoacetate. So those sensitization studies are not sufficient.

DR. COHEN: Hold on. Let me clear this because I'm not getting the page numbers. Okay. Here?

MS. FIUME: Yes.

DR. COHEN: Sodium lauroamphoacetate is at 0.15 percent for humans as opposed to 5.4 percent. So, and then let me look at the others. Are you going to --

MS. FIUME: There's -- the animal studies in there.

DR. COHEN: Yeah, I know he's going to -- I know that -- I know it --

MS. FIUME: As I said, I'm preparing you for tomorrow.

DR. COHEN: Positive reactions were observed in 5 in 20 test animals during challenge. Positive.

MS. FIUME: But the study was deemed unsensitive and I don't remember why. The substance was classified to be non-sensitive

DR. ROSS: Non-sensitizing, yeah. But 5 of 20 test animals.

MS. FIUME: I know. Yeah. I read the last part first.

DR. ROSS: But the induction was only done with half percent, and the challenge was 20 percent.

DR. COHEN: Right. Yeah. It's, yeah. So, we can have that discussion tomorrow. It's definitely coming. I saw the launch before it happened, but we'll see.

DR. ROSS: So, the IDA basically stands.

DR. COHEN: Yeah.

DR. ROSS: Okay.

MS. CHERIAN: But would you like the addition of the disodium lauroamphodiacetate at 5.4 percent for sensitization because of that liquid hand soap study?

DR. COHEN: So, the liquid soap study is disodium lauroamphodiacetate.

MS. CHERIAN: Mm-hmm.

DR. COHEN: What's its max use?

MS. CHERIAN: 5.4.

DR. COHEN: That was 5.4?

DR. ROSS: I thought it was 9.9.

MS. CHERIAN: Oh, 5.4 for disodium lauroamphodiacetate for leave on.

MS. FIUME: Rinse off because that's not typically used at max concentration in HRIPTs.

DR. COHEN: So, what's the sodium -- what's the max use of sodium lauroamphoacetate?

MS. FIUME: It's usually the leave ons has been what the Panel has typically done.

DR. COHEN: Okay.

MS. CHERIAN: I think 1.1 in leave on and 9.9 in rinse off.

DR. COHEN: This one's 9.9 --

MS. CHERIAN: Rinse off.

DR. COHEN: Rinse off -- and what?

MS. CHERIAN: 1.1 from what I remember, I think. Yes, 1.1.

DR. COHEN: Leave on. And then we're amending the IDA for disodium, right?

MS. CHERIAN: You can still ask for sodium lauroamphoacetate too.

DR. COHEN: Yeah. We still will.

MS. CHERIAN: Okay. But I think you want sodium lauroamphodiacetate at max use of 5.4.

MS. FIUME: 5.4 is the disodium lauroamphodiacetate. It's a leave on hair product.

DR. ROSS: Oh, okay.

DR. COHEN: Acetate at 5.4 percent.

MS. FIUME: Mm-hmm.

DR. COHEN: Yep, okay. Good. That extra discussion helped. Any other further comments on the amphocarboxylates?

DR. BERGFELD: I'm sorry, I'm going to just ask you to summarize what you're going to say.

DR. COHEN: No, that's perfectly fine. So, we're going to come out with an IDA for dermal absorption data on the whole group. DART on disodium cocoamphodiacetate. Further information on composition and impurities of these ingredients in cosmetics. Sensitization data on sodium lauroamphoacetate at max use, which is 9.9 in rinse off, 1.1 in leave on. Sensitization data on disodium laurodiacetate up to 5.4 percent. Ocular concentrations of use of products used near the eye that don't have them listed now.

DR. BERGFELD: So, you're actually on the sensitization on sodium lauro, going to give a concentration of 5.4 or a max --

DR. COHEN: No. I'm just going to say max use.

DR. BERGFELD: Okay.

DR. COHEN: That was just for our -- because we might have a discussion tomorrow and the need for the concentrations at hand may be necessary. Okay. Let me just check that one off. I don't know if we're a third of the way through.

DR. ROSS: Downhill from here.

DR. COHEN: I'd like to think so.

Day 2 - Full Team – June 04, 2024

DR. COHEN: This is a Revised Draft Report on the safety assessment of Fatty Amphocarboxylates. This report was reviewed at the June 2023 meeting at which time the Panel tabled the review due to receipt of data received in Wave 2. These data include information regarding various fatty acid chain mixtures that comprised ingredients reviewed in this report and REACH dossiers for some of the substances.

The read-across coterie members on this team expressed apprehension regarding some of the following. The apprehension on the read-across was problems reading across for mixtures, reading across for certain endpoints like DART which they found concerning, and read-across for the betaines which was not supported.

So our motion, given these read-across headwinds, is an Insufficient Data Announcement with the following needs: dermal absorption data for the whole group, DART data on Disodium Cocoamphodiacetate which we understand is due to be completed in September-October, further information regarding the composition and impurities of these ingredients in cosmetics particularly percentage of actives in ingredients and fatty acid compositions, sensitization data on Sodium Lauroamphoacetate at max use and Disodium Lauroamphoacetate which is the highest concentration of use reported in leave-on products, and ocular concentration of use in products used around the eye. That's my motion. I'm sure there will be some discussion.

DR. BELSITO: Well, you had a lot more insufficiencies than we did, number one. Number two, I think, again, the read-across needs to go to the Read-Across Working Group. Concerning the betaine, I think it's important that read-across is endpoints specific and they were looking at that just for absorption, and not for other endpoints. And that the use of the betaine for the absorption was approved by ECHA, so there are other authorities who have accepted that as a read-across for absorption.

I'm not sure that we need sensitization data. We have data in the report I think that clears that. It can be irritating, and of course that would end up in our conclusion. If we found these safe as used they'd be formulated to be nonirritating. You said you want absorption on all of them?

DR. COHEN: I don't think we have absorption on any of them.

DR. BELSITO: But, you're asking for absorption on each and every one in the group?

DR. COHEN: Well, so, Don, if there's no read-across on these --

DR. BELSITO: But we don't know that yet.

DR. COHEN: I was under the impression that we couldn't do much read-across.

DR. RETTIE: For the betaines initial meeting of the working group, we're really not in favor of that at all for the betaines for arguments related to differing ionization across the pH range. Which is not an issue for the betaines, but they do vary for the other compounds. So we need to go back and take a closer look at that.

I had a comment about read-across as it relates to mixtures. In the working group we had a strong feeling that that was a complication. And I still think for two mixtures it's a complication that we have to acknowledge exists. But for this particular group of compounds that we're looking at here, just over the last day I've seen my attention has been drawn to citations that abrogate a lot of my concerns about heterogeneity. My concerns about heterogeneity were at the level of monoacetates and diacetates being in the same preparation.

It would appear that there is another view on this, that in fact the compounds at the level of monoacetates, diacetates, monopropionates, dipropionates, is pretty pure. The confusion as I had in my head seems to exist at the level of a wrong hypothesis being proposed for how these things were synthesized.

Now, in the exponent report there's a reference to a foreign book chapter, which my team have now to take a look at in detail. And that really lays out another view of those impurities, vis-à-vis, no impurities at the level of the monoacetate versus diacetate, etcetera.

I still think we have some level of heterogeneity, of course, the level of the different e-cell site chains that comes from the oils that are being use. But that's just inherent in there, and this group has seen that in the alcohol betaines and probably other reports in the past. And given that by far the major constituent there is the C12, we know a quite a bit about it. And so a lot of these impurities concerns that I was raising yesterday have fallen away for me. And I think we're dealing with a more homogenous group than I originally thought.

DR. ROSS: If I can just make a comment that we haven't seen that paper or papers you're referring to, Allan.

DR. RETTIE: I emailed it to you at 12:02 last night.

DR. ROSS: Oh, I stand corrected. But, I think the RAW Group needs to consider that again. I think it wasn't just you that was "confused" on the composition and impurities of these things. I think that was a joint RAWG decision. And it appeared to us these were variable composition biomaterials that basically have -- and the components of these mixtures had very different physical properties. So you're looking at solubility and LogPs. It's an order of magnitude different. And so a lot of the conclusion was predicated on that analysis. Now, if that's different, then I think the RAW Group needs to look at that again.

DR. RETTIE: Absolutely. I feel it's different, and you'll be able to assess that with this foreign document that you now have.

DR. ROSS: I look forward to reading it on the plane at 12:02 -- no, okay.

DR. BELSITO: Don, on PDF 65, in animal sensitization, there seems in the results to be signals there. And, there's a case report on contact sensitization to Disodium Lauroamphoacetate where they patch tested it at one and two percent it was positive. So I think this early in the game with the animal, right, you see in Table 10?

DR. BELSITO: Yes.

DR. COHEN: So, I thought having some more sensitization, whether that be animal in silco, or HRIPT, getting this dossier a little bit more beefed up in sensitization would be helpful.

DR. BELSITO: Well, we have to be careful. I mean, we can't ask for new animal data, right.

DR. COHEN: No, no, they just may be out there, right, and we don't need to ask for new animal data.

DR. BELSITO: I mean, we think it's insufficient based upon definitely the genotox. Curt looked at the exponent report and it actually were two of three studies showing some cardiac abnormalities. So we look forward to the report that's promised. So we have no problem going out with insufficiencies. If you want to add your insufficiencies, we've done this before. We can eliminate them when we look at them later on, so I'm fine.

DR. COHEN: Did you want to add your geno? I don't know if I'm -- I mentioned DART.

DR. BELSITO: I think you mentioned the study that has been promised on the DART endpoints, but if not, yeah, I think that's the biggest data point that we need.

DR. COHEN: It's in there.

DR. ROSS: There is another paper as Don points out. There are at least two or three of those studies. I think I pointed this out last time that that should be added to our Discussion. I think that reference was Greens, et al 2022, with the cardiac malformations and the DART data.

DR. COHEN: Okay.

DR. BERGFELD: So we have a motion and a second that we're going out for an IDA. Do we have a list of things that are needed, David?

DR. COHEN: Yeah.

DR. BERGFELD: Great discussion. I call the question, all those in favor of this conclusion? Thank you, very much. And, Paul, I'm assuming you agree?

DR. SNYDER: I concur.

DR. BERGFELD: Okay, thank you. Okay, moving on to Inositol, Dr. Belsito.

DECEMBER PANEL MEETING – STRATEGY MEMO

Belsito Team – December 2, 2024

DR. BELSITO: Then the fatty amphocarboxylates. Oh, no, before we move into this it sounds like this was a major discussion with the Read-Across Working Group and what amidoamine's mean, et cetera. I guess maybe we can have Allan update us there.

DR. RETTIE: Sure. We spent 30 minutes with two representatives from industry who were there to help us try and navigate this very confusing set of chemicals. We were asked two questions, and you weighed in on one of them there, Don, about QSAR sensitization predictions and asked whether they helped fill the data gaps. You had sent the OECD guideline, and we discussed that a little bit. Complications there for industry is, of course, these are detergents and so if you go into cell-based systems, you can't really do that. You can't do those experiments or at least we can't interpret them because you destroy the cells.

At the end of the day, what I came away with from our discussion. While none of us like the notion of only using QSAR sensitization predictions for these compounds, it may be the most useful approach given the cell-based system limitations and the fact that it sounds like we're very much back to believing that ingredients like these go into cosmetics or mixtures of monoacetates and diacetates and likely monopropionates and diproprionates. It's a profoundly heterogenous system.

This makes it very hard. I was hoping it would all devolve down to the monoacetates and the monoproprionates. But of course not. That's not how it works. We're getting a fair bit of help from the Evonik rep. She said she'd go back; she'd look at what she could share with us to expand the data and Alex also weighed in and said she would talk to U.S. suppliers and see what we might get from them.

At the end of the day, the composition heterogenicity seems to be very confuddled by the fact that even today there doesn't appear to be robust analytical procedures that would allow you always to know that you've separated a monoacetate from a diacetate. I find that hard to believe but I haven't done any of this work. We're hoping to get clarification on that from both Alex's efforts and the industry people. So, we don't know a lot more about what I'd hoped we'd learn from this Read-Across Working Group.

We're going to take a closer look, it looks like, on the reach data which has got a fair bit of information in there and I'd be generally discounting that until now working under the erroneous presumption that we only had monoacetates and monoproprionates to deal with. But it looks like we'll go back and we'll looking at that really quite closely now and maybe relying on a lot of that for our read across.

DR. BELSITO: Okay. Are we still keeping all 11 of these fatty amphocarboxylates in our report?

DR. RETTIE: So, there's a question. I'd love to get rid of some of them. Not really sure how we'd --

DR. BELSITO: Did the Read-Across Working Group discuss this grouping?

DR. RETTIE: Yeah, yeah. But we've just got the new information that they're profoundly heterogenous. The group seemed to be moving towards culling the ingredient list to just the monoacetates but that's just unrealistic if the ingredients that are being used are mixtures of mono and diacetates/mono and diporoprionates. Unless there's a way you can see that we can do that, Bart, to cull this group. We're not going to get information, it sounds like, on the pure monoacetates anyway.

DR. HELDRETH: Yeah, it does not sound like anybody is standing up and confidently saying, yep, we just -- we have purely the mono. But what's worse is that even if we can say that this supplier is going to stand up and say we're a hundred percent confident that our product is only the monoacetate then how do we utilize the study data where the test article -- we're back to square one of unsure of was the test article mono and di? Maybe it was even more di than it was mono in the 60/40 kind of split there and what does that mean, especially if we're talking about read-across.

So, yeah, I think we're in a spot where it's hard to say, well, let's cut out these because they're monosubstituted or disubstituted when we don't know if the test article was monosubstituted or disubstituted. So, I think it's almost an all or nothing situation at least until we know more. Now, like Allan said, our friends in Europe and our industry colleagues here in the U.S. have stuff that they're going to go back and they're going to talk to their scientists and see what's available. So, I mean, it does seem reasonable, especially if the full panel is going to end up tabling this for data that's supposed to come middle of next year.

Why not give industry and Europe and the U.S. time to come back and maybe tell us a little bit more about the read-across situation as well?

DR. SNYDER: I think that's a good strategy, Bart.

DR. BELSITO: Well, yeah, but we still have issues in terms of the DART effects, right? I mean, there's a lot of issues here and whether -- wasn't there a discussion whether we could read across for dermal absorption? Is that going to be resolved with this information? Allan, your thoughts?

DR. RETTIE: Well, I'm trying to recall the dermal absorption read-across question feeling there. But you're right. There are a lot of issues that we have in front of us.

DR. BELSITO: And composition and impurities, that's what we're hoping to get from manufacturers. I wasn't clear on that.

DR. RETTIE: Well, I wasn't clear after we finished having this discussion with the industrial reps amidoamine was something I brought up and I asked whether it's possible to get solid data on the amidoamine impurities that might help us with the sensitization questions. And that seems to be kind of obfuscated as well and I can't really describe it to you, but it could be very significant, right? It's in some syntheses amidoamine was up to five percent.

DR. BELSITO: But I was in on the tail end of the Read-Across Working Group, she was saying that that's not an amidoamine as we were aware of with Cocamidopropylbetaine, that it was a different molecule under the same sort of generic heading and needed to be clarified was my understanding. Is that correct?

DR. RETTIE: Yeah, that's a better summary. Thanks.

DR. HELDRETH: Yeah. But we're also waiting on the prenatal developmental toxicity study in rabbits performed on the C18 diacetate the consortium apparently is planning to have finalized by the end of April. So that is out there as well. I mean, if the Panel as a whole tomorrow is looking to say, yes, we're going to table this and wait on the consortium data.

Table this and wait to hear back from industry about the identities of these ingredients whether they're mono or di and same thing with the test articles, I don't think it would be out of sorts if the Panel wanted to say we have some additional insufficiencies we wanted to make as part of our announcement.

You know, just kind of beef up the IDA's based on what we have in front of us now. Here are some additional things we would like clarified since we're going to be waiting six months or possibly nine months before we come back and talk about these again.

DR. BELSITO: Well, first of all, we were promised the DART data in October of 2023, no? And now it's April. But beyond that, Bart, we have no choice but to table it because we haven't been presented with a full report here, right? And even if we assume that we're going to go ahead and do an insufficiency it's not going to come back to us until March. So, it's like the Panel has really been left with no option other than to table it in my opinion which isn't quite fair.

I mean, we don't have the full report. The next meeting isn't until March so, again, the question is really moot. I mean, yeah, let's wait for the DART data in June but then that pushes it to June and two years ago they were supposed to give us this data. Why didn't we get it in October of 2023?

DR. HELDRETH: Unfortunately, I'm not aware of why there's been a delay in the data. I mean --

MS. KOWCZ: We have a raised hand, Bart. Dr. Schmitt.

DR. HELDRETH: Go ahead, Dr. Schmitt.

DR. SCHMITT: Yeah, maybe I can also comment on that because those have been sponsored by our REACH consortium. We did face quite some delay because we wanted to go to the same lab that also ran this OCD-414 (phonetic) in rats where we had seen these cardiovascular malformations in 2019. So, we wanted to get the same rats from the same supplier, same strain, and also the same pathologists. And, yeah, so getting a time slot at this specific lab Charles River in Den Bosch in the Netherlands, that's one of the best labs in the world and everyone wants to run experiments with this laboratory.

And this is really the driver for the delay. So, getting a suitable time slot for the main study, for the dose range finders and so on. So, we do have a draft report now available, so we are very confident that we're being able to provide something not by end of April but by end of March which as I understand still too late for your March meeting, unfortunately. But yeah, it's really close to finalization and yeah. Maybe should've communicated the delay that was foreseeable since two years, maybe a bit earlier. So, our apologies for that.

DR. BELSITO: Again, I really can accept QSAR data to clear sensitization. I mean, if you have a QSAR prediction that it's not going to be a sensitizer then do a confirmation of no induction. A CNIH/HRIPT on humans to show that it's not a sensitizer at those levels. Because the 497 guidelines do not include QSAR alone as a predictive test for something that's not sensitizing.

DR. SCHMITT: We note that. We will do what we can. We have been investigating that route as well.

DR. BELSITO: Okay. So, I mean, again, I don't think we have any options but to table. The question is when we bring it back. I mean, it's going to be the earliest March and that seems silly since we're not going to have the DART data, which is promised by June, but I think we should bring it back by June and if we don't have the DART data, go ahead anyway. It's been over two years.

And in addition to DART, we need some skin sensitization. And the Read-Across Working Group I guess needs to work on how many of these they want to include, right, Allan?

DR. RETTIE: Yeah, I'm down to eight at the moment today.

DR. BELSITO: How frequently is that group meeting? Is it only occurring in conjunction with our meetings?

DR. RETTIE: Well, there's some offline stuff happening immediately before -- not immediately before -- but in the run-up to the meetings. But we're not meeting on a weekly or monthly basis. When it comes to these amphocarboxylates, though, we definitely probably have to ramp up our discussions and the frequency with which we meet.

DR. HELDRETH: Yeah, if we get a significant amount of data and it comes in far enough in advance of a panel meeting, certainly, the Read-Across Working Group can have a separate meeting leading up in advance of a full panel meeting. But in this case, this read across data came in not that far ahead of the meeting and it seemed to fit in with the agenda that we have for this meeting that was a little on the lighter side for discussions.

DR. RETTIE: But unlike RIFM, Don, I think which has regular standing read-across meetings.

DR. BELSITO: We have weekly meetings.

DR. RETTIE: Wow. Well, weekly meetings might be a bit much for us but certainly upping the frequency for these ingredients, I think, is probably warranted.

DR. BELSITO: Okay. So, we're tabling this. I mean, it wasn't even a full report, so I don't know. Do we consider it a full report and table it or --

DR. HELDRETH: I think it's just a matter of considering when the Panel would like to see it back.

DR. BELSITO: June.

DR. HELDRETH: June. Okay.

DR. BELSITO: That's me. I mean, Allan, Curt, Paul?

DR. KLAASSEN: Yes. That should be realistic.

DR. SNYDER: Yeah. I support that -- June as a deadline for when we have to move forward. We need to see a report, then.

DR. HELDRETH: Absolutely.

DR. RETTIE: So, in June do we know when the meeting is? Look it up.

DR. BELSITO: Yeah, June 3rd or something.

DR. RETTIE: Well, yeah. I think we would like it fairly early. I mean, I think June 1 is not a realistic deadline.

DR. HELDRETH: So, you're saying that you would like to have a Read-Across Working Group meeting in advance of the panel meeting?

DR. RETTIE: No, I thought we were talking about Panel's deadline for receiving the data.

DR. HELDRETH: Oh, yeah, yeah. Yeah. It needs to come in about a month beforehand so that we have time to incorporate it into your dossier.

DR. RETTIE: So that would be May the 1st just for the sake of putting the data.

DR. BELSITO: The June meeting is June 9th and 10th of 2025.

DR. HELDRETH: Right.

DR. KLAASSEN: Correct.

DR. RETTIE: So, May 1 for me.

DR. BELSITO: I mean, we heard that the data should be there by March but just not in time for a wave two or a submission for a March report. Am I correct with that?

DR. SCHMITT: Yeah, we are very confident to have everything available much earlier than 1st of May, yes.

DR. BELSITO: Thank you.

DR. HELDRETH: That's great.

DR. BELSITO: Anything else?

DR. SCHMITT: Thank you all for your patience. Okay.

DR. HELDRETH: Thank you.

DR. KLAASSEN: Allan, we might try to have a read-across conference call around that same time --

DR. RETTIE: Sure.

DR. KLAASSEN: -- so we can get everybody together and see if we get some more information from industry. Our hands are kind of tied until we get more data.

DR. HELDRETH: Yeah. I can forward along any relevant data to the Read-Across Working Group the moment we receive it and then we can discuss is there a time when the Read-Across Working Group would be available to meet together in advance of the meeting and then I would like to publish that meeting in advance on the CIR website so that folks like Dr. Schmitt or in the U.S. Don Bjerke or Alex can also be part of those meetings because as we saw today they can really provide quite a bit of help in those situations.

DR. KLAASSEN: Yeah, they're essential.

DR. HELDRETH: Absolutely.

DR. RETTIE: I'll be in Europe for much of May, but I can dial in from anywhere.

DR. HELDRETH: Okay, wonderful.

DR. BELSITO: Well, not from some of the area's in Scottland that you're from, Allan.

DR. RETTIE: No, I took my area off the itinerary so we're not going to the north.

DR. BELSITO: Okay. Telephone service can be spotty up there. Okie doke.

CohenTeam – December 2, 2024

DR. COHEN: Okay. Fatty Amphocarboxylate. I have that one tomorrow.

DR. ROSS: A lot of that's going to be driven by the. The chemical discussion.

DR. COHEN: You mean the read across group?

DR. ROSS: Yeah.

DR. COHEN: Right. So look, this is not a review, this is a strategy memo with some questions. Okay. At the June meeting, the Panel reviewed the Revised Draft Report of the 11 Fatty Amphocarboxylates along with justification tables on potential read-across and issued an IDA in order to conclude on the safety of these ingredients. And we asked for dermal absorption, DART on Disodium Cocoamphodiacetate, further information regarding the composition and impurities of these ingredients as cosmetics, particular percentages of actives in ingredients and fatty acid compositions. Sensitization data on Sodium Lauroamphoacetate at max use, and sensitization data of Disodium Lauroamphodiacetate at max use concentration.

Since issuing the IDA, QSAR skin sensitization predictions for C12 diacetate and others here were received by the REACH Amphoacetate Consortium. In addition, we got prenatal development tox study in rabbits, performed using C8-18 diacetate form. No, I'm sorry, this is still ongoing. This prenatal development study is still going on and should read out by the end of April.

So we have a couple of questions for us. Number one, does anyone want to comment on the report that was presented to us, that QSAR report?

DR. ROSS: Sure. What do you want to know?

DR. COHEN: What'd you think of it? It's suggesting it's not a sensitizer.

DR. ROSS: This is just my personal opinion until the RAWG meets and comes to some sort of conclusion. My sense of this is that read-across based only on QSAR, for any endpoint, let alone something as complicated as skin sensitization, if you only have QSAR, I think it's tricky. I think it's a very difficult thing to do.

This QSAR catches all of the skin sensitization chemicals. I think if you look in the literature you can probably find various estimates, but you probably miss about 30 percent of them just by QSAR. And then QSAR is iffy. If it's due to impurities and not the chemical then QSAR is a nonstarter.

I think that discussion has to be had in the RAWG to answer that question correctly, but philosophically from a tox perspective I think if you only have QSAR, for any endpoint, then I think it's very difficult.

DR. COHEN: My comments or question was does this mean we're not getting human data? This was my response to the question.

DR. ROSS: Susan may have a totally different opinion. We've not talked about this and, you know, we'd do it at lunchtime. But go ahead, Susan. What do you think?

DR. TILTON: You know, I do agree that it could be difficult with QSAR only data. I am possibly a little more supportive of this approach and it would certainly be on an endpoint by endpoint, case by case basis. Skin sensitization is complex. But in

terms of our understanding and being able to make predictions and understand all of the steps along the way that leads to skin sensitization, we probably have the most understanding of this as an endpoint compared to almost anything else. So I may have a little more confidence because this is for the endpoint of skin sensitization.

I think in the RAWG meeting we're going to talk a little bit more about how these are synthesized and some of the updates that need to be made to the report. Assuming that what we've been reading is true about sort of these newer methods that are used to synthesize these with fewer impurities. And even with the goal to generate these, such that they're sort of typically neutral or slightly acidic, with like a glycolic acid content of less than 1 percent. That we would tend to believe they would be less likely to cause skin sensitization.

I think if we have some agreement on the synthesis and what it is we're actually dealing with, then it may be possible. I'm open, I guess, to that discussion of being able to make comparisons by QSAR to appropriate comparators.

DR. ROSS: I think the chemistry discussion will be quite complicated. Because, as Susan alluded to, we have diacetates as well as monoacetates. And it appears from the chemistry discussion that we've been having in advance here, is that the diacetates are really monoacetates. I know, it's complicated. And so we need to have that discussion with industry scientists to sort that out. And that's where we'll end up.

But this issue of should we use the QSAR read across, it looks like just on chain length, I think the lauros are C12s. I had that wrong initially in an e-mail to you, Susan. But I think they're C12. But you could read across because they have C12 data from their read-across dossier there. It's whether or not you want to if that's all you have.

I guess my response would be, yeah, we know quite a bit about sensitization and there are many assays for it. So it shouldn't be too difficult to have at least some supporting evidence in addition to the QSAR for lack of skin sensitization.

DR. COHEN: You mean other in silico methods.

DR. ROSS: Yeah. But we don't have anything. We just got this QSAR. So I guess I'd like to see some data, but that's where I was coming down, so.

DR. TILTON: I think in general there was some idea that this is -- trying to think what the conclusion was. Essentially, to just push this forward, because we know that we're waiting for the DART data.

DR. COHEN: Right. We're going to table, right?

DR. TILTON: Yes.

DR. ROSS: Yeah. You can still make a decision of whether to push this down the road and wait. Yeah. I mean we could table the discussion until after the chemistry group on the read across.

DR. COHEN: What about the development tox data, don't we want that?

DR. ROSS: I think we need that. And if they're going to have it available I think we should see it.

DR. COHEN: Well it's April 2025. Do we wait until the June meeting?

DR. ROSS: I would say so.

DR. BERGFELD: You can say that in the minutes, that it's tabled until the April meeting.

DR. COHEN: We would table to the June meeting.

DR. BERGFELD: June meeting. Yeah. In hopes of receiving it in April, I guess.

DR. ROSS: I would support that. Maybe a simpler reason is not to have prostaglandins and ampicarboxylates at the same meeting. At least the way prostaglandins were planned was going to be the March meeting. I don't know if that's still the case, but I wouldn't want to see both of them at the same meeting.

DR. COHEN: Just have two things.

DR. ROSS: Yeah.

DR. COHEN: Okay. By the way, any specific in silico methods?

DR. ROSS: Oh, you mean in vitro methods for skin sensitization?

DR. COHEN: Yeah. In vitro or.

DR. ROSS: Yeah, the DPRA. There's the KeratinoSens. I mean, there's many in vitro methods that could be used. I just didn't see any.

DR. COHEN: I agree with that. Okay. It was an interesting question posed to us, like, is this okay to just jump in for everything we'd normally be receiving?

DR. ROSS: And there are arguments for and against.
And as Susan says it's often endpoint specific. Again, it's good to have some data to hang your QSAR hat on, and to back it up.

DR. COHEN: In our IDA we have composition and impurities. And that IDA is not going away with any of this discussion.

DR. ROSS: No. Well, actually the new synthetic methods, again, pointed out in that that brief summary there, they will minimize some of the glycolic acids and the amine impurities.

DR. COHEN: That's fine, the specificity of the impurities needs to be in there and the percentages.

DR. ROSS: Yeah, these new synthetic methods, they seem totally different to the descriptors, the chemical descriptors we were given originally. So that's the need. That's why we have to have this discussion first.

DR. TILTON: Yeah. And if that is how things are being done, it would really help to have all of that information in a report for us to review together, the way that we're looking at it now.

DR. ROSS: I suspect the report could be. I know Monice and Priya won't want to hear this, but it might be reorganized with respect to how these things are classified, i.e., which groups and how many groups and do we still have this number of chemicals or is this reduced down, and how do we actually look at this? Are we going to reclassify this on a chemical basis? So that's part of the discussion. The answer might be no, we've got the perfect classification. But that discussion needs to be had.

DR. COHEN: Okay.

DR. ROSS: I can see Priya and Monice being very excited about that.

DR. COHEN: Who wouldn't be?

DR. BERGFELD: I think we should do lunch now. They have to have a few minutes to have lunch.

DR. COHEN: Okay. Yeah, okay, that sounds fine.
I think we come back to the resource documents. And then some other ones shouldn't be too bad.

MS. FIUME: David and Susan, we will see you at 1:00.

DR. COHEN: I'm not going to sign off, I'm just going to go silent on this. We'll stay on this channel and we'll be back at 1:30.

DR. BERGFELD: Okay. Right.

Day 2 – Full Team – December 3, 2024

DR. COHEN: Remember what we're dealing with is a strategy memo here, not the report. In June, we reviewed a revised draft report on 11 Fatty Amphocarboxylates and issued an IDA with --

DR. BELSITO: June of 2023.

DR. COHEN: Oh, I'm sorry. This was 2023? I don't know how I have 2024.

DR. BELSITO: Yeah. We were promised DART studies in October of 2023.

DR. COHEN: Okay. Thank you, Don. Our IDA included dermal absorption, DART for Disodium Cocoamphodiacetate, further information about composition and impurities, sensitization data for Sodium Lauroamphoacetate and Disodium Lauroamphodiacetate at max use concentrations.

Since issuing the IDA, we received a QSAR on a number of the mono and diacetates. We also received prenatal development tox study in rabbits. I'm sorry, there is an ongoing development toxicity study in rabbits. That is due in April of 2025.

The read across group met yesterday and discuss this. And the questions to the group at hand are the following: Does the QSAR skin sensitization predictions for C-12 diacetate, and others listed there, help fill the data gaps for sensitization for Sodium Lauroamphoacetate and Disodium Lauroamphodiacetate? And our response is, no.

We wouldn't be satisfied solely with the QSAR data as a sole metric for sensitization. We'd be interested in other surrogates, HRIPT, surrogate animal tests, in vitro methods like KeratinoSens, DPRA, reconstructed epidermis. We also want further information about the synthesis methods and any impurities. That's question one.

Would the Panel like to table this report? Yes. And what's the Panel's deadline? If we're expecting the prenatal development tox at the end of April, perhaps we could do this at the June meeting or the September meeting even.

I don't know if that's really a motion for any of this.

DR. BERGFELD: I don't believe so.

DR. COHEN: For a strategy method, that's our discussion summary.

DR. BERGFELD: Don, do you have anything to add to that?

DR. BELSITO: No, I agree. The question to table is moot since we weren't given a full report here, right? So we're not going to be able to pass on this anyway and the earliest we'd be able to see it back in March. And so it sort of makes no sense to go for March if we're told we're not going to get the DART data until around that time.

Again, I will only point out that we're told we're going to get DART data in October of 2023. So we're already a little behind here. So I hope that they can come up with the DART data, but there are still going to be insufficiencies even if that data is clear and explains to us why there were all these cardiac effects in one of the DART studies.

We agree with David. The QSAR has to be combined with other in vitro tests according to the guidelines of 497 by the OECD. We had a number of other issues at the prior meeting and that was whether we could read across for absorption as well. And that's going to be an issue that will come up again.

And I know that I sort of hung around and listened off cuff to the discussions of the working group, and apparently one of the representatives from the manufacturer said that the amidoamine in these Amphocarboxylates was not the same chemical as the amidoamine that we are concerned about, in the butanes for example. But I would like further information on that obviously.

DR. BERGFELD: Allan, can you respond?

DR. RETTIE: Yeah. We've come full circle, really, in the working group and its interactions with industry members. We met yesterday with Don Bjerke, Lauren Kavanagh, from Innospec, and Barbara Schmitt from Evonik. And we got quite a different take from them, as basically European suppliers, as to what the composition was. Which was unfortunate because I felt we were getting to some clarity that in fact there were no diacetates in these things.

That was a fairly strong statement, I thought, from the Procter and Gamble rep, conveyed to us by Don Bjerke, very helpful. But they're diametrically opposed in terms of what they think the composition of these things are. And that's a real data insufficiency for me. It's hard for me to move forward if I don't what we're looking at here, and we can't agree on whether they are monoacetates or diacetates. Because it brings up the question of what kinds of impurities might there be depending on the modes of synthesis.

So we're at an impasse there, but we've got information from the REACH delegates, they'll get together and try to put something down on paper for us. And the same thing from PCPC. So we're supposed to get some of that information, or maybe all of that information, by early May and I'm certainly looking forward to it.

DR. BERGFELD: Bart, regarding this; so there's a lot of ambiguity here. I think that we have to -- it's not really an official table, we're waiting on information and it's been promised for April or May. What do we do strategically here? Can you respond as to when we would see this and when we would act on it?

DR. HELDRETH: I think depending on when the promised data comes in, maybe June. Maybe it'll be better in September if it come in really close to our "mail date" to send out the dossier to all of you for the June meeting, then we'll just push back and wait for the September one. But I would suggest that we make the September one a drop dead, cut off deadline. As Dr. Belsito mentioned, we've been waiting and we're supposed to get this in October and that didn't happen. So let's set up a deadline and proceed even if we don't receive it by then now.

Dr. Rettie mentioned the representatives from industry that talked about it yesterday. I didn't know if any of them wanted to interject. All four of them are on the line here. We've got Alex and Doctors Bjerke, Schmitt and Kavanagh. I didn't know if they wanted to add anything here. I see Don Bjerke has his hand up.

DR. BJERKE: Yeah, I think we did talk about whether they were monoacetates or diacetates, and we're committed to firming that up. I think what we want to make sure that we do is we have all the correct structures that are being evaluated. So, if there are diacetates in there, we want to make sure that Table 1 represents those diacetates.

And so we're committed to working with the REACH consortium to resolve that. And then we can also at the same time ask for impurities of the various chemical ingredients that are in there as well, because that came up as well. So we're committed to working with suppliers to get that information, so that we're all on the same page and we can assist and facilitate the review.

DR. BERGFELD: So Don, how will you get this information for us? Will you be sending a memo to these individuals, or giving us an outline of what is being requested and the deadline?

DR. BJERKE: Yeah, I think we'll work with Alex on how best to coordinate that through PCPC. But I think we've got two very good -- you know, Dr. Schmitt and Dr. Kavanagh, from Evonik and from Innospec, that we can immediately reach out to if not others.

DR. BERGFELD: Okay.

DR. BJERKE: Alex, do you agree with that?

DR. KOWCZ: Totally, Don. I would have said the same thing you said. We'll definitely work with the two companies that are very gracious to help us with this, because the REACH consortia is a consortia, so they'll have to release this data.

So we will work through them to make sure that the Panel has the right structures, as Allan requested, that you know what you're talking about, that you know what you're evaluating. I think it's really critical because there is a lot of confusion at the moment, but we have to rely on the ingredient suppliers because they know the chemistry and they know the ingredients best. So we will work through that and we'll work with you, Bart, if that's Okay with you.

DR. HELDRETH: Thank you.

DR. BERGFELD: Is it appropriate to give them a deadline for the September meeting?

DR. KOWCZ: Yesterday when we talked to them, they were very open. Dr. Schmitt, from Evonik, and Dr. Kavanagh, from Innospec were very willing to work with us. So I think that we will work with them directly to give you the information, or as much information as possible, to make sure that we're all looking at the same things and the right things. And that everybody has the same foundational framework and the same foundation of information.

DR. BJERKE: And I think the reference that was initially provided for the 2006, foreign reference, that talked about the monoacetates, that's a little older. And the suppliers clearly indicated that being able to find the diacetates is very important on the analytical method that's being used.

So again, I think we're not going to settle for monoacetates and Diacetates, we want exactly what are the chemical structures that you need to evaluate? So we're going to try to get clarity on this as quickly as we can.

DR. RETTIE: A couple of things that came out of our meeting yesterday that was interesting to me, the difficulty for chemical analysis and discrimination between monoacetates and diacetates was raised. So I kind of thought it was a bit odd, but I went into the literature and did a bit of a dive last night to see what was maybe out there in terms of modern analytical procedures. And while I'm nowhere near as competent as our writers and finding this information, I was disappointed to find nothing. So I'll be interested to see what comes up.

And the other thing that struck me was the fact that we're working with detergents. It's just tough, as we've discussed here analytically. But trying to do cell based assays with these things can be very tricky, maybe not even possible depending on what concentrations they need to get to. So those were two complications that made me understand a little more why this has been so cloudy.

DR. BERGFELD: Don Bjerke?

DR. BJERKE: Yes, I did follow up with some of my colleagues that have more expertise in skin sensitization in the different NAM models. And you're exactly right, there's a lot of effort going on across industry, including in Europe with surfactant manufacturers, to evaluate these new approach methodologies, both the cell-based assays and the in chemical direct-peptide reactivity assay.

I think the concern is legitimate on getting false positives. And when you have a cell culture and you're adding surfactants you can see strange things. There's a lot of work going on across the industry to get a better handle on this.

DR. ROSS: Yeah, you have got to use pretty low concentrations, Don, as we discussed yesterday. I would say that whatever comes out of this discussion in the rogue, and we talked a little bit about this yesterday, touched on it, it may lead to some reorganization of the chemistry in the dossier and the compounds in the dossier. It's possible it might not, but it may take a little longer even to do that so.

DR. BERGFELD: Well we'll certainly have an update in September, where we stand and what we have to do. I think that we've concluded this discussion and a lot of good points. It's my understanding that we'll be tabling this until September with the expectation of getting all this information.

DR. BELSITO: Can I just make one more comment, Wilma?

DR. BERGFELD: All right, sure, go ahead.

DR. BELSITO: I would really appreciate it in the future, that when we get something like this that the old report be attached. Because I had to dig through my data to find the old report to really make sense of what was being put in front of me with this document.

DR. BERGFELD: Good point. Thank you.

DR. HELDRETH: Okay.

DR. COHEN: I agree. I was going to say something similar. We met in both June 23 and June 24. Two times we've been through this in the last year.

DR. BERGFELD: Okay. Well, we're going to move on now to the Oxyquinoline, Dr. Belsito.

SEPTEMBER 2025 PANEL MEETING – DRAFT TENTATIVE REVIEW

Belsito Team – September 8, 2025

DR. BELSITO: Okay. Fatty Amphocarboxylates, we also have a Wave 2 on this one. The Wave 2 was to address our concerns about Amidoamine impurity in amphoacetates, but I don't know, again, I'm not a chemist. Maybe Allan can comment, but I thought that the Amidoamine in the Amphocarboxylates would likely cross react with the amidoamine in betaines. I mean, the reactive end of the molecule looked the same to me. But, Allan, what were your thoughts there?

DR. RETTIE: Yeah. I thought it was useful that we got a little bit of clarification around the structures in the new data. In terms of cross reactivity, I guess that's true, quite possibly. One thing I hadn't realized was that Amidoamine itself, not from the betaines but from the amphocarboxylates, is drawn as two isomers. So, that was new information. I'm not sure it really makes a big difference to us, but that was part of the clarification for composition, which I was happy to see.

Amidoamines we discussed in the first two iterations, I think, of this report as possible reasons for some of the toxicities. But my recollection was that we got away from that. We decided in a previous discussion on the amphocarboxylates that the amidoamine impurities weren't really something we needed to worry about for this report. I rather glossed over that. I thought we had (audio skip).

DR. BELSITO: Well, no, I mean the concern with the amidoamines and the response from the Consortium is the fact that when we went to betaines, we basically said that they were safe as used when formulated to be non-sensitizing based upon a QRA or other approaches. I think we still need that language here because to me that R double bond NH is the reactive part of the molecule. And it's the same in both the betaines and in the amphocarboxylates.

DR. RETTIE: Right. So, the betaine piece that you're discussing certainly predates me. So I don't remember any of that. I didn't have access to it. The betaines that we considered was when we were thinking about including them. But then we decided against that because of the permanent positive charge on them, the charge distributions being different. So, we didn't roll those into the fatty amphocarboxylates.

But I hear what you're saying. I'm just not really able to kind of connect the two right now because it predated me. But you are right, they have the same reactive center, if you will. So, cross reactivity, I would imagine, is a possibility.

DR. BELSITO: Yeah. So, I mean, I appreciate their input, but I don't think it changes our concern about the amidoamine impurity in the amphocarboxylates, at least that's what I thought. Anyway, this is a Draft Tentative Report Safety Assessment as used in cosmetics.

In June of 2024, we issued an IDA, dermal absorption, DART data on disodium cocoamphodiacetate, further information regarding the composition and impurities of these ingredients as cosmetics, particularly the percentage of actives in ingredients, fatty acid composition, degree of esterification, how much of sodium cocoamphoacetate has zero, 1, or 2 acetate substitutions, sensitization data on sodium Lauroamphoacetate at max concentration of use, sensitization on disodium Lauroamphodiacetate at maximum concentration of use, and any information to clear composition to support the use of read-across sources previously suggested.

In December of 2024, we decided to table the report to look at REACH Consortium. And, since tabling the report, we've received a whole bunch of data that's listed and I will not go over. We also got in data from the read-across working group, as Allan mentioned, incorporating the majority of this data into the report.

Then, we discussed a lot of this this morning. And, I think, based upon that and the data that we had that was in the read-across working group document that included LLNA at 50 percent that was positive, likely secondary to irritation, a guinea pig maximization test, although the challenge was suboptimal. Five of 20 animals were sensitized, you need 30 to call it positive, but still is concerned with sensitization.

I think the Wave 2 only convinced me that the amidoamine and ethyl acetates would likely cross react with the amidoamine in betaines. But I thought sensitization likely could be covered by the betaine caveat, which is formulated to be non-sensitizing, as determined by QRA or other methodologies. DART studies in the read-across working group doc were negative to 1,000 milligrams per kilogram body weight per day for the C18 diacetate.

And, again, I think we agreed that the DART was no longer an issue given the studies we saw in rabbits, so that cardiac toxicity. DEREK predictions were negative for sensitization as well, but I think we used the sensitization caveat.

So, in the end, after looking at the data in this report, the data and the read-across working group report that wasn't in this report, we could go with safe in cosmetics as long as they're formulated to be non-sensitizing, which may be based on a QRA or other methodologies, which is a conclusion we had for the betaines

DR. SNYDER: I agree.

DR. RETTIE: I'm good with that.

DR. SNYDER: I agree. I appreciate that nice synthesis of all this morning's data and all new data, Don, but I agree.

DR. BELSITO: Curt?

DR. KLAASSEN: Yes, I'm fine with that.

DR. BELSITO: Allan?

DR. RETTIE: A relief. I agree.

DR. BELSITO: Good. Okay. Well, let's move on because we have more to do here.

DR. RETTIE: Yes, sir.

DR. BELSITO: And it's 4:24. Paul needs to belly up to the bar soon. Is your house done, Paul? You got a bar there?

DR. SNYDER: The house is 99 percent done. It's just a laundry list of things yet to be done that are irritating Erica (phonetic). But we're in our house, so thank you. Thank you. Thanks for asking.

DR. BELSITO: Wonderful.

DR. RETTIE: Congratulations.

DR. BELSITO: Did you put a bar in? When we meet down in Naples, we can belly up to the bar at 5:00?

DR. SNYDER: Yes, exactly. Yeah.

DR. BELSITO: Okay.

Cohen Team – September 8, 2025

DR. DAVID COHEN: Our first agenda item is the Fatty Amphocarboxylates. We reviewed the revised draft report in June and issued an IDA, and we went through much of this. I'm just going to top line this that our IDA asked for dermal absorption, DART on Disodium Cocoamphodiacetate, further information about the composition, sensitization data on Sodium Lauroamphoacetate at max use and the same for Disodium Lauroamphodiacetate at max use, and any information to support the read-across.

And we had a very long conversation about this**.** I suppose two questions came to mind because we spent so much time we don't have to redeliberate. But we didn't get absorption data but there was inference about its lack of absorption. And the question is, are we accepting that or are we maintaining our insufficient data on that? That was one thing.

And the other thing is the HRIPT data is way below max use. So while the read-across group got a lot of comfort around things, I think it's incumbent upon the team breakouts for us to really interrogate the data further. And so, look, there's a lot of read-across members here, what are we doing? And third, is there anything else that we need to discuss on this?

DR. KLAASSEN: Can you hear me?

DR. DAVID COHEN: Who's talking?

MS. FIUME: You should be good now, Curt.

DR. HELDRETH: We hear you, Curt, in the Cohen team.

DR. DAVID COHEN: Curt's on the wrong team.

DR. HELDRETH: He's leaving.

DR. ROSS: He can join us. We'll have him.

DR. DAVID COHEN: Curt, if you want to stay -- if you're a refugee from the other we can give you a temporary citizenship here with us.

DR. HELDRETH: He split. He's gone.

DR. DAVID COHEN: Give him refugee status. So, I'll just randomly call on folks. Susan, what are your thoughts on the two issues and any other issues you might have?

DR. TILTON: For the dermal absorption, I mean, we did spend some time talking about this in the RAWG group, because we had a lot of discussions previously about what would be required for read across for dermal absorption, and a lot of that was out of concern for potential systemic effects, so the developmental cardiac effects. But if we no longer seem to -- we can revisit that data, but we discussed, as the group, that data looked pretty clean. There's not a lot of concern. Like, there's no real particular systemic effects that are of concern.

And so, the question is even if we had dermal absorption data, what would we be using it for? What are the concerns that we have about systemic toxicity? What level of dermal absorption would be acceptable? And we really don't have any systemic concerns that we were discussing, so I'm comfortable with lack of dermal absorption data.

DR. DAVID COHEN: I suppose your tack on this is when we asked for dermal absorption data, if it's positive, then we want other data, but you have that other data.

DR. TILTON: That's right. I think previously we weren't sure if we were going to get this data on the developmental cardiac effects. I mean, of course we were told, but in lieu of having that data we certainly would've wanted to have had dermal absorption data.

DR. DAVID COHEN: Sam?

DR. SAM COHEN: I don't think there's any systemic toxicity issues here at all. I think the only concern I had was the dermal sensitization and patch testing. The results seemed very confusing and that's really the only issue that I think we have to deal with.

DR. DAVID COHEN: David?

DR. ROSS: Yeah, I went into this thinking that we would need the dermal absorption data and frankly I would still prefer it, because I think it's really easy to show these things are not absorbed very much. They're zwitterionic, they're not going to be absorbed much at all.

It's a bit disappointing we didn't see that, but Susan summarizes the argument nicely. Now that the major systemic toxicity endpoint of concern has been cleared -- i.e. the DART -- do we really need it? And the answer is probably no. Would it be nice to have? Yes.

DR. DAVID COHEN: Why would it be nice to ha- -- I mean, listen, I kind of came out by you, David, on this but this is a consensus. But what's the scenario where we want it? Is it just to demonstrate a lack? Is it a second layer of comfort in that we don't have the systemic effects as far as we know, as far as we could tell but not having systemic absorption sort of adds a layer of safety for this?

DR. ROSS: It would be confirmatory rather than absolutely required. I mean, I think that's where we're at right now. But it would be nice to have.

DR. DAVID COHEN: If we just say it's going to be nice to have, I think they'll be pack of hyenas tomorrow asking why I need something.

DR. ROSS: I don't think you need it, I mean, given the argument that Susan summarized. You know, the concern, the major systemic concern is gone. So, we don't have any systemic endpoints. We're assuming this would be -- based on the structure -- little to no absorption anyway, but we don't have that confirmed so that's where we are. I'm okay with proceeding without it. Would I prefer it? Course I would. But that's where I am on that.

The other issue. Do you want to go on to the Lauroamphoacetate and the lack of HRIPT sufficient at the high concentration? Our max is 9.9 percent rinse off. We didn't receive anywhere near high enough concentrations. But I wanted David's opinions on this because in the documents there's a guinea pig maximization test using a challenge concentration of 20 percent. We saw positive reactions in 5 of 20 animals and the conclusion was the test substance was non-sensitizing. So, David, can we take that?

DR. DAVID COHEN: I don't think so. I wanted HRIPT at max concentration. There are rare reports of amphoacetates causing allergic contact dermatitis. And we got HRIPT at more than an order of magnitude lower concentrations than that, and some of these are in pretty high concentrations. The current leave on is 1.1 percent for Sodium Lauroamphoacetate and we have an HRIPT of 0.27. For Disodium Cocoamphoacetate, 5.4 percent, and we have a HRIPT at 0.046 percent. And there's a rinse off concentration at 20 percent and 5.4 percent from mucus membranes in babies.

So no, I don't see in what world this HRIPT data passes the tests for us, and I don't think the current animal studies mollify my concerns.

DR. ROSS: That was my specific question. You're a no on that. I think that's very clear.

DR. DAVID COHEN: I'm a no.

DR. SAM COHEN: I would be no, also. I think that it's not acceptable.

DR. BERGFELD: It only would be acceptable if you cleared everything but that and made that insufficient.

DR. EISENMANN: What I would just say is that it's mostly used in rinse off products and they always test rinse off products diluted, because the rinse off products are expected to be irritating. So, you're not necessarily going to get some of the maximum concentrations just because they don't test rinse off products full strength.

DR. DAVID COHEN: It doesn't mean we can't have HRIPT on diluted neat material.

DR. EISENMANN: Most of the tests that were provided, that's what they are.

DR. DAVID COHEN: No, they're diluted final product, right? They're not the --

DR. EISENMANN: Oh, you're talking about the ingredient.

DR. DAVID COHEN: Yeah. My clinic is replete with people with face dermatitis from rinse off products, so I just think this is just way too far off. So, there's no reason not to have it and I think we need more. There are rare reports. The problem is the absence of data is not data here because we're not really testing these Amphocarboxylates in routine patch test series. So, if we're seeing it, we wouldn't know it.

DR. SAM COHEN: Question I have, David, if these are all going to test positive at the higher concentrations, what are we going to do with that data then?

DR. DAVID COHEN: Why do you think they're going to test positive at higher concentrations?

DR. SAM COHEN: Just from what the ladies have said there and --

DR. DAVID COHEN: No, no, no, no. I think the point that she was making, which was is right on, if you take a cleanser that might have five percent Sodium Lauroamphoacetate, it has got 95 percent other ingredients in there and the product is designed to be lathered on and rinsed off. If you took shampoo, lathered your head with it and decided not to rinse it off, and just left the lather in your head, it's going to be pretty irritating. The product isn't designed for that kind of thing, or detergents or things like that.

So, the total product design is meant to go on and off to reduce irritancy. The issue is the exposure to various locations, like your eyelids, like your neck folds, like behind your ears, may not be totally rinsed off and there's a decent chance you'll have, I think, a reasonably high exposure to that product sitting there for quite a while that can cause a problem. We saw it in Cocamidopropyl betaine. We see it with very low concentrations of isothiazolinones in products that just rinse on and rinse off and give people pretty remarkable contact dermatitis from it.

So, did the final product need to be diluted 20 and 30 and 40-fold? I don't know. I'm not sure that's the case but there is ample opportunity to do HRIPT on the neat amphocarboxylates that they have, and just dilute them down to something near maximum.

DR. ROSS: So, we have the maximum rinse off product with this compound is -- let's see.

DR. DAVID COHEN: Twenty or?

DR. ROSS: I'm just looking at the updated tables.

DR. DAVID COHEN: Yeah, go to that table.

DR. TILTON: At almost ten percent?

DR. DAVID COHEN: Hold on.

DR. TILTON: At 9.9 percent.

DR. ROSS: That's what I had previously in my notes, 9.9 percent.

DR. DAVID COHEN: Disodium Cocoamphodiacetate is 20 percent.

DR. ROSS: Yeah, the lauro is 9.9. But I would comment that the propionate derivative of the first compound, the Cocoamphodiacetate -- so this is the Disodium Cocoamphodipropionate, has increased in concentration from 1.8 to 14.8. That's a big increase.

DR. DAVID COHEN: Which one, David?

DR. ROSS: That's the Disodium Cocoamphodipropionate; that's now gone up to 14.8. It was at 1.8 so it might've been a typo I suppose. But anyway, yes. With the lauro we've got 9.9 percent, getting back to the point, and we don't have HRIPT's anywhere near that concentration. David says that in his opinion the animal study is not going to cut it. Sam agrees. So, I think we're still deficient with that. Is that where we're going here?

DR. DAVID COHEN: Yeah.

DR. BERGFELD: David, could I ask a question? If your testing was at, what, 5.6 percent in the HRIPT, would you consider putting that as the highest concentration in a rinse off?

DR. DAVID COHEN: I want to make sure I understand the question. If I had HRIPT at 5 percent?

DR. BERGFELD: At 5. Yeah, that's where the HRIPT, that's where the testing was. I have here at 5.25, Sodium Lauro and the active concentration.

DR. DAVID COHEN: The shampoo contained 5.25 percent. The final concentration of Sodium Lauroamphoacetate was 0.16 percent.

DR. BERGFELD: 0.16 percent, yeah. Yeah, I have that. I mean, you could set the concentrations according to the human testing. I'm just asking the question.

DR. DAVID COHEN: Well, I'm not sure -- I think I understand what you're saying.

DR. BERGFELD: Well, we have a rinse off and what we're talking about is a residual active in it, and we have human testing on that. And then we have another note that it's used at higher concentrations in rinse offs. But your testing is only at 5.25, and then the act of 0.16 percent of that. I mean, you could set your safety on that number or you could ask for more data. I'm just asking the question.

DR. DAVID COHEN: No, no, no. I understand the logic string on that. The only question is, I have no evidence that the residual concentration after rinsing is 0.16 percent. Unless I don't remember something from the report, I don't think -- what?

DR. ROSS: That was the final test concentration.

DR. DAVID COHEN: Yeah, but it's not based on anything, is it?

DR. ROSS: No. No, I mean the prep concentration was, as you pointed out previously, 5.25. The final test concentration was 0.16 percent. So, I think that's where we're at. And as you point out we're up to 9.9 rinse off.

DR. BERGFELD: Basically 10 percent. Yeah.

DR. ROSS: Yeah.

DR. DAVID COHEN: Yeah.

DR. ROSS: I mean -- sorry, go ahead, Susan.

DR. TILTON: I mean, I was just going to ask, I mean, we've had conversations before about the guinea pig maximization tests, HRIPTs, and just being able to get -- our ability to request HRIPT data, especially at higher concentrations. I mean, how likely is it that this is something that we would be able to get? There are times where we've really had to rely on the animal data.

DR. ROSS: And Don's point would be you couldn't do this in Europe, right, when we have this discussion tomorrow.

DR. DAVID COHEN: Right.

DR. ROSS: We're not in Europe, obviously, but that will be a point that comes up and --

DR. DAVID COHEN: I'll go back and let's just see something. I'll go back before tomorrow but I still from, one, when I read this yesterday -- I don't know. We have guinea pig data and then we have human data that just doesn't seem to fulfil -- doesn't corroborate anything for me. I'll go back and look at it again for tomorrow.

DR. BERGFELD: We also have something called compounded or formulated to be non-irritating.

DR. ROSS: I think that's how this one would come out, Wilma, yeah.

DR. DAVID COHEN: Yeah, this one I think would come out as non-irritating, but the thing is we would never use it not to be non-sensitizing, because we tend to reserve non-sensitizing for botanicals.

DR. BERGFELD: Yeah.

DR. TILTON: And the irritation concerns were really ocular.

DR. DAVID COHEN: Right. I suppose if we had data on what the residual concentrations were after rinsing. I mean, why are these valuable clinical data, these 0.16 and 0.096?

DR. ROSS: I didn't see that there, and I think you --

DR. DAVID COHEN: I didn't see it either.

DR. ROSS: -- you're going to be hard pushed to get that data, I would think, because that's not straightforward to get, I think.

DR. DAVID COHEN: I think it's really important though. I might ask for it. It may not be practical to get it.

DR. ROSS: When I look at the other compounds, the other materials here, and their sensitization effects, I think we're okay on the major compound up to 32 percent. We're okay at two of the other major compounds at 10 percent. One of the propionates is only at five percent, but the big data gap is the lauro and everything else looks okay, to me anyway. Could you read across?

DR. DAVID COHEN: I knew you were going to bring that up.

DR. ROSS: I hate to even raise it.

DR. DAVID COHEN: I'm going to throw that back to you guys in the Read-Across Working Group, because I don't know if I know how we would be able to do that.

DR. ROSS: Yeah, I mean, read-across is endpoint specific, right? So, I don't think we've dealt with too many instances of reading across for sensitization, which is a complex endpoint.

DR. EISENMANN: And the mixtures will include the lauro.

DR. ROSS: Yeah, that's right, Carol. That's a good point. So, all of those other compounds that are cleared at 10 percent and 32 percent, from the old data, will include some lauro, but you're not sure how much, Carol, right? So that's the issue here.

DR. DAVID COHEN: What is the justification for a 32 times dilution? Is there data on that, Carol?

DR. EISENMANN: I don't know. But my guess is it's different companies have different policies in how much they dilute their -- I will discuss this with CIR SSC at our next meeting, why they picked dilution factors and how they picked them, and maybe we can get some more information for you. But I just know they always dilute -- and it might be what the test -- where they go get the material tested on how they dilute it. But I will make a note to add this as an agenda item for CIR SSC to see if we can get any more information.

DR. DAVIDE COHEN: Because you can take any contact sensitizer in a rinse off product that can cause contact dermatitis and dilute it down that you'll never get a positive HRIPT. It'll just never be positive.

DR. EISENMANN: I also know that they're more likely to do a confirmatory HRIPT on a product than like a straight out HRIPT on an ingredient, because this concern is also about human testing; whereas, the product you're actually going to be using. I think they try to emulate how the product is being used, is what they're trying to do. But I will have that discussion and see if I can get more information from our members.

DR. DAVID COHEN: Yeah, but doing an HRIPT with a diluted product is about as far from how a product is used that I can think of.

DR. EISENMANN: What are you recommending, David?

DR. DAVID COHEN: No, I'm just commenting on the remark that a 10- or 30-times dilution put on the back and multiply applied to the same site on the back is not at all like lathering your head up and rinsing it off on a daily basis. Ones under occlusion, one is not under occlusion. One will wind up in skinfolds without proper rinsing often. So the HRIPT is an experimental methodology trying to get as much data as possible.

One of the lauroamphoacetates is diluted ten times, the other one's diluted 32 times. So, it doesn't seem like there's a standardization there.

DR. EISENMANN: Well, that's why I said I think some companies go to use tests instead of an HRIPT. Give the product to so many people and they use it for four weeks.

DR. DAVID COHEN: Yeah, yeah. One was a shampoo; one was a facial cleanser. The facial cleanser was diluted ten-fold, and the shampoo was diluted 32-fold. Okay, I'll review the data again. So, right now we're insufficient on sensitization, but I'll look at it again. I think Don's presenting this tomorrow, and I can have the discussion tomorrow about it.

DR. ROSS: Just one last comment from me. The ocular concern, which I had last time, Susan sort of touched on this that went away. The updated concentrations are now between 1 and 1.5 percent max, were generally up to 3 percent okay in head(inaudible) and compounds. One of the major compounds looks okay in humans at 1.2 percent with a current max use of 1 percent. So, I was okay on the ocular use.

DR. DAVID COHEN: Yeah.

DR. BERGFELD: That could support the irritation on the cutaneous surface too.

DR. DAVID COHEN: I agree. I agree with that. Look, the issue to me is sensitization and I'm not -- I certainly understand all the points that are being made. I really do. It's just, you know, 30 years of seeing rinse off products cause contact dermatitis, I'm kind of concerned that we get as much data as we can.

DR. HELDRETH: I think our CIR Science and Support Committee, chair Dr. Enrico Gilberti, has something he would like to add.

DR. DAVID COHEN: Oh, great. You're on mute.

DR. GILBERTI: Can everybody hear me now?

DR. ROSS: Yeah, we can hear you.

DR. GILBERTI: All right. So, thank you and thank you for inviting me today. I'm kind of losing my voice here so we're going to kind of play it by ear here. So, in terms of, Dr. Cohen, your question about the allergy data. What many member companies will do is, as Carol indicated, when we're conducting an HRIPT would be considered a confirmatory type of study; and that type of study would be conducted if it was a rinse of product at a particular dilution. Typically, that is a one percent dilution because the fact that, that's how we would expect the product to be used by the consumer in a particular exposure where you're diluting the product.

So, when you're looking at different types of levels of ingredients, it depends on how that formula was actually formulated in the first place. What levels of that ingredient, which may be a dilution of itself. So you may have a particular ingredient that may contain this particular test article or act as a particular sub ingredient. And that ingredient then through a series of dilutions may end up to that 0.16 percent.

It was not done for a hazard identification; it was done for a confirmatory test. And the reality is, is that if you go backwards and if you're tying to set a max use level based on data that has been generated in a confirmatory test, you're not going to get it at the level that you're necessarily going to be using it in a finished product.

So, what does that mean? Let's say I'm using the ingredient at 10 percent in a rinse off product. That formulation contains that raw material at 10 percent, I'm diluting it by 1 percent on the patch; so it's 10 percent times 1 percent. That would be the confirmatory test.

If somebody else, a member company is using it at 20 percent, well that 20 percent formulation, depending upon the company, they may decide not to run a confirmatory test, so therefore even though they're using at 20 percent, they won't have the allergy data. So, it really depends on the company and whether or not a member company will conduct a confirmatory test.

So, understanding your concern that if we have a use level at 20 percent or a much higher level, you may not have a corresponding HRIPT on that particular ingredient because they are disconnected, they're not always linked. A company may be using a 10 percent, they'll do a confirmatory test. Another company may be using it at 20 percent, and they won't do a confirmatory allergy study.

So, unfortunately you don't always have that consistency in terms of how the confirmatory testing is going to be conducted on a finished product.

DR. DAVID COHEN: Yeah, no, no. I appreciate that. I certainly get it. I think some of the issues here are rinse off products are not applied diluted. Nobody takes shampoo and takes a teaspoon into ten gallons of water and submerges their head in that. They actually take neat material on a wet head, and sometimes not on a wet head. Some people go on a dry head first. They lather the material on for some period of time and then they rinse it off.

That's very different from diluting a product before use, which people do occasionally but rarely. They'll dilute retinoids in moisturizer before they put it on, or they'll mix products together, but these products are applied rather neat -- rather neat. And then they stay on for a variable period of time before they're rinsed. Rinsing and diluting are two different things.

DR. GILBERTI: Right. But in order to create the lather you need to add water. These products won't create lather without having the concurrent application of water, and that is the dilution that is taking place to generate the lather. The 1 percent is not looking at what the one percent residual that's remaining on the skin, it's anticipating the amount of dilution that would take place to generate that lather, and that would be the exposure -- intended exposure.

DR. DAVID COHEN: Yes. So, the question is, is there any science to that dilution?

DR. GILBERTI: So, the sci- -- we would have to go back into the literature to see where that 1 percent. We know that from industry standard, 1 percent is typically the dilution that is used for rinse off products, just as if it's 10 percent if it was a hair leave-on product, a hundred percent if it was a leave on.

So, these dilutions are used in industry. And I think what we'll find is that, and as Carol indicated, we can go back to our member companies to see through CIR SCC, what type of data, what you'll find is 1 percent is the industry standard for testing surfactant based or rinse off products.

DR. DAVID COHEN: Okay. No, no. That's fair. That really is very helpful. And I think Carol's point, your point, Susan's point are just the straight facts and are helpful in helping make this determination. I'm going to go back before tomorrow, and I'll look at it again.

DR. SAM COHEN: So, where are we as far as our recommendation then? Acceptable or requiring more?

DR. DAVID COHEN: Right now, we're putting as insufficient. Right now, we're insufficient. My intent is to review it. I'll hear what Don's group came across. I want to hear what his opinion is on that, and I'll let you guys know before -- or I'll let you guys jump in before I either second or not second. I think that this discussion is really good.

DR. HELDRETH: Priya, did you have a comment or question?

MS. FERGUSON: Yeah, I have two questions. First one is, did we land on keeping the Vriends studies or no? The PC-2020-926, I think, or including them in the report or are we not including them in the report?

DR. DAVID COHEN: What did you guys want to do with that?

DR. ROSS: This is from the cardiac data right, Priya?

MS. FERGUSON: Yeah.

DR. ROSS: Well, my impression of the discussion was that it went along the lines that it's not an INCI product but it's a related compound and it had low effects, and it wasn't dose related, and a new study with this compound came out with no cardiac effects and so it was not thought to be a concern. Somewhere along those lines anyway. If anyone else has other opinions, please, let's hear them.

DR. SAM COHEN: But I think we have to have a discussion in our Summary or in the Discussion, I'm not sure where, stating basically what you just said. That we have no concern based on the weight of the evidence and the more recent study.

DR. BERGFELD: I think that was well said during the working group.

DR. SAM COHEN: I agree, Wilma.

DR. ROSS: And, of course, it would be much stronger if we had absorption. Sorry, I'm going back to the point in there.

MS. FERGUSON: And my second question, I just wanted to know what specific discussion points you want to have in the Discussion.

DR. DAVID COHEN: Relating to that, Priya?

MS. FERGUSON: Just in general.

DR. DAVID COHEN: In general. But so much of that was covered in the Read-Across Working Group meeting. If there are any final points, Susan, David, Sam, that you wanted from the read -- because certainly none of the conversation we just had now needs to be heavily in the Discussion, other than perhaps that the concentrations on the skin, on a rinse off product, would be anticipated to be much lower than the concentration in the final product.

I mean, I think we've spent like 45 minutes on it. It probably deserves a line in the Discussion.

DR. BERGFELD: I think that the tox data needs to be clarified and they did it nicely in the working group in the end, so, to add that. The lack of cardiac abnormalities. And I think the second point was that the third ingredient, that is not an INCI ingredient, would be included, and the reason why it's a mixture and it's is contained in the C8-C18.

DR. ROSS: It's a related compound. Yeah.

DR. BERGFELD: Yeah.

MS. FERGUSON: All right. Thanks.

DR. TILTON: I'm okay with that data being included in the report. And then we also discussed, in the RAWG meeting, expanding that section in the report. This isn't related to the Discussion necessarily, but just to be --

DR. BERGFELD: The DART stuff?

DR. TILTON: Yes. Just to be transparent about those studies and then our conclusions of them. So, the fact that these aren't dose-dependent effects. And we do have that for the earlier study and if the PC- -- I can't remember the name of it --

DR. BERGFELD: But is that (inaudible)?

DR. TILTON: Yeah. I mean, if we have the description of what that is and so that's clear, that it's related, even if it's not specifically in the INCI dictionary ,I would be okay including that too.

DR. ROSS: It's got a catchy name, Susan, PC-2020-926, and so --

DR. TILTON: Easy to remember.

DR. ROSS: Yeah. I agree with your comments.

DR. BERGFELD: Okay.

DR. DAVID COHEN: Okay, so.

DR. BERGFELD: Moving on?

DR. DAVID COHEN: It's 11:00. We can move on to the second chemical. Should be done by midnight.

DR. ROSS: We'll speed up.

DR. SAM COHEN: Some of these will go quicker.

DR. DAVID COHEN: Right before the next meeting starts, we should be okay.

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DR. BELSITO: Yeah, so, the Fatty Amphocarboxylates, they were actually two different reports in this report. There was a whole Panel report, and there was a Read-Across Working Group document that also provided a lot of additional information.

We heard from the Read-Across Working Group yesterday about their issues with this. We also got some additional data from the Consortium where they believe that their amidoamine impurities in amphoacetates would not cross-react with the amidoamine in betaines. But if you look at that impurity, the reactive end of both of those amidoamines is really the same. They are double bond NH. And I thought they would, so I didn't buy their argument.

Based upon the data that we have in our report, as well as the data that the Read Across Working Group has in their report, we thought that we could go with safe in cosmetics as long as they're formulated to be non-sensitizing, which may be based on a QRA, which is the same conclusion we had for the Betaines.

DR. BERGFELD: Dr. Cohen, your comments?

DR. DAVID COHEN: I don't want to second it yet because I'd like to have a discussion. I didn't see that motion coming. So, Don, I get the -- I'm actually very interested. So your formulated to be non-sensitizing, you said, right?

DR. BELSITO: Yeah, that's what we did with the Betaines.

DR. DAVID COHEN: Right, but my impression was formulated to be non-sensitizing was something we tended to reserve for plants, right? And I understand -- I thought of the Betaines exactly the same way and brought it up yesterday in that regard. I felt that the HRIPT data wasn't anywhere near max use for wash-on/wash-off products. For the leave-on products we weren't even close. So, I had this sort of as an insufficiency on max use sensitization for the lauroamphodiacetate and lauroamphoacetate.

Is that conclusion -- I'm not trying to use accurate terminology -- but is it a copout saying formulate to be non-sensitizing?

DR. BELSITO: But I think regardless where we go with this, we going to have to do it because we don't know the level of the amidoamine impurity, right?

DR. DAVID COHEN: Yes.

DR. BELSITO: So, even if we get sensitization and irritation on one product at 4 percent or 10 percent, or whatever percent that clears that particular material that comes from that particular manufacturer, it doesn't across the board say that the amidoamine impurity in that specific material with be the same. So, I think if we cover ourselves with that caveat, which then covers the range, they have to show that the product is non-sensitizing.

DR. BERGFELD: Are you suggesting that go into the Discussion, that particular discussion point?

DR. BELSITO: This is the actual conclusion from the Betaine report, safe --

DR. BERGFELD: No, I meant in this report in the Discussion, regarding the sensitization that you discussed in the Discussion, if what you're worried about is the impurity.

DR. BELSITO: Well, of course, that would go in the Discussion.

DR. BERGFELD: Yeah. Okay.

DR. DAVID COHEN: So, yesterday we were having the conversation with PCPC as well, is that the HRIPT data that we got was for wash-off products and they were diluted anywhere between one and 32 times, which I think loosely can be interpreted as a dilution issue, but my comment is shampoo is not applied diluted. It is rinsed. It's not the same as putting something in a bathtub and diluting it.

But there are leave-on products that have very high concentrations close to the rinse-off concentrations. And we don't even have any senses to where this is a sensitizer. I get the contaminants in there, but do you feel comfortable? We have no real sense of what the sensitizing component of these chemical are with or without the amidoamine.

DR. BELSITO: Again, our conclusion would cover that, right?

DR. DAVID COHEN: Yeah, but, Don, formulated to be non-sensitizing. Then just walk me through this. Why ask for sensitization and irritation data on anything if we could conclude formulated to be non-sensitizing?

DR. BELSITO: Because most of the time we're looking at the sensitization potential of the material, rather than the sensitization potential of an ingredient that -- or not an ingredient -- a component --

DR. SNYDER: Impurity.

DR. BELSITO: -- residual in manufacturing.

DR. DAVID COHEN: So, you feel that you have enough data to suggest that the amphocarboxylates that are listed here, not their impurities, are not sensitizer?

DR. BELSITO: Is there any clinical data to support that? I mean, granted they're not part of any standard tray, but, you know.

DR. DAVID COHEN: That's the point, Don. They are rare reports of amphocarboxylates causing allergic contact dermatitis. We don't screen for them. And, we only have HRIPT data on maybe one-tenth or one-one hundredth with max use concentration. So we don't have any data even close to what it is.

And, I didn't have the sense of mind yesterday when we were having the conversation about justifying 30 times reduction of the wash-on/wash-off products for the fact that these products have leave-on products. There are like leave-on products at 4 percent. Why didn't we get a HRIPT on leave-on products that would have no reason to be diluted before they're used?

So, I completely get what you mentioned, but if you look at the leave-on concentrations for disodium coco -- you know -- for a lot of these, it's 5 percent for the disodium lauroamphodiacetate leave-on, 5.4 percent. And we have HRIPT data at .046, .27, nothing that we asked for.

DR. BELSITO: You proved my team's opinion, which is also my opinion. But I'll ask Curt and Paul and Allan what their thoughts are based upon this discussion so far.

DR. SNYDER: I still stay with our conclusion, and we talk about in the Discussion why we are basing the restriction regarding the non-sensitization, non-sensitizing. So, I stick with our original conclusion.

DR. RETTIE: I go along with Paul.

DR. DAVID COHEN: How many times have we used formulated to be non-sensitizing for a non-botanical product?

DR. SNYDER: But, again, I think we're going to discuss that and present a reasoning why. I don't think we should be pigeonholed just because we haven't done something before.

DR. BELSITO: But we have; we did in the Betaines.

DR. SNYDER: Betaines, you're right.

DR. BELSITO: Even if we got this data, wouldn't your conclusion be the same? The question I always ask myself is, when I'm asking for data is it going to change my conclusion. And if not, then it's, you know, silly to ask for the data. And in this case it's not going to change my conclusion.

DR. DAVID COHEN: Wait a second. So if you got disodium lauroamphodiacetate HIRPT data up to max use, and you saw sensitization at 1 or 2 percent, you'd clear the product not to be sensitizing?

DR. BELSITO: No, I would still say formulated to be non-sensitizing, and that product wouldn't clear.

DR. DAVID COHEN: I don't know if I'd clear the product. I don't know if I'd clear that product.

DR. BELSITO: I wouldn't clear the product. Again, it's not formulated to be non-sensitizing so it wouldn't clear.

DR. KLAASSEN: Another way of looking at this. I'll ask this to Allan and David. How about just analytically looking to see if we have this contaminant?

DR. BELSITO: Well, we do. That was the data we got from the Consortium. It's there, they're argument was it's not the same amidoamine as it is present in Betaines. But if you look at the reactive end of the molecule, it is. It would cross-react.

DR. RETTIE: Can I just say something about that? We discussed this in our group meeting yesterday and I wasn't exactly sure what we were talking about, but overnight it became clear. To just amplify on that, we got some structures for the amidoamine and amphoacetates and the amidoamine and CAPB useful.

After hydrolysis, which seems very likely, we'd end up with a primary amine at the end of each molecule. I was viewing that as the main reactive species. I'd ask David and Curt if they would agree with that. Because the amine, the primary amine, the free unhindered primary amine, I would expect it to be able to react with lysine and protein and we go down the track from there.

They're not identical as a 2-carbon spacer between the 2-nitrogen and the amphoacetates, 3-carbon spacer in CAPB. That small different may make a difference at the level of immunogenicity, because immunogenicity is its own beast, and I can't really comment on that. But just looking structurally and what I consider to be the reactive center here, after hydrolysis, I would have thought they would have cross-reacted to some extent.

DR. DAVID COHEN: I'm not sure I have any objection to that argument. But what you're doing is you're creating a conclusion based on a contaminant, when you don't even have the data on the actual ingredients that we're looking at. I mean,

it's a critically important component to the adjudication of this dossier for sure. But, we asked for sensitization data at max use for sodium lauroamphoacetate and disodium lauroamphodiacetate. We did not get that data, right?

And, I think we're using an unconventional conclusion. I understand why we're doing it. I'm not saying it's not legitimate. But I think if I saw sensitization data at level way below max use, I would have more concerns about issuing a safe as used. We would also probably lower the concentration.

DR. BELSITO: We're not issuing safe as used. We're issuing safe a used when formulated to be non-sensitizing.

DR. DAVID COHEN: I know.

DR. BELSITO: Bart, did you raise your hand?

DR. HELDRETH: Yeah, let me just interject a little bit about historically how the Panel has used this qualification. So, you're right, David, in some respect, in some instances when we're talking about a botanical or natural complex substance, we use safe when formulated to be non-sensitizing in those situation because we're worried about accumulative exposure of some component. And so, we use it in that way in those reports.

However, the Panel has also historically, numerous times, used safe when formulated to be non-sensitizing, which may be based on a QRA or other test methodology, when it goes with more discrete molecules or things that aren't necessarily botanicals, for a number of reasons.

One in part that we saw in MCI/MI, was we found that sensitization was very formulation dependent. Even at the same percentage in different formulations, the only way we could be sure that the consumer was protected was for the formulators to actually test the product or do a QRA on the final formulation to ensure that there wouldn't be induction or elicitation, so forth.

And, then, as Dr. Belsito mentioned, also, (inaudible), we also had to do that there, because we had a very similar situation of this where we had these mixtures and there's potential for a contaminant. And so, the only way to be sure that the consumer was protected was to even go beyond a percentage limitation, but to actually be testing it some way, a QRA or otherwise, each actual formulation.

DR. DAVID COHEN: That's very helpful. And I can't even a little argue with the formulated to be non-sensitizing for the contaminants, right, I can't. It's just, we asked for data on specific chemicals. We did not get that data, right, so I'm going to leave it to -- yeah?

DR. ROSS: Can I just ask a question of Don? When I look at the data here, Don, with respect to what I've got in my notes, it looks like the top five or six ingredients here we've got sensitization at more than max through HRIPTs. The only one we were lacking, I think, was the Lauro.

DR. DAVID COHEN: That's right.

DR. ROSS: And, so I think that's why we went that way. And if it's when formulated to be non-sensitizing, we know we have max concentrations for most of these products anyway, sensitization data for the max concentration of most of these products anyway, at least the most frequently used ones.

DR. DAVID COHEN: You feel we can read across on sensitization?

DR. ROSS: I'm not saying we read across on sensitization, that's a pretty complex endpoint. I'll get Allan's opinion, and Susan's opinion, and Curt's opinion on that. But, I think it's a tricky one. But, certainly, what my point is, that for most of these that we use most frequently, we already have the sensitization data.

DR. DAVID COHEN: It was the lauroamphoacetates that we had the IDA on.

DR. ROSS: Getting back to the chemistry, I'm just looking at the scheme here, I see Allan's point. I see the amine, Allan, and, yeah.

DR. RETTIE: I was just looking in the report and no one's brought up the fact that we list 5 percent amidoamine (audio skip) in one of the ingredients. Seems pretty high to me.

DR. ROSS: Yeah, there was some concern, you know, initially, where that was a concern for the cardiac effects, but that was discounted. So it's been in there and it's been around our discussions for a while.

Yeah, but getting back to non-sensitizing, I'm just not sure we would need it for most of the compounds. It doesn't necessarily mean we don't put it in, but.

DR. BELSITO: But, David, I mean it's possible that those compounds have low levels of the amidoamine impurity and that they would be sensitizing with higher levels, which is why -- I mean, it was the same thing with Cocamidopropyl Betaine. We had very good HRIPT data that was negative, but that doesn't mean all of it would be negative if there were more of the impurity.

So I think to cover -- and that would be in the Discussion -- to cover the potential for the impurity, it would need to be formulated to be non-sensitizing based on QRA or other methodologies.

DR. DAVID COHEN: You know that part of the argument (audio skip).

DR. ROSS: Yeah, that makes sense. It's just that we got, you know, all the most frequently used one we have it where they need to be, but not the Lauro. But I guess we didn't receive it, so.

DR. BERGFELD: Well, you have another option. You could go out as safe with the majority and unsafe or insufficient for the Lauro's group.

DR. BELSITO: Well, my motion remains the same, the entire group is safe as used.

DR. BERGFELD: It hasn't been seconded.

DR. BELSITO: Right.

DR. SNYDER: I'll second it.

DR. BERGFELD: Okay, it's been seconded. Okay.

DR. DAVID COHEN: I think it's fair to go to a vote for everybody on it.

DR. BERGFELD: Okay. Bart, do you want to call out the names? And we're going to be voting for the motion, I believe. The motion is to give a safe.

DR. BELSITO: As used when formulated to be non-sensitizing, based on QRA or other methodologies.

DR. BERGFELD: Okay. So Bart will call your names and he will record.

DR. HELDRETH: Correct. So, then, I know we've already heard it, but, Dr. Belsito?

DR. BELSITO: Yea.

DR. HELDRETH: And, Dr. Snyder?

DR. SNYDER: Yea.

DR. HELDRETH: Dr. Klaassen?

DR. KLAASSEN: Yes.

DR. HELDRETH: Dr. Rettie?

DR. RETTIE: Agreed.

DR. HELDRETH: Dr. David Cohen?

DR. DAVID COHEN: No.

DR. HELDRETH: Dr. Sam Cohen?

DR. SAM COHEN: Abstain.

DR. HELDRETH: Dr. Tilton?

DR. TILTON: I support.

DR. HELDRETH: Okay. And, Dr. Ross?

DR. ROSS: No.

DR. HELDRETH: And, then, Dr. Bergfeld?

DR. BERGFELD: No.

DR. HELDRETH: No. All right, so we have three against, one abstained. That means we have five for it. So that's five out of the nine.

DR. BERGFELD: Majority.

DR. HELDRETH: So that passes.

DR. BERGFELD: That passes. All right. Now, my understanding is the Discussion will contain all that has been discussed about the non-sensitizing portion. Anything else that would need to go into that? You need to talk about the Lauro?

DR. DAVID COHEN: Yeah, that's where our data needs were. And I think Don's group made very good arguments for the final conclusion. And I think our points were made. I suspect that it might go this way, but, yeah.

DR. BELSITO: I think the most important part of the Discussion is why we discounted the cardiac effects seen in the DART studies, because that really was hanging us up before.

DR. DAVID COHEN: Yeah.

DR. ROSS: Agreed, agreed.

DR. BERGFELD: All right, anything else to go in the Discussion, comments? All right, seeing none we're going to move on to the next ingredient, Alkonium Chlorides and Bromides, 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: Draft Final Report for Panel Review
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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	*International Cosmetic Ingredient Dictionary*
ECHA	European Chemicals Agency
ET_{50}	effective time of exposure to reduce tissue viability to 50%
EU	European Union
EPA	Environmental Protection Agency
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
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
ND	not determined
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NR	not reported
NOAEL	no-observed-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
QRA	quantitative risk assessment
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
RLD	Registration and Listing Data
SI	stimulation index
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

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 11 fatty amphocarboxylates (4 of which were previously reviewed by the Panel), which are reported to function as surfactants and hair-conditioning agents in cosmetic products. The Panel concluded that the 11 fatty amphocarboxylates are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing, based on a quantitative risk assessment (QRA) or other appropriate methodology.

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 FDA Voluntary Cosmetic Registration Program (VCRP). Four structurally-similar ingredients (i.e., Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate) have previously been reviewed by the Panel in a safety assessment that was published in 1990.[1] The 4 fatty amphocarboxylates reviewed were considered to be safe as used, in the present practices of use and concentration, as stated in that safety assessment. This conclusion was re-affirmed in a re-review published in 2008.[2] Accordingly, in that these ingredients would soon be considered for another re-review, it was deemed appropriate to include the 4 previously-reviewed ingredients in this safety assessment. Additionally, 6 other fatty amphocarboxylate ingredients are included in this grouping. Hence, all ingredients reviewed in this report are structurally similar as they are alkylamido alkylamines.

According to the *International Cosmetic Ingredient Dictionary* (*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 May 2026. 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.

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, these constituents are not provided for all studies included in this report. It should be noted that sodium glycolate (common constituent of ingredients reviewed in this report) has previously been reviewed by the Panel (assessment published in 1998), and it was concluded that this ingredient is safe for use in cosmetic products at concentrations $\leq$ 10%, at final formulation pH $\geq$ 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]

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).

The Panel recognizes that read-across is complex and should be done in a compound-specific and endpoint-specific manner, and decisions thereon should be made on a case-by-case basis; the Panel also recognizes that read-across is especially challenging and should be approached with extreme caution when dealing with poorly-defined mixtures. However, the Panel considered certain endpoint data from submitted specific-source chemicals, as defined, suitable to read-across to certain target ingredients in this report. Specifically, the term "amphoacetates C8-C18" was found to be synonymous with Disodium Cocoamphodiacetate (and thus, the data from studies reported as "amphoacetates C8-C18," are included herein under the name, Disodium Cocoamphodiacetate), and certain data for test materials that are cuts of "C12-14" and "C12" were considered to be valid read-across sources to the ingredient target, Sodium Lauroamphoacetate. Likewise, the resulting weight-of-evidence for these 2 ingredients was considered informative for the remaining ingredients in this report.

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 (Figure 1) is an amphoteric organic compound that generally conforms to the structure:

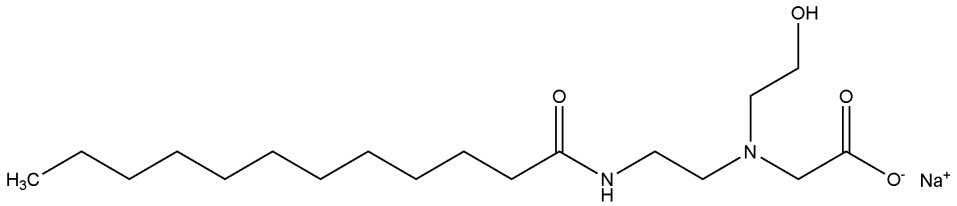


Figure 1. Sodium Lauroamphoacetate

The definitions and structures of all the fatty amphocarboxylates included in this review are provided in Table 1.[3]

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.[1,4,12-18] Additionally, the formula weights of the two read-across sources, "amphoacetates C12" and "amphoacetates C12-C14," are both reported to be 367 g/mol.[19]

Method of Manufacture

Fatty amphocarboxylates, such as Sodium Cocoamphoacetate, are synthesized by reacting fatty acid derivatives (e.g., coconut or cottonseed fatty acids; compositions of relevant fatty acids used in the manufacturing of these ingredients may be found in Table 3)[8,20] with hydroxyethyl ethylenediamine or aminoethylethanolamine (AEEA).[21] This reaction first forms a substituted imidazoline intermediate (such as 2-(2-undecyl-2-imidazolinyl)ethanol)), which is then hydrolyzed (ring-opened) to yield an amido-ethanolamine.[10,22,23] This intermediate undergoes carboxymethylation via reaction with sodium chloroacetate. When 1 equivalent of sodium chloroacetate is used, the major products are monoacetates (sodium amphoacetates), whereas reaction with 2 equivalents produces diacetates (disodium amphodiacetates). Amphopropionates are synthesized by reacting primary or ether amines with acrylic acid or its esters (e.g., methyl or ethyl acrylate); 1 mole of acrylate per mole of amine produces monoesters (monopropionates), while 2 moles produce diesters (dipropionates). The final structure and surfactant properties are influenced by factors such as pH, molar ratios, and the composition of the original fatty acids.

Disodium Cocoamphodiacetate

According to a supplier, Disodium Cocoamphodiacetate is prepared by reacting the fatty acid with amine to produce imidazoline.[24] 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, a key reagent in the synthesis of amphoteric surfactants, may be present as an impurity in ingredients such as coco- and lauroamphoacetates, amphopropionates, amphodiacetates, and amphodipropionates.[21] In trade name mixtures corresponding to Disodium Cocoamphodiacetate, Sodium Cocoamphoacetate, and Sodium Lauroamphoacetate, AEEA concentrations have been reported to range from 4.9 ± 0.2 to 1130 ± 50 ppm. Other residual byproducts of the synthesis process may include amidoamine, amido-functional ethanolamine, and glycolic acid (e.g., one trade name mixture corresponding to Sodium Lauroamphoacetate, was reported to contain up to 5% amidoamine).[7,8,10] It should be noted that according to industry, the "amidoamines" found as impurities in amphoacetates are amido hydroxyethyl ethylenediamines, and not amidopropyl dimethylamines.[23]

The type of amine, the alkylating agents used, and the source of fatty acids (e.g, coconut oil, hydrogenated coconut oil, or pure lauric acid) all influence the final composition and performance of the ingredients in this report.[22] These variables affect the balance of monoacetate, diacetate and quaternized species, which in turn impact key performance characteristics such as surface activity and foaming behavior. As a result, commercial amphoacetate surfactants typically consist of a mixture of structurally diverse components, arising from differences in esterification and quaternization, with their proportions determined by reaction stoichiometry and raw material selection.

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

The compositions of the majority 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.[7,9,25-28] The compositions, per those datasheets, can be found in Table 4. The majority of these ingredients consist of aqueous mixtures containing 30 - 60% of the ingredients in question.

Disodium Lauroamphodiacetate

According to a supplier, Disodium Lauroamphodiacetate is sold as an aqueous blend containing 20 – 50% active ingredient.[29] This blend includes sodium chloride, water, and sodium glycolate. The alkyl chain profile is as follows: C12 (66 – 78%), C14 (22 – 30%), C10 (< 3%), and C16 (< 3%).

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.[30] 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 Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[31] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

According to RLD obtained from the FDA in 2025, Disodium Cocoamphodiacetate is reported to have the highest frequency of use (it is reported to be used in 3010 formulations; Table 5.[32,33] The results of the concentration of use survey conducted by Council in 2025 indicate that Sodium Cocoamphoacetate has the highest maximum concentration of use in leave-on products (it is used at up to 3% in leave-on (not spray) face and neck and body and hand products) and Disodium

Cocoamphodipropionate has the highest maximum concentration of use overall, in rinse-off products (it is used at up to 14.8% in rinse-off non-coloring shampoos).[34] It should be noted that no frequency of use or concentration of use were reported for Sodium Cottonseedamphoacetate.

Several of these ingredients are reported to be used in products that are applied near the eye; for example, Sodium Cocoamphoacetate is used at 1.5% in eyebrow pencils. In addition, these ingredients are reported to be used in products that may result in mucous membrane exposure (e.g., Sodium Lauroamphoacetate is reported to be used in bath soaps and body washes at 5.5%) and in baby products (e.g., Sodium Lauroamphoacetate is reported to be used in baby shampoos at 0.8%).

Additionally, some of these ingredients are used in products that may be incidentally inhaled (e.g., Sodium Cocoamphoacetate is used in cologne and toilet water; concentration not stated). 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. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

It is possible that some products containing fatty amphocarboxylates may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined therein, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. None of the reported product categories for these ingredients as listed in the RLD include a designation using airbrush application, so it is possible that these ingredients are used with airbrush delivery systems, but not reported as such. Additionally, the concentration of use surveys are conducted based on product categories as stated in the RLD, but airbrush use was not reported in response to the survey. No consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with airbrush technology, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. If these ingredients were to be used in airbrush formulations, the data are insufficient to evaluate the exposure resulting from cosmetics applied in such a manner.

The ingredients reviewed in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[35]

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.[4,36] 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%.[37]

TOXICOKINETIC STUDIES

Based on their amphiphilic structure, high water solubility, and moderate lipophilicity, fatty amphocarboxylates are expected to be systemically absorbed to some extent via the dermal route.[38] However, their dermal absorption potential is likely limited due to the presence of charged functional groups (e.g., as sodium salts or zwitterionic forms), which significantly reduce skin permeability.

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 6. 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).[39] 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 7.

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).[4,40] No maternal toxicity was observed in this assay (maternal NOAEL = 1000 mg/kg bw/d). Severe cardiac abnormalities were observed in some of the 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.] The NOAEL for developmental and reproductive toxicity in the F0 and F1 generation was determined to be ≥ 1000 mg/kg bw/d in an assay in which Wistar Han rats (10 – 25/sex/group) were treated with up to 1000 mg/kg bw/d Disodium Cocoamphodiacetate (in water; gavage administration).[41] In this assay, F0 males were treated for a minimum of 11 wk (prior to and during mating) and F0 females were treated for a minimum of 16 wk (covering pre-mating, pregnancy, and lactation). A fetal and maternal NOAEL of 75 mg/kg bw/d was determined in a developmental and reproductive toxicity assay in which female New Zealand White rabbits (22/group) were treated with up to 350 mg/kg bw/d Disodium Cocoamphodiacetate (in water, gavage administration on GD 7 - 28). Adverse effects in this assay at higher doses included increased mortality, body weight loss, and increased post-implantation loss.[42]

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).[4,40] 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. No treatment-related, dose-dependent effects were observed in a dose range-finding assay in which female Wistar Han rats (6/group) were treated with up to 1000 mg/kg bw/d

amphoacetates C12 – C14 (used as read-across for Sodium Lauroamphoacetate; in water, gavage treatment on GD 6 – 20). A maternal and developmental NOAEL of 1000 mg/kg bw/d was established in an assay in which female Wistar Han rats (22/group) were given amphoacetates C12 – C14 (used as read-across for Sodium Lauroamphodiacetate), in water, via gavage, on GD 6 – 20 at doses of up to 1000 mg/kg bw/d.

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 8.

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.[43] 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.[44] 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%)[45] 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 9.

In an in vitro study, Sodium Cocoamphopropionate (40% a.i.; tested neat) was determined to be non-irritating in a reconstructed human epidermis assay.[39] 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).[46,47] Test substances (Disodium Cocoampho-diacetate (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.[4,36,48,49] Erythema and scaling was observed in a 48-h occlusive patch test performed in 12 subjects using Sodium Cocoamphoacetate (10%) in citrate buffer.[50] 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.[36] No irritation was observed in a 4-wk use assay performed in 32 subjects using a facial cleanser containing 2.7% Sodium Lauroamphoacetate.[51]

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% (results considered inconclusive by study authors as surfactants have clear irritating effects that may lead to false positives). 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. Similarly, no irritation or sensitization were observed in HRIPTs (n = 51 – 216) performed using products containing ingredients reviewed in this report (Disodium Lauroamphodiacetate (tested at 0.02 and 0.046%), Sodium Cocoamphoacetate (tested and 0.028 and 0.096%), and Sodium Lauroamphoacetate (tested at 0.044 – 0.27%)).[52-58] In addition, no irritation or sensitization was observed in an HRIPT using 99 subjects tested with Sodium Lauroamphoacetate (0.15% solids; tested at 0.5%).[4]

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] Test sites were exposed to ultraviolet A light (4.0 J/cm^2 for 22 – 25 sec) within 10 min of patch removal, with 13 subjects also receiving additional ultraviolet B exposure (2 – 5 mJ/cm^2 for 2 – 5 min).

OCULAR IRRITATION STUDIES

Several ocular irritation assays were performed using Disodium Cocoamphodiacetate, Disodium Cocoampho-dipropionate, 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 10.

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 a prediction of moderate irritation.[36,59] 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.[59] Severe irritation was noted in an EpiOcular™ assay evaluating the ocular irritation potential of 50% Disodium Cocoamphodiacetate.[60] Severe ocular irritation was also observed in a hen's egg test-chorioallantoic membrane (HET-CAM) assay using 40% Sodium Lauroamphoacetate.[61]

In ocular irritation studies performed in rabbits according to OECD TG 405, Disodium Cocoamphodiacetate was non-irritating when tested at concentrations up to 5%, Sodium Cocoamphoacetate was non-irritating at 1.9%, and slightly irritating at 3.2%, and Sodium Lauroamphoacetate was non-irritating at up to 3.25% and slightly to mildly irritating at 5%.[62] In several additional 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 assays performed in New Zealand White rabbits (n = 3 - 6).[4] 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 used a micellar water cleanser containing Disodium Cocoamphodiacetate (0.4 and 1.2%) once per day for 21 d.[63]

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).[64] 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.[65] 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).[66] 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 the eye makeup remover formulation elicited a response in the control subjects.

Sodium Cocoamphopropionate

Four individuals reported hand and forearm dermatitis following use of a skin protection cream containing Sodium Cocoamphopropionate.[67] 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.[21] 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.[68] 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.[69] 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 RLD obtained from the FDA in 2025, Disodium Cocoamphodiacetate is reported to have the highest frequency of use (it is reported to be used in 3010 formulations. The results of the concentration of use survey conducted by

Council in 2025 indicate that Sodium Cocoamphoacetate has the highest concentration of use in leave on products (it is used in non-spray leave-on face and neck and body and hand products at up to 3%).

Based on their amphiphilic structure, high water solubility, and moderate lipophilicity, fatty amphocarboxylates are expected to be systemically absorbed to some extent via the dermal route. However, their dermal absorption potential is likely limited due to the presence of charged functional groups, which significantly reduce skin permeability

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). A 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 a few fetuses of all treated test groups (not including control group) in a non-dose-dependent manner. 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). 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). The NOAEL for developmental and reproductive toxicity in the F0 and F1 generation was determined to be ≥ 1000 mg/kg bw/d in an assay in which Wistar Han rats were treated with Disodium Cocoamphodiacetate (in water; gavage administration). A fetal and maternal NOAEL of 75 mg/kg bw/d was determined in a developmental and reproductive toxicity assay in which female New Zealand White rabbits (22/group) were treated with up to 350 mg/kg bw/d Disodium Cocoamphodiacetate (in water, gavage administration on GD 7 - 28). 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 (treatment on GD 6 – 20). No treatment-related, dose-dependent effects were observed in a dose range-finding assay in which female Wistar Han rats (6/group) were treated with up to 1000 mg/kg bw/d amphoacetates C12 – C14 (used as read-across for Sodium Lauroamphoacetate; in water, gavage treatment on GD 6 – 20). A maternal and developmental NOAEL of 1000 mg/kg bw/d was established in an assay in which female Wistar Han rats (22/group) were given amphoacetates C12 – C14, in water, via gavage, on GD 6 – 20.

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 Cocoampho-diacetate, 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 irritation was observed in a 4-wk use assay performed in 32 subjects using a facial cleanser containing 2.7% Sodium Lauroamphoacetate.

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% (results considered inconclusive by study authors as surfactants have clear irritating effects that may lead to false positives). 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)). Similarly, no irritation or sensitization were observed in HRIPTs (n = 51 – 216) performed using products containing the ingredients reviewed in this report (Disodium Lauroamphodiacetate (tested at 0.046%), Sodium Cocoamphoacetate (tested and 0.028 and 0.096%), and Sodium Lauroamphoacetate (tested at 0.044 and 0.16%). 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 a prediction of 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 EpiOcular™ assay evaluating the ocular irritation potential of 50% Disodium Cocoamphodiacetate. Severe ocular irritation was also observed in a HET-CAM assay using 40% Sodium Lauroamphoacetate. In ocular irritation studies conducted in rabbits, Disodium Cocoamphodiacetate was non-irritating at concentrations up to 5%, Sodium Cocoamphoacetate was non-irritating at 1.9% and slightly irritating at 3.2%, and Sodium Lauroamphoacetate was non-irritating up to 3.2% and showed slight to mild irritation at 5%. In additional rabbit studies, Sodium Lauroamphoacetate (10 – 50% solids; water and sodium chloride; tested undiluted) was not considered an ocular irritant. However, in a different study Sodium Lauroamphoacetate (50% solids; water and sodium chloride; tested undiluted) was classified as a Category 2 ocular irritant under CLP criteria. In human studies (n = 10), no ocular irritation was observed following once-daily use for 21 days of a micellar water cleanser containing Disodium Cocoamphodiacetate (0.4 and 1.2%).

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, Sodium Cocoamphoacetate, Sodium Cocoamphopropionate, Sodium Lauroamphoacetate, all at 1 - 10%), performed in these individuals yielded positive results.

DISCUSSION

In 2021, Sodium Lauroamphoacetate was included on the Priority List due to high frequency of use. Four structurally-similar ingredients (i.e., Disodium Cocoamphodiacetate, Disodium Cocoamphodipropionate, Sodium Cocoamphoacetate, and Sodium Cocoamphopropionate) have previously been reviewed by the Panel in a safety assessment that was published in 1990. The 4 fatty amphocarboxylates reviewed were considered to be safe as used, in the present practices of use and

concentration, as stated in that safety assessment. This conclusion was re-affirmed in a re-review published in 2008. 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, along with 6 other previously un-reviewed related fatty amphocarboxylates. Therefore, this assessment reviews the safety of 11 fatty amphocarboxylates as used in cosmetic formulations, in accordance with the product categories and concentrations of use identified in the Use section and Use table. The Panel concluded that these ingredients are safe as used in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-sensitizing, which may be based on a QRA or other appropriate methodology.

The Panel initially expressed concern regarding the cardiac findings reported in a developmental and reproductive toxicity study with Disodium Cocoamphodiacetate. However, this concern was mitigated by the weight of the evidence, including in part the lack of a dose response and negative results in subsequent studies.

The Panel also noted the lack of dermal absorption data. It was determined that dermal absorption data were not required for the evaluation of these ingredients, given the absence of systemic toxicity endpoints of concern.

The Panel discussed the potential presence of residual amine impurities. These impurities are of toxicological concern because they may contribute to dermal sensitization and could act as precursors for *N*-nitrosamine formation under nitrosating conditions. To mitigate these risks, the Panel emphasized that these ingredients should not be used in cosmetic formulations containing *N*-nitrosating agents.

The Panel concluded that skin sensitization is not a concern with the use of these ingredients as currently used in cosmetic products. This applies when a QRA (or other appropriate methodology) demonstrates that the concentration, product type, and product usage will not result in exposures capable of inducing sensitization.

The Panel discussed the issue of incidental inhalation exposure resulting from these fatty amphocarboxylates (e.g., Sodium Cocoamphoacetate is used in cologne and toilet waters (concentration not stated)). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded that if these ingredients are used in airbrush formulations, the data are insufficient to support safe use when applied with such delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 11 fatty amphocarboxylates are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing, based on a quantitative risk assessment (QRA), or other appropriate methodology:

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

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

TABLES

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

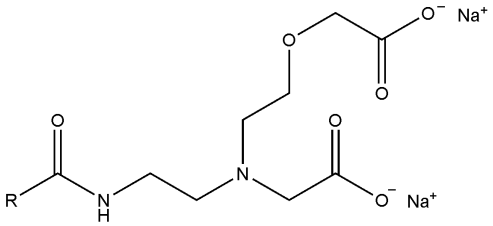
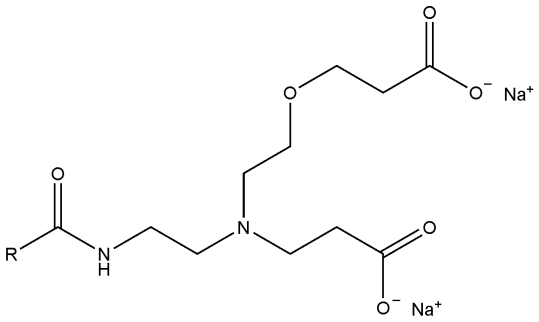
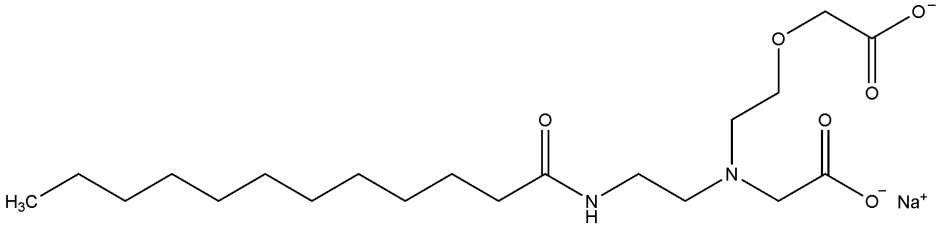
Ingredient	Definition	Function
Disodium Cocoamphodiacetate [CAS: 68650-39-5]	Disodium Cocoamphodiacetate is the amphoteric organic compound that conforms generally to the structure:  where RC(O)- represents the acyl groups derived from coconut oil.	Hair Conditioning Agents; Surfactants – Cleansing Agents;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

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

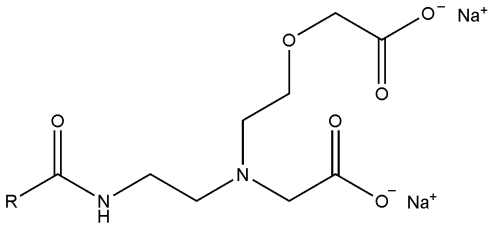
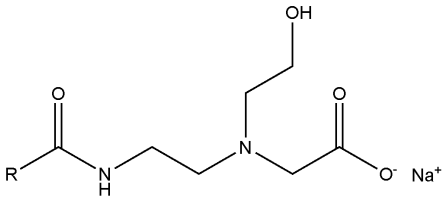
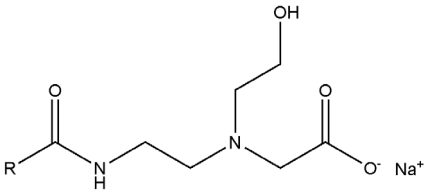
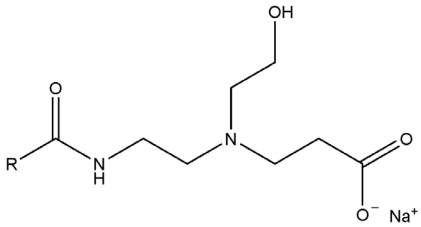
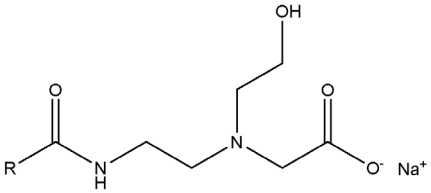
Ingredient	Definition	Function
Disodium Wheatgermamphodiacetate	Disodium Wheatgermamphodiacetate is the amphoteric organic compound that conforms to the structure:  where RC(O)- represents the acyl groups derived from wheat germ oil.	Hair Conditioning Agents Surfactants - Cleansing Agents Surfactants - Foam Boosters Surfactants - Hydrotropes
Sodium Arganamphoacetate	Sodium Arganamphoacetate is the amphoteric organic compound that conforms generally to the structure:  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 structure:  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 structure:  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 structure:  where RC(O)- represents the acyl groups derived from cottonseed oil.	Surfactants - Cleansing Agents

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

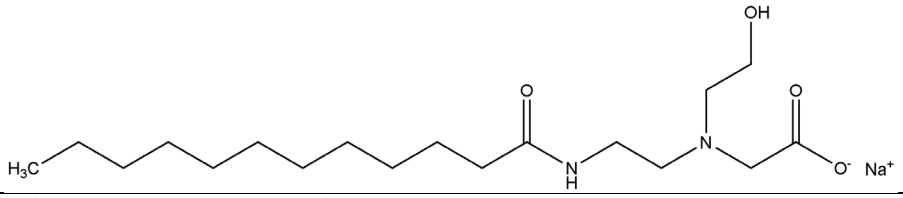
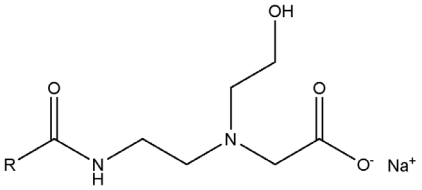
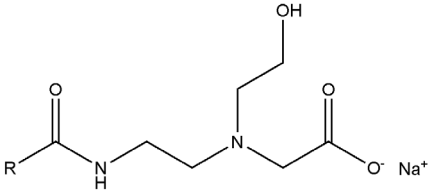
Ingredient	Definition	Function
Sodium Lauroamphoacetate [CAS: 68608-66-2; 156028-14-7; 66161-62-4]	Sodium Lauroamphoacetate is the amphoteric organic compound that conforms generally to the structure: 	Hair Conditioning Agents; Surfactants - Cleansing Agents; Surfactants - Foam Boosters
Sodium Olivamphoacetate	Sodium Olivamphoacetate is the amphoteric organic compound that conforms generally to the structure:  where RC(O)- represents the acyl groups derived from olive oil.	Hair Conditioning Agents Surfactants - Cleansing Agents Surfactants - Foam Boosters
Sodium Sweetalmondamphoacetate	Sodium Sweetalmondamphoacetate is the amphoteric organic compound that conforms generally to the structure:  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)	12
Specific Gravity (@ 25ºC)	1.17	13
Melting Point (ºC)	298.94 (C8 chain; est.) - 349.84 (C18 chain; est.)	14
log K_{ow}	-5.67 (C8 chain; est.) - -0.75 (C18 chain; est.)	14
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)	12
Specific Gravity (@ 25ºC)	1.05	15
Vapor Pressure (mmHg @ 25ºC)	0.0000225	15,16
Boiling Point (ºC)	≥ 100; ≤ 101	15,16

Table 2. Chemical properties

Property	Value	Reference
log K_{ow}	-7.57	15,16
Water Solubility	soluble	1
Alcohol Solubility	soluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Disodium Lauroamphodiacetate		
Physical Form	liquid	17
Formula Weight (g/mol)	446.5	17
log K_{ow}	-3.70 (est.)	14
Melting Point (ºC)	320.63 (est. MPBPVP v1.43)	14
Vapor Pressure (mmHg @ 25ºC)	1.12×10^{-17} (est. Modified Grain method)	14
Water Solubility (mg/l @ 25ºC)	111,100 (WSKOW v1.42)	14
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	18
Color	clear – light amber	1
Odor	faintly fruity	1
Formula Weight (g/mol)	310.37 (C8 chain) – 450.64 (C18 chain)	12
Melting Point (ºC)	297.88 (C8 chain; est.) – 349.84 (C18 chain; est.)	14
log K_{ow}	-3.58 (C8 chain; est.) - 1.33 (C18 chain; est.)	14
Water Solubility	soluble	1
Alcohol Solubility	insoluble	1
Nonpolar Organic Solvent Solubility	insoluble	1
Sodium Cocoamphopropionate		
Physical Form	liquid	1
Color	light amber	1
Odor	faintly fruity	1
Formula Weight (g/mol)	324.40 (C8 chain) – 464.67 (C18 chain)	12
Melting Point (ºC)	303.30 (C8 chain; est.) - 349.84 (C18 chain; est.)	12
log K_{ow}	-3.09 (C8 chain; est.) - 1.82 (C18 chain; est.)	12
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	12
log K_{ow}	-1.62 (C12 chain; est. WSKOW v1.42)	70
Water Solubility (mg/l @ 20ºC)	5810 (est. WSKOW v1.42)	70
Water Solubility (g/l @ 20ºC)	1000	4
Specific Gravity (@ 20ºC)	1.09	4
Vapor Pressure (mmHg @ 20ºC)	< 0.000011	4
Melting Point (ºC)	40	4

ND = not determined

Table 3. Fatty chain length distributions (%)[8,20]

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. Reported ingredient and read-across source compositions

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	26,28
Disodium Cocoamphodiacetate	type of substance: monoacetate form (contains approximately 95% monoacetates and 5% diacetates); diacetate form (contains approximately 40% monoacetates and 60% diacetates) compositional information (as manufactured, w/w): water: 47 – 64% total solids: 36 – 53% total alkylamphoacetate derivatives: 27 – 43% sodium chloride: 0 – 15% sodium glycolate: 0 – 6% amido hydroxyethyl ethylenediamines: 0 – 3% sodium chloroacetate: 0 – 600 ppm 2-(2-aminoethylamino)ethanol: 0 – 6 ppm compositional information (solvent-free condition, w/w): total alkylamphoacetate derivatives: ≥ 78% **Cn / mono / di / total** C8: 0 – 11% / 0 – 2% / 0 – 11% C10: 0.1 – 10% / 0 – 2% / 0 – 11% C12: 16 – 56% / 0 – 36% / 42 – 64% C14: 5 – 20% / 0 – 15% / 6 – 26% C16: 1 – 22% / 0 – 8% / 4 – 22% C18: 0.1 – 16% / 0 – 7% / 0.1 – 18% C18:1 and/or C18:2: 0 – 9% / 0 – 12% / 0 – 20% sodium chloride: 0 – 26% sodium glycolate: 0 – 12% amido hydroxyethyl ethylenediamines: 0 – 6% sodium chloroacetate: 0 – 1500 ppm 2-(2-aminoethylamino)ethanol: 0 – 14 ppm	19
Disodium Cocoamphodipropionate	30 - 40% Disodium Cocoamphodipropionate, 60 - 70% water, < 0.1% other components (not specified)	25
Disodium Lauroamphodiacetate	15 - 40% Sodium Lauroamphoacetate (remaining components not stated)	71
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
amphoacetates C12	type of substance: monoacetate form only (contains approximately 75 – 100% monoacetate and 0 – 25% diacetates)	19

<table>
<tr><th>Ingredient</th><th>Composition</th><th>Reference</th></tr>
<tr><td></td><td>compositional information (as manufactured, w/w):
water: 60 – 70%
total solids: 30 – 40%
total alkylamphoacetate derivatives: 23 – 31%
sodium chloride: 5 – 8%
sodium glycolate: 0.5 – 4%
amido hydroxyethyl ethylenediamines: 0 – 0.3%
sodium chloroacetate: 0 – 500 ppm
2-(2-aminoethylamino)ethanol: 0 – 4 ppm

compositional information (solvent-free condition, w/w):
total alkylamphoacetate derivatives: 76 – 80%
<table><tr><th>Cn</th><th>mono</th><th>di</th><th>total</th></tr><tr><td>C12</td><td>61 – 93%</td><td>0.1 – 21%</td><td>80 – 99.9%</td></tr><tr><td>unknown</td><td>-</td><td>-</td><td>0.1 – 20%</td></tr></table>sodium chloride: 16 – 20%
sodium glycolate: 4 – 8%
amido hydroxyethyl ethylenediamines: 0 – 0.5%
sodium chloroacetate: 0 – 9000 ppm
2-(2-aminoethylamino)ethanol: 0 – 10 ppm</td><td></td></tr>
<tr><td>amphoacetates C12 – 14</td><td>type of substance: diacetate form only (contains approximately 40 – 45% monoacetate and 55 – 60% diacetates)

compositional information (as manufactured, w/w):
water: 50 – 51%
total solids: 49 -50%
total alkylamphoacetate derivatives: ≥ 39%
sodium chloride: 0 – 10%
sodium glycolate: 2 – 4%
amido hydroxyethyl ethylenediamines: 0 – 2%
sodium chloroacetate: 0 – 65 ppm
2-(2-aminoethylamino)ethanol: 0 – 5 ppm

compositional information (solvent-free condition, w/w):
total alkylamphoacetate derivatives: ≥ 78%
<table><tr><th>Cn</th><th>mono</th><th>di</th><th>total</th></tr><tr><td>C8</td><td>ND</td><td>ND</td><td>ND</td></tr><tr><td>C10</td><td>≤ 2%</td><td>≤ 2%</td><td>≤ 4%</td></tr><tr><td>C12</td><td>26 – 37%</td><td>36 – 49%</td><td>67 – 80%</td></tr><tr><td>C14</td><td>7 – 16%</td><td>10 – 20%</td><td>20 – 32%</td></tr><tr><td>C16</td><td>≤ 2%</td><td>≤ 2%</td><td>≤ 4%</td></tr><tr><td>C18</td><td>ND</td><td>ND</td><td>ND</td></tr><tr><td>C18:1 and/or C18:2</td><td>ND</td><td>ND</td><td>ND</td></tr></table>sodium chloride: 0 – 20%
sodium glycolate: 6 – 11%
amido hydroxyethyl ethylenediamines: 0 – 6%
sodium chloroacetate: 0 – 130 ppm
2-(2-aminoethylamino)ethanol: 0 – 14 ppm</td><td>19</td></tr>
</table>

ND = not determined

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)	% (2025)	RLD (2025)	% (2025)	RLD (2025)	% (2025)
	Disodium Cocoamphodiacetate		Disodium Cocoamphodipropionate		Disodium Lauroamphodiacetate	
Totals*	**3010**	**0.001 – 6**	**185**	**2 – 14.8**	**231**	**0.088 – 4.8**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*562*	*0.1 – 2.8*	*21*	*NR*	*9*	*NR*
Rinse-Off	*2728*	*0.001 - 6*	*201*	*2 – 14.8*	*234*	*0.088 – 4.8*
Diluted for (Bath) Use	*89*	*NR*	***1***	*NR*	***2***	*NR*
Unknown	*28*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Baby Products	66	NR	1	NR	7	NR
Children's Makeup	NR	NR	NR	NR	NR	NR
Eye Area	56	0.45 – 1	3	NR	4	0.088
Incidental Ingestion	2	NR	NR	NR	NR	NR
Mucous Membrane	996	1.2 – 5.4	13	NR	116	NR
Incidental Inhalation-Spray	4; 692[a]; 144[b]	1.5 – 2.8[a]; 0.41 – 1.5[b]	14[a] 12[b]	NR	21[a]; 7[b]	NR
Incidental Inhalation-Airbrush	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	144[b]; 1[c]	0.41 – 1.5[b]; 0.45 – 2.8[c]	12[b]	NR	7[b]	NR
Dermal Contact	2422	0.45 – 6	51	NR	158	0.088 – 4.8
Deodorant (underarm)	1	NR	NR	NR	NR	NR
Hair - Non-Coloring	725	0.001 – 3.8	169	2 – 14.8	85	NR
Hair-Coloring	212	0.48	5	NR	1	NR
Nail	8	NR	NR	NR	NR	NR
Other Preparations (Unknown Exposure Type)	28	NR	NR	NR	NR	NR
as reported by product category						
Baby Products						
Baby Shampoos	17	NR	1	NR	3	NR
Baby Lotions/Oils/Powders/Creams	1	NR				
Baby Wipes	16	NR				
Other Baby Products	3 (l.o.); 29 (r.o.)	NR			4 (r.o.)	NR
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts	1	NR				
Bubble Baths	34	NR	1	NR	1	NR
Bath Capsules	2	NR				
Other Bath Preparations	52	NR			1	NR
Eye Makeup Preparations (not children's)						
Eyebrow Pencil						
Eye Lotion	3	NR				
Eye Makeup Remover	37	0.45 - 1	2	NR	4	0.088
False Eyelashes						
Mascara	2	NR				
Eyelash and Eyebrow Adhesives/Glues/Sealants						
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)						
Eyelash Cleansers	13	NR	1	NR		
Other Eye Makeup Preparations	1	NR				
Fragrance Preparations						
Cologne and Toilet Water	1	NR				

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)
Perfumes						
Other Fragrance Preparation	1	NR				
Hair Preparations (non-coloring)						
Hair Conditioners	1 (l.o.); 30 (r.o.)	0.1 (l.o.); 0.001 (r.o.)	29 (r.o.)	4 (r.o.)	6 (r.o.)	NR
Hair Sprays (aerosol fixatives)	2	NR				
Hair Straighteners	2	0.2				
Permanent Waves	1	0.2				
Rinses (non-coloring)	10	NR	2	NR		
Shampoos (non-coloring)	6 (l.o.); 604 (r.o.)	0.34 – 3.8 (r.o.)	1 (l.o.); 128 (r.o.)	2 – 14.8 (r.o.)	65 (r.o.)	NR
Tonics, Dressings, Other Hair Grooming Aids	22	0.41	3	NR	4	NR
Wave Sets	1	NR				
Other Hair Preparations	4 (l.o.); 25 (r.o.)	2.8 (r.o.)	1 (l.o.): 4 (r.o.)	NR	1 (l.o.); 6 (r.o.)	NR
Hair Coloring Preparations						
Hair Dyes and Colors (all types requiring caution statements and patch tests)	137	0.48	1	NR	1	NR
Hair Tints						
Hair Rinses (coloring)						
Hair Shampoos (coloring)	57 (r.o.)	NR	3 (r.o.)	NR		
Hair Lighteners with Color	1	NR				
Hair Bleaches			1	NR		
Other Hair Coloring Preparation	2 (l.o.); 15 (r.o.)	NR				
Makeup Preparations (not eye or children's)						
Blushers and Rouges (all types)						
Foundations	2 (traditional application)	NR				
Lipsticks and Lip Glosses	2	NR				
Makeup Bases	1 (traditional application)	NR				
Makeup Fixatives						
Other Makeup Preparations	7 (traditional application)	NR				
Manicuring Preparations						
Other Manicuring Preparations	8	NR				
Oral Hygiene Products						
Dentifrices						
Personal Cleanliness						
Bath Soaps and Body Washes	386	1.2 – 5.4	6	NR	97	NR
Deodorants (underarm)	1 (spray)	NR				
Douches	4	NR				
Feminine Deodorants	17 (r.o.)	NR			1 (r.o.)	NR
Disposable Wipes	276	NR	5	NR		
Other Personal Cleanliness Products	16 (l.o.); 190 (r.o.)	3 (r.o.)	1 (r.o.)	NR	16 (r.o.)	NR
Shaving Preparations						
Aftershave Lotions	7	NR				
Beard Softeners	1	NR				
Pre-shave Lotions (all types)						
Shaving Cream (aerosol, brushless, lather)	6	NR				
Shaving Soap (cakes, sticks, etc.)			1	NR		

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)	% (2025)	RLD (2025)	% (2025)	RLD (2025)	% (2025)
Other Shaving Preparations	6	NR	1	NR		
Skin Care Preparations						
Cleansing	573	0.77 – 6	16	NR	19	0.18 – 4.8
Face and Neck (excluding shaving preps)	73 (l.o.); 197 (r.o.)	0.45 – 2.8 (l.o.; not spray); 2.8 – 5.4 (r.o.; not spray)	7 (l.o.); 5 (r.o.)	NR	2 (l.o.); 10 (r.o.)	NR
Body and Hand (excluding shaving preps)	17 (l.o.); 324 (r.o.)	NR	1 (r.o.)	NR		
Foot Powders and Sprays	1	NR			1	NR
Moisturizing	50	0.48 (not spray)	2	NR		
Night	8	NR				
Paste Masks (mud packs)	11	NR				
Skin Fresheners	8	1.5	2	NR	1	NR
Other Skin Care Preparations	19 (l.o.); 48 (r.o.)	1.5			2 (r.o.)	NR
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Other Preparations (i.e., those that do not fit another category)	28		NR			
	Disodium Wheatgermaphodiacetate		**Sodium Arganamphoacetate**		**Sodium Cocoamphoacetate**	
Totals*	**169**	**0.38 – 0.41**	**12**	*NR*	**2246**	**0.3 – 5.8**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*NR*	*NR*	*12*	*NR*	*368*	*0.3 – 3*
Rinse-Off	*169*	*0.38 – 0.41*	*6*	*NR*	*2171*	*0.3 – 5.8*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*93*	*NR*
Unknown	*NR*	*NR*	*NR*	*NR*	*8*	*NR*
Exposure Type						
Baby Products	NR	NR	NR	NR	49	NR
Children's Makeup	NR	NR	NR	NR	NR	NR
Eye Area	NR	NR	NR	NR	11	1.5
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	3	NR	907	0.3 – 3.5
Incidental Inhalation-Spray	NR	NR	12[a]	NR	5; 466[a]; 125[b]	2.2[b]
Incidental Inhalation-Airbrush	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	125[b]; 3[c]	2.2[b]; 0.3 – 3[c]
Dermal Contact	NR	NR	15	NR	1781	0.3 – 3.6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	3	NR	654	1 – 5.8
Hair-Coloring	169	0.38 – 0.41	NR	NR	219	NR
Nail	NR	NR	NR	NR	NR	NR
Other Preparations (Unknown Exposure Type)	NR	NR	NR	NR	8	NR
as reported by product category						
Baby Products						
Baby Shampoos					22	NR
Baby Lotions/Oils/Powders/Creams					3	NR
Baby Wipes					5	NR
Other Baby Products					1 (l.o.); 1 (r.o.)	NR
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts					5	NR
Bubble Baths					67	NR

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)
Bath Capsules						
Other Bath Preparations					21	NR
Eye Makeup Preparations (not children's)						
Eyebrow Pencil					NR	1.5
Eye Lotion					2	NR
Eye Makeup Remover					3	NR
False Eyelashes						
Mascara						
Eyelash and Eyebrow Adhesives/Glues/Sealants						
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)						
Eyelash Cleansers					5	NR
Other Eye Makeup Preparations					1	NR
Fragrance Preparations						
Cologne and Toilet Water					4	NR
Perfumes						
Other Fragrance Preparation					1	NR
Hair Preparations (non-coloring)						
Hair Conditioners					19 (r.o.)	NR
Hair Sprays (aerosol fixatives)						
Hair Straighteners					1	3.1
Permanent Waves					18	3.1
Rinses (non-coloring)					4	1
Shampoos (non-coloring)			3 (r.o.)	NR	487 (r.o.)	1.7 – 5.8 (r.o.)
Tonics, Dressings, Other Hair Grooming Aids					52	NR
Wave Sets					1	NR
Other Hair Preparations					7 (l.o.); 43 (r.o.)	NR
Hair Coloring Preparations						
Hair Dyes and Colors (all types requiring caution statements and patch tests)	169	0.38			154	NR
Hair Tints					2	NR
Hair Rinses (coloring)					8 (r.o.)	NR
Hair Shampoos (coloring)					1 (l.o.); 51 (r.o.)	NR
Hair Lighteners with Color						
Hair Bleaches	NR	0.41				
Other Hair Coloring Preparation					2 (l.o.); 1 (r.o.)	NR
Makeup Preparations (not eye or children's)						
Blushers and Rouges (all types)					1	NR
Foundations					1 (traditional application)	NR
Lipsticks and Lip Glosses						
Makeup Bases						
Makeup Fixatives						
Other Makeup Preparations					1 (traditional application)	NR
Manicuring Preparations						
Other Manicuring Preparations						

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)
Oral Hygiene Products						
Dentifrices						
Personal Cleanliness						
Bath Soaps and Body Washes			3	NR	348	0.3 – 3.5
Deodorants (underarm)						
Douches					1	NR
Feminine Deodorants						
Disposable Wipes					12	NR
Other Personal Cleanliness Products					1 (l.o.); 447 (r.o.)	2.8 (r.o.)
Shaving Preparations						
Aftershave Lotions						
Beard Softeners					1	NR
Pre-shave Lotions (all types)					2	NR
Shaving Cream (aerosol, brushless, lather)					4	NR
Shaving Soap (cakes, sticks, etc.)						
Other Shaving Preparations					4	NR
Skin Care Preparations						
Cleansing					338	0.96 – 3.6
Face and Neck (excluding shaving preps)					48 (l.o.); 136 (r.o.)	0.3 – 3 (l.o.; not spray); 3.2 (r.o.; not spray)
Body and Hand (excluding shaving preps)					2 (l.o.); 39 (r.o.)	3 (l.o.; not spray); 0.3 – 2.1 (r.o.; not spray)
Foot Powders and Sprays						
Moisturizing			6	NR	205	NR
Night					2	NR
Paste Masks (mud packs)					3	NR
Skin Fresheners			6	NR	5	NR
Other Skin Care Preparations					10 (l.o.); 35 (r.o.)	2.2
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Other Preparations (i.e., those that do not fit another category)					8	NR

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)	% (2025)	RLD (2025)	% (2025)	RLD (2025)	% (2025)
	Sodium Cocoamphopropionate		Sodium Lauroamphoacetate		Sodium Olivamphoacetate	
Totals*	**50**	**0.1 – 4**	**1152**	**0.72 – 7.1**	**40**	
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*7*	*0.1*	*156*	*2.1*	*3*	*NR*
Rinse-Off	*37*	*4*	*1009*	*0.8 – 7.1*	*41*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*143*	*0.72 – 2.8*	*NR*	*NR*
Unknown	*NR*	*NR*	*4*	*NR*	*NR*	*NR*
Exposure Type						
Baby Products	*NR*	*NR*	52	0.8	3	NR
Children's Makeup	*NR*	*NR*	NR	NR	NR	NR
Eye Area	*NR*	*NR*	40	NR	NR	NR
Incidental Ingestion	*NR*	*NR*	1	NR	NR	NR
Mucous Membrane	1	NR	460	0.72 – 5.5	21	NR
Incidental Inhalation-Spray	19[a]; 6[b]	0.1[b]	9; 170[a]; 68[b]	2.1[b]	1; 4[a]; 1[b]	NR
Incidental Inhalation-Airbrush	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	6[b]	0.1[b]	68[b]; 1[c]	2.1[b]	1[b]	NR
Dermal Contact	14	NR	953	0.72 – 7.1	28	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	30	0.1 – 4	349	0.8 – 5.5	16	NR
Hair-Coloring	7	NR	6	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Other Preparations (Unknown Exposure Type)	NR	NR	4	NR	NR	NR
as reported by product category						
Baby Products						
Baby Shampoos			30	0.8	1	NR
Baby Lotions/Oils/Powders/Creams			1			
Baby Wipes						
Other Baby Products			21 (r.o.)	0.8 (r.o.)	2 (r.o.)	NR
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts			7	NR		
Bubble Baths			70	0.72		
Bath Capsules						
Other Bath Preparations			66	2.8		
Eye Makeup Preparations (not children's)						
Eyebrow Pencil						
Eye Lotion						
Eye Makeup Remover			9	NR		
False Eyelashes			1	NR		
Mascara			1	NR		
Eyelash and Eyebrow Adhesives/Glues/Sealants			2	NR		
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)			4	NR		
Eyelash Cleansers			20	NR		
Other Eye Makeup Preparations			3	NR		
Fragrance Preparations						
Cologne and Toilet Water						
Perfumes			1	NR	1	NR

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)
Other Fragrance Preparation			5	NR		
Hair Preparations (non-coloring)						
Hair Conditioners	6 (r.o.)	NR	2 (l.o.); 5 (r.o.)	NR		
Hair Sprays (aerosol fixatives)			3	NR		
Hair Straighteners			2	NR		
Permanent Waves	6	NR				
Rinses (non-coloring)	1	NR	3			
Shampoos (non-coloring)	6 (r.o.)	4 (r.o.)	9 (l.o.); 233 (r.o)	0.8 – 5.5 (r.o.)	13 (r.o.)	NR
Tonics, Dressings, Other Hair Grooming Aids	5	0.1	22	2.1	1	NR
Wave Sets			2	NR		
Other Hair Preparations	1 (l.o.); 5 (r.o.)	NR	7 (l.o.); 31 (r.o.)	NR	1 (r.o.)	NR
Hair Coloring Preparations						
Hair Dyes and Colors (all types requiring caution statements and patch tests)	4	NR				
Hair Tints	1	NR				
Hair Rinses (coloring)	1 (r.o.)	NR				
Hair Shampoos (coloring)			6 (r.o.)	NR		
Hair Lighteners with Color						
Hair Bleaches						
Other Hair Coloring Preparation	1 (r.o.)	NR				
Makeup Preparations (not eye or children's)						
Blushers and Rouges (all types)						
Foundations						
Lipsticks and Lip Glosses						
Makeup Bases						
Makeup Fixatives			1	NR		
Other Makeup Preparations			17 (traditional application)	NR		
Manicuring Preparations						
Other Manicuring Preparations						
Oral Hygiene Products						
Dentifrices			1	NR		
Personal Cleanliness						
Bath Soaps and Body Washes	1	NR	232	0.8 – 5.5	21	NR
Deodorants (underarm)						
Douches			2	NR		
Feminine Deodorants						
Disposable Wipes			6	NR		
Other Personal Cleanliness Products			76 (r.o.)	0.8 (r.o.)		
Shaving Preparations						
Aftershave Lotions			3	NR		
Beard Softeners			1	NR		
Pre-shave Lotions (all types)			5	NR		
Shaving Cream (aerosol, brushless, lather)			4	NR		
Shaving Soap (cakes, sticks, etc.)			2	NR		
Other Shaving Preparations			8	NR		
Skin Care Preparations						
Cleansing			213	0.96 – 7.1	1	NR

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)
Face and Neck (excluding shaving preps)			21 (l.o.); 59 (r.o.)	NR	1 (r.o.)	NR
Body and Hand (excluding shaving preps)	7 (r.o.)	NR	2 (l.o.); 15 (r.o.)	5.6 (r.o.)	1 (r.o.)	NR
Foot Powders and Sprays						
Moisturizing	1	NR	25	NR	1	NR
Night			1	NR		
Paste Masks (mud packs)			7	NR		
Skin Fresheners			6	NR		
Other Skin Care Preparations	5 (r.o.)	NR	7 (l.o.); 28 (r.o.)	NR		
Suntan Preparations						
Suntan Gels, Creams, and Liquids			5	NR		
Other Preparations (i.e., those that do not fit another category)			4	NR		
	Sodium Sweetalmondamphoacetate					
Totals*	**31**					
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*4*	*NR*				
Rinse-Off	*29*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*				
Unknown	*NR*	*NR*				
Exposure Type						
Baby Products	2	NR				
Children's Makeup	NR	NR				
Eye Area	NR	NR				
Incidental Ingestion	NR	NR				
Mucous Membrane	19	NR				
Incidental Inhalation-Spray	1; 8[a]	NR				
Incidental Inhalation-Airbrush	NR	NR				
Incidental Inhalation-Powder	NR	NR				
Dermal Contact	31	NR				
Deodorant (underarm)	NR	NR				
Hair - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Other Preparations (Unknown Exposure Type)	NR	NR				
as reported by product category						
Baby Products						
Baby Shampoos						
Baby Lotions/Oils/Powders/Creams						
Baby Wipes						
Other Baby Products	2 (r.o.)	NR				
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts						
Bubble Baths						
Bath Capsules						
Other Bath Preparations						
Eye Makeup Preparations (not children's)						
Eyebrow Pencil						

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)
Eye Lotion						
Eye Makeup Remover						
False Eyelashes						
Mascara						
Eyelash and Eyebrow Adhesives/Glues/Sealants						
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)						
Eyelash Cleansers						
Other Eye Makeup Preparations						
Fragrance Preparations						
Cologne and Toilet Water						
Perfumes	1	NR				
Other Fragrance Preparation						
Hair Preparations (non-coloring)						
Hair Conditioners						
Hair Sprays (aerosol fixatives)						
Hair Straighteners						
Permanent Waves						
Rinses (non-coloring)						
Shampoos (non-coloring)						
Tonics, Dressings, Other Hair Grooming Aids						
Wave Sets						
Other Hair Preparations						
Hair Coloring Preparations						
Hair Dyes and Colors (all types requiring caution statements and patch tests)						
Hair Tints						
Hair Rinses (coloring)						
Hair Shampoos (coloring)						
Hair Lighteners with Color						
Hair Bleaches						
Other Hair Coloring Preparation						
Makeup Preparations (not eye or children's)						
Blushers and Rouges (all types)						
Foundations						
Leg and Body Paints						
Makeup Bases						
Makeup Fixatives						
Other Makeup Preparations						
Manicuring Preparations						
Other Manicuring Preparations						
Oral Hygiene Products						
Dentifrices						
Personal Cleanliness						
Bath Soaps and Body Washes	14	NR				
Deodorants (underarm)						
Douches						
Feminine Deodorants	2 (r.o.)	NR				

Table 5. Frequency and concentration of use according to likely duration and exposure and by product category[32-34]

	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)	# of Uses RLD (2025)	Max Conc of Use % (2025)
Disposable Wipes						
Other Personal Cleanliness Products	3 (r.o.)	NR				
Shaving Preparations						
Aftershave Lotions						
Beard Softeners						
Pre-shave Lotions (all types)						
Shaving Cream (aerosol, brushless, lather)						
Shaving Soap (cakes, sticks, etc.)						
Other Shaving Preparations						
Skin Care Preparations						
Cleansing	5	NR				
Face and Neck (excluding shaving preps)	1 (r.o.)	NR				
Body and Hand (excluding shaving preps)	1 (r.o.)	NR				
Foot Powders and Sprays						
Moisturizing	3	NR				
Night						
Paste Masks (mud packs)						
Skin Fresheners						
Other Skin Care Preparations	1 (r.o.)	NR				
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Other Preparations (i.e., those that do not fit another category)						

NR – not reported
l.o. – leave-on; r.o. – rinse-off
*The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.
**Likely duration and exposure are derived from survey data 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] 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
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 6. Acute toxicity studies

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	39
ORAL						
Sodium Cocoamphopropionate (40% a.i.; water)	NR	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	39
Sodium Cocoamphopropionate (40% solids)	NR	Sprague-Dawley rats (5/sex/dose)	100%; 16 ml/kg	OECD TG 401; gavage; 14-d observation	LD_{50} > 16 ml/kg bw	39
Sodium Lauroamphoacetate (water and sodium chloride)	NR	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 a.i..	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 Co-operation and Development; TG = Test Guidelines

Table 7. Oral reproductive and developmental toxicity studies

Test Article	Vehicle	Animals/Group	Dose	Procedure	Results	Reference
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 (from 2 different litters); 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.	4,40
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.	4,40
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.	4,40

Table 7. Oral reproductive and developmental toxicity studies

Test Article	Vehicle	Animals/Group	Dose	Procedure	Results	Reference
Disodium Cocoamphodiacetate	Water	Wistar Han rats (F0: 25/sex /group; F1: 10 – 20/sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 443; gavage administration; F0 males were dosed daily for a minimum of 11 wk (prior to and during mating); F0 females treated for a minimum of 16 wk (covering pre-mating, pregnancy, and lactation, except during littering); pups exposed indirectly until weaning, after which selected F1 animals were dosed daily until necropsy; control animals treated with vehicle; parameters evaluated: mortality, clinical observation, body weight, food consumption, water consumption, reproductive data, hematology, clinical chemistry, thyroid hormone, urinalysis, estrous cyclicity, sperm parameters, and litter indices	In F0 animals, no adverse treatment-related effects were observed at 100 mg/kg bw/d. At 300 mg/kg bw/d, non-adverse, non-significant increases in T4 were noted in females. At 1000 mg/kg bw/d, non-adverse salivation, statistically significantly increased liver and kidney weights in both sexes, and a non-adverse, statistically significant decrease in urea in males were observed. All other parameters—including body weight, food consumption, hematology, coagulation, urinalysis, estrous cycle, sperm, gross pathology, and histopathology—were unaffected. Reproductive performance, including mating, fertility, pregnancy, implantation, and microscopic evaluation of reproductive organs, was unaffected. In F1 animals, at up to 1000 mg/kg bw/d, no treatment-related effects were observed. At 300 mg/kg bw/d, non-adverse abnormal breathing sounds were noted in both sexes and T4 levels were statistically significantly increased in females. At 1000 mg/kg bw/d, non-adverse salivation, abnormal breathing sounds, and statistically significantly increased liver and kidney weights in both sexes were observed, along with a non-adverse, statistically significant decrease in male body weight and body weight gain. All other parameters—including food consumption, estrous cycle, sperm analysis, hematology, coagulation, clinical chemistry, urinalysis, sexual maturation, anogenital distance, nipple retention, macroscopic and microscopic pathology—were unaffected. Post-weaning developmental parameters (vaginal patency, balanopreputial separation, first estrus) revealed no treatment-related effects. The NOAEL for F0 and F1 reproductive and developmental toxicity was ≥1000 mg/kg bw/d.	41
Disodium Cocoamphodiacetate	Water	New Zealand White rabbits (22 females/group)	0, 75, 175, or 350 mg/kg bw/d)	OECD TG 414; animals treated via gavage; treatment on GD 7 – 28; animals sacrificed on GD 29; control animals treated with vehicle; maternal examination parameters: mortality, clinical observation, body weight, food consumption, water consumption, post-mortem examination, ovaries and uterine content; fetuses examined for external, visceral, and skeletal variations; also evaluated were pregnancy rate, pre-implantation loss, post-implantation loss, live number of fetuses/litter, and litter % fetuses with abnormalities	The maternal NOAEL was determined to be 75 mg/kg bw/d. The test material showed no treatment-related effects at 75 mg/kg/d. At 175 mg/kg/d, reduced food intake, lower body weight gain, and occasional mortality were observed, while at 350 mg/kg/d, marked effects occurred including high mortality, reduced food consumption, and body weight loss. Clinical signs such as erected fur and softer feces were noted but were generally minor or incidental. No treatment-related gross pathological changes were detected. The number of corpora lutea and implantation sites, and pre-implantation loss was considered unaffected at doses up to 175 mg/kg bw/d. A non-statistically significant increase in post-implantation loss was observed at 175 mg/kg bw/d. At 350 mg/kg/d, similar findings occurred, including one case of total litter loss, but these data were not considered valid for drawing developmental toxicity conclusions due to insufficient surviving females. Up to 175 mg/kg/d, there were no treatment-related effects on fetal body weights, sex ratio, litter size, or external, skeletal, or visceral malformations; the few abnormalities observed were isolated and considered chance findings. At 350 mg/kg/d, although some findings were noted (e.g., one fused caudal vertebra), the group had too few pregnant females for valid evaluation. The NOAEL for fetuses was determined to be 75 mg/kg bw/d due to increased post-implantation loss at higher doses.	42

Table 7. Oral reproductive and developmental toxicity studies

Test Article	Vehicle	Animals/Group	Dose	Procedure	Results	Reference
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.	4,40
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.	4,40
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.	4,40
Amphoacetates C12 – C14 (read-across for Sodium Lauroamphoacetate)	Water	female Wistar Han rats (6/group)	0, 300, 600, or 1000 mg/kg bw/d	OECD TG 414; dose range-finding prenatal toxicity study; animals treated via gavage on GD 6 – 20; necropsy on GD 21; parameters evaluated: mortality, clinical observations, body weight, food consumption, liver weight, and reproductive indices (number of pregnant females, number of corpora lutea, implantation sites, resorptions, implantation loss), fetus evaluations	No treatment-related mortality or clinical signs of toxicity were observed. Maternal body weights in treated groups were comparable to controls; however, gravid uterine weight-corrected body weight gain was slightly reduced at 1000 mg/kg/d (compared to controls), liver weights were unaffected. Fetal evaluations showed no treatment-related effects on pregnancy outcomes, numbers of corpora lutea or implantation sites, resorptions, litter size, fetal sex ratio, or fetal weights. Compared to controls, post-implantation loss was higher at 300 mg/kg/d and pre-implantation loss was higher at 600 mg/kg/d, but no effects were observed at 1000 mg/kg/d, and no fetal malformations were detected.	40

Table 7. Oral reproductive and developmental toxicity studies

Test Article	Vehicle	Animals/Group	Dose	Procedure	Results	Reference
Amphoacetates C12 – C14 (read-across for Sodium Lauroamphoacetate)	Water	female Wistar Han rats (22/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 414; animals treated via gavage on GD 6 – 20; necropsy on GD 21; parameters evaluated: mortality, clinical observations, body weight, food consumption, thyroid hormones, organ weight (uterine and thyroid glands), reproductive indices (number of pregnant females, number of corpora lutea, implantation sites, resorptions, implantation loss), and fetus evaluations	No treatment-related mortality or clinical signs were observed, aside from increased salivation at 1000 mg/kg/d which was considered a physiological response. Body weights, food consumption, maternal thyroid hormone levels, thyroid weights, and histopathology were unaffected by treatment. Reproductive and developmental parameters, including numbers of corpora lutea and implantation sites, resorptions, pre- and post-implantation loss, litter size, fetal sex ratio, fetal weights, anogenital distance, and external, visceral, and skeletal malformations, were also unaffected. Regarding cardiovascular malformations, findings were limited to two fetuses in the 100 mg/kg/d group (including ventricular septal defects, transposition of the great vessels, and interrupted aortic arch) and were not considered treatment-related, as no such findings occurred at higher doses. Other fetal variations (e.g., supernumerary liver lobes, convoluted ureters, absent renal papilla, diverse skeletal variations) were observed without a dose relationship and considered unrelated to treatment. The maternal and developmental NOAELs were established at 1000 mg/kg bw/d.	19

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

Table 8. Genotoxicity studies[4]

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results
IN VITRO					
Gene Mutation					
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
Chromosomal Damage					
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 Co-operation and Development test guidelines

Table 9. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
IN VITRO						
Sodium Cocoamphopropionate (40% a.i.; water)	NR	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 %	39
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	39
Sodium Lauroamphoacetate (35% solids; water, sodium chloride, and sodium glycolate)	NR	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)	NR	Tested neat; 0.5 g	3 female New Zealand white rabbits	OECD TG 404; semi-occlusive dressing; single patch application for 4 h; evaluation 1, 24, 48, and 72 h after patch removal	Non-irritating; very slight erythema observed 24 h after patch removal, fully reversed within 72 h	4
Trade name mixture consisting of Sodium Lauroamphoacetate, sodium trideceth sulfate, isopropyl alcohol (2%), and water (67.9%) (concentration of Sodium Lauroamphoacetate and sodium trideceth sulfate combined: 30.1%)	NR	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)	46
Trade name mixture containing Sodium Lauroamphoacetate (36%) and water (64%)	NR	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)	47
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	48
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)	36
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)	36

Table 9. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
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.	49
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)	36
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)	36
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.	49
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.	50
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)	36
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)	36
Facial cleanser containing 2.7% Sodium Lauroamphoacetate	None	100%	32 subjects	4-wk use study; subjects used product in morning and night with a small amount of water; massaged cleanser for 30 – 60 sec, then washed	Non-irritating	51

Table 9. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
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
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. SI values at 1, 3, 6, 12, and 30% in experiment 1: 1.16, 0.74, 0.68, 1.3, and 1.86, respectively SI values at 30, 40 and 50% in experiment 2: 0.65, 1.17, and 3.44, respectively SI value of positive control in experiment 1 and 2: 10.18 and 9.76, respectively.	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

Table 9. Dermal irritation and sensitization

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
			Human			
Product containing 2.04% Disodium Lauroamphodiacetate	NR	1% (tested solution contained 0.02% Disodium Lauro-amphodiacetate); 0.2 ml/mg	193	HRIPT -9 total induction exposures; 24-h induction periods -patch size: 1 cm^2 - 2-wk non-treatment period followed by a challenge exposure -all exposures were performed under occlusive conditions	Non-irritating and non-sensitizing	58
Rinse-off product containing 4.56% Disodium Lauroamphodiacetate	NR	1% (tested solution contained 0.046% Disodium Lauroamphodiacetate); 200 µl	216	HRIPT; occlusive conditions; patch size: 4 cm^2; no other details provided	Non-irritating and non-sensitizing	52
Rinse-off product containing 2.8% Sodium Cocoamphoacetate	NR	1% (tested solution contained 0.028% Sodium Cocoamphoacetate); 200 µl	51	HRIPT; semi-occlusive conditions; patch size: 1 cm^2; no other details provided	Non-irritating and non-sensitizing	53
Body soap containing 9.6% Sodium Cocoamphoacetate	distilled water	1% (tested solution contained 0.096% Sodium Cocoamphoacetate); 200 µl	53	HRIPT -9 total induction exposures; 24-h induction periods -approximately 2-wk rest period followed by a challenge exposure -all exposures were performed under occlusive conditions	Non-irritating and non-sensitizing	54
Product containing 4.39% Sodium Lauroamphoacetate	NR	1% (tested solution contained 0.044% Sodium Lauroamphoacetate)	106	HRIPT; occlusive conditions; patch size: 4 cm^2; no other details provided	Non-irritating and non-sensitizing	55
Shampoo containing 5.25% Sodium Lauroamphoacetate	NR	3% (tested solution contained 0.16% Sodium Lauroamphodiacetate); 20 – 50 µl	108	HRIPT -9 total induction exposures; 24-h induction periods -patch size: 0.5 cm^2 -approximately 2-wk rest period followed by a challenge exposure -all exposures were performed under occlusive conditions	Non-irritating and non-sensitizing	56
Facial cleanser containing 2.7% Sodium Lauroamphoacetate	NR	10% (tested solution contains 0.27% Sodium Lauroamphoacetate); 200 µl	100	HRIPT -9 total induction exposures; 24-h induction periods -patch size: 0.5 cm^2 -approximately 10 d rest period followed by a challenge exposure -all exposures were performed under occlusive conditions	Non-irritating and non-sensitizing	57
Sodium Lauroamphoacetate (0.15% solids)	Water	0.5%; 200 µl	99 subjects	HRIPT -9 total induction exposures; 24-h induction periods -approximately 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 Co-operation and Development; SLS = sodium lauryl sulfate; TG = test guideline

Table 10. 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	36
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)	36
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)	59
Disodium Cocoamphodiacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient = 0.63 (quotient ≤ 0.8 indicates slightly irritating)	36
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)	60
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	36
Sodium Cocoamphoacetate	Water	1%	3	Red blood cell test	Non-irritating; H_{50}/DI = 102.40 (score > 100 indicates non-irritating)	36
Sodium Cocoamphoacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient = 0.42 (quotient ≤ 0.8 indicates slightly irritating)	36
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)	59
Sodium Lauroamphoacetate	Water	1%	3	Red blood cell test	Non-irritating; H_{50}/DI = 222.13 (score > 100 indicates non-irritating)	36
Sodium Lauroamphoacetate	Water	3%	6	HET-CAM assay	Slightly irritating; irritation quotient: 0.79 (quotient ≤ 0.8 indicates slightly irritating)	36
Sodium Lauroamphoacetate	Water	40%	6	HET-CAM assay	Severely irritating; irritation quotient: 3.41 (quotient ≥ 2 indicates severely irritating)	61
ANIMAL						
Disodium Cocoamphodiacetate	NR	1.9%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Non-irritating	62
Disodium Cocoamphodiacetate	NR	3.2%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Non-irritating	62

Table 10. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Disodium Cocoamphodiacetate	NR	5%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Non-irritating	62
Sodium Cocoamphoacetate	NR	1.9%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Non-irritating	62
Sodium Cocoamphoacetate	NR	3.2%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Slightly irritating	62
Sodium Lauroamphoacetate	NR	1.5%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Non-irritating	62
Sodium Lauroamphoacetate	NR	3.2%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Non-irritating	62
Sodium Lauroamphoacetate	NR	5%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Mildly irritating	62
Sodium Lauroamphoacetate	NR	5%	New Zealand White rabbits (n = 3; sex not stated)	Modified Draize assay; OECD TG 405; eye irritation response was classified into five grades: non-irritating, slightly irritating, mildly irritating, irritating, and corrosive, based on the mean of the irritation response scores and the recovery time	Slightly irritating	62
Sodium Lauroamphoacetate (10% solids: water and sodium chloride; 10% aqueous dilution)	NR	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

Table 10. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Sodium Lauroamphoacetate (15% solids; water and sodium chloride; 30% aqueous dilution)	NR	Tested neat; 0.1 ml	3 rabbits (strain and sex not specified)	Assay performed according to the same procedure as above.	The test substance was not considered to be an ocular irritant based on CLP criteria. Mean corneal opacity, iris, conjunctivae irritation and chemosis scores were 0/4, 0/2, 0.7/3, and 1.1/4, respectively. All effects were fully reversible within 7 d.	4
Sodium Lauroamphoacetate (50% solids; water and sodium chloride; 50% aqueous dilution)	NR	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)	NR	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)	NR	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, and at 7 and 21 d	No symptoms of eye irritation or adverse effects were noted.	63
Micellar water cleanser containing 1.2% Disodium Cocoamphodiacetate and 1% cetearyl alcohol (remaining product composition not stated)	NR	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, and at 7 and 21 d	No symptoms of eye irritation or adverse effects were noted.	63

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 Co-operation and Development; SI = stimulation index; TG = test guidelines

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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.

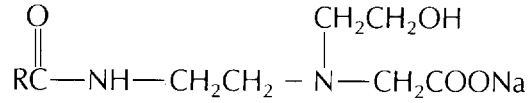
INTRODUCTION

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]

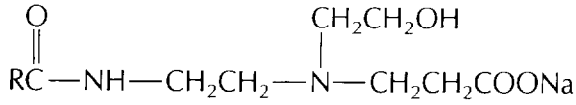
CHEMICAL AND PHYSICAL PROPERTIES

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



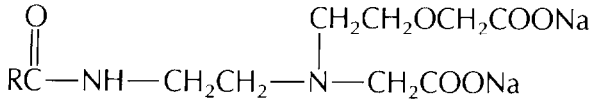
Cocoamphoacetate

I

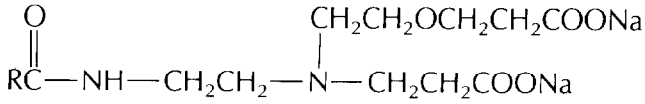


Cocoamphopropionate

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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Personal Care Products Council

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 6, 2026

SUBJECT: Summary of an HRIPT on a product containing 2.04% Disodium Lauroamphodiacetate

Anonymous. 2026. Summary and data tables of an HRIPT of a product containing 2.04% Disodium Lauroamphodiacetate.

Product Number	% Disodium Lauroamphodiacetate	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response
1	2.04	rinse-off	YES	occlusive	193	NO

Product Number 1

Calculation of Amount of Disodium Lauroamphodiacetate mg/cm2	
Concentration of Disodium Lauroamphodiacetate in %	2.04
Amount of Product applied to Skin during HRIPT in ml/mg	0.2
Patch Size cm^2	1
Dose density of product applied to patched skin in mg/cm2	50
Dose Density of Disodium Lauroamphodiacetate applied to patch skin in mg/cm2	0.01020000
Was the product diluted or undiluted? Diluted 1%	

ICDRG Reading scale	
0	No Visible Reaction
±	Faint Minimal Erythema
1	Erythema
2	Intense Erythema, Induration
3	Intense Erythema, Induration, Vesicles
4	Severe reaction with Erythema, Induration, Vesicles (may be weeping)

E	Edema
–	No reading

Details of Test methodolgy and Results	
0	panelist discontinued due to test material reactions
24 hrs	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge
24, 48, 72, 96 hrs post patching	Challenge readings

Grading Scale interpretation	
Low Level Reactions	1
High Level Reaction	2 and above

[redacted]

TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS EMPANELED: 221

Reaction Grade	Induction Reading 1	2	3	4	5	6	7	8	9	Challenge Reading (HR) 24	48	72	96
0	210	205	205	203	201	198	199	199	196	194	191	191	174
±						1				1	1	1	
1	1												
1E													
2													
2E													
3													
4													
-											2	1	19
N9R									3				
NUMBER OF SUBJECTS ON PANEL	211	205	205	203	201	199	199	199	199	195	194	193	193

SCORING SYSTEM:

0	=	No visible reaction
±	=	Faint, minimal erythema
1	=	Erythema
2	=	Intense erythema, induration
3	=	Intense erythema, induration, vesicles
4	=	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	=	Edema
-	=	No reading
N9R	=	No 9th reading

[redacted]

[redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

		Induction Reading									Challenge Reading (hr)			
Sub	[redacted]	1	2	3	4	5	6	7	8	9	24	48	72	96
1		0	0	0	0	0	0	0	0	0	0	0	0	0
2		0	0	0	0	0	0	0	0	0	0	0	0	0
3		0	0	0	0	0	0	0	0	0	0	0	0	0
4		0	0	0	0	0	0	0	0	0	0	0	0	0
5		0	0	0	0	0	0	0	0	0	0	0	0	0
6		0	0	0	0	0	0	0	0	0	0	0	0	0
7		0	0	0	0	0	0	0	0	0	0	0	0	0
8		0	0	0	0	0	0	0	0	0	0	0	0	0
9		0	0	0	0	0	0	0	0	0	0	0	0	0
10		0	0	0	0	0	0	0	0	0	X	X	X	X
11		0	0	0	0	0	0	0	0	0	0	0	0	0
12		0	0	0	0	0	0	0	0	0	0	0	0	0
13		0	0	0	0	0	0	0	0	0	0	0	0	0
14		0	0	0	0	0	0	0	0	0	0	0	0	0
15		0	0	0	0	0	X	X	X	X	X	X	X	X
16		0	0	0	0	0	0	0	0	0	0	0	0	0
17		0	0	0	0	0	0	0	0	0	0	0	0	0
18		0	0	0	0	0	0	0	0	0	0	0	0	0
19		0	0	0	0	0	0	0	0	0	0	0	0	0
20		0	0	0	0	0	0	0	0	0	0	0	0	0
21		0	0	0	0	0	0	0	0	0	0	0	±	±
22		0	0	0	0	0	0	0	0	0	0	0	0	0
23		0	0	0	0	0	0	0	0	0	0	0	0	0
24		0	0	0	0	0	0	0	0	0	0	0	0	0
25		0	X	X	X	X	X	X	X	X	X	X	X	X
26		0	0	0	0	0	0	0	0	0	0	0	0	0
27		0	0	0	0	0	0	0	0	0	0	0	0	0
28		0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

FINAL REPORT REPEATED INSULT PATCH TEST (RIPT) (Page 6 of 14)

[redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

	[redacted]	Induction Reading									Challenge Reading (hr)			
		1	2	3	4	5	6	7	8	9	24	48	72	96
29		0	0	0	0	0	0	0	0	0	0	0	0	0
30		0	0	0	0	0	0	0	0	0	0	0	0	0
31		0	0	0	X	X	X	X	X	X	X	X	X	X
32		0	0	0	0	0	0	0	0	0	0	0	0	0
33		0	0	0	0	0	0	0	0	0	0	0	0	0
34		0	0	0	0	0	0	0	0	0	0	0	0	0
35		0	0	0	0	0	0	0	0	0	0	0	0	0
36		0	0	0	0	0	0	0	0	0	0	0	0	0
37		0	0	0	0	0	0	0	0	0	0	0	0	0
38		0	0	0	0	X	X	X	X	X	X	X	X	X
39		0	0	0	0	0	0	0	0	0	0	0	0	0
40		X	X	X	X	X	X	X	X	X	X	X	X	X
41		0	0	0	0	0	0	0	0	0	0	0	0	0
42		0	0	0	0	0	0	0	0	0	0	0	0	0
43		0	0	0	0	0	0	0	0	0	0	0	0	0
44		0	0	0	0	0	0	0	0	0	0	0	0	0
45		0	0	0	0	0	0	0	0	0	0	0	0	0
46		0	0	0	0	0	0	0	0	0	0	0	0	0
47		0	0	0	0	0	0	0	0	0	0	0	0	0
48		0	0	0	0	0	0	0	0	0	0	0	0	0
49		0	0	0	0	0	0	0	0	0	0	0	0	0
50		0	0	0	0	0	0	0	0	0	0	0	0	0
51		0	0	0	0	0	0	0	0	0	0	0	0	0
52		0	0	0	0	0	0	0	0	0	0	0	0	0
53		0	0	0	0	0	0	0	0	0	0	0	0	0
54		0	0	0	0	0	0	0	0	0	0	0	0	0
55		0	0	0	0	0	0	0	0	0	0	0	0	0
56		0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

FINAL REPORT REPEATED INSULT PATCH TEST (RIPT) (Page 7 of 14)

[redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

	[redacted]	Induction Reading									Challenge Reading (hr)			
		1	2	3	4	5	6	7	8	9	24	48	72	96
57		0	0	0	0	0	0	0	0	0	0	0	0	0
58		0	0	0	0	0	0	0	0	0	0	0	0	-
59		0	0	0	0	0	0	0	0	0	0	0	0	-
60		0	0	0	0	0	0	0	0	0	0	0	0	0
61		0	0	0	0	0	0	0	0	0	0	0	0	0
62		0	0	0	0	X	X	X	X	X	X	X	X	X
63		0	0	0	0	0	0	0	0	0	X	X	X	X
64		0	0	0	0	0	0	0	0	0	0	0	0	0
65		0	0	0	0	0	0	0	0	0	0	0	0	0
66		0	0	0	0	0	0	0	0	0	0	0	0	0
67		0	0	0	0	0	0	0	0	0	0	0	0	0
68		0	0	0	0	0	0	0	0	0	0	0	0	0
69		0	0	0	0	0	0	0	0	0	0	0	0	0
70		0	0	0	0	0	0	0	0	0	0	0	0	0
71		0	0	0	0	0	0	0	0	0	0	0	0	0
72		0	0	0	0	0	0	0	0	0	0	0	0	0
73		0	0	0	0	0	0	0	0	0	0	0	0	0
74		0	0	0	0	0	0	0	0	0	0	0	0	0
75		0	0	0	0	0	0	0	0	0	0	0	0	0
76		0	0	0	0	0	0	0	0	0	0	0	0	0
77		0	0	0	0	0	0	0	0	0	0	0	0	0
78		0	0	0	0	0	0	0	0	0	0	0	0	0
79		0	0	0	0	0	0	0	0	0	0	0	0	0
80		0	0	0	0	0	0	0	0	0	0	0	0	0
81		0	0	0	0	0	0	0	0	0	0	0	0	-
82		0	0	0	0	0	0	0	0	0	0	0	0	0
83		X	X	X	X	X	X	X	X	X	X	X	X	X
84		0	0	0	0	0	0	0	0	0	0	X	X	X

[redacted]

[redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

	[redacted]	Induction Reading								Challenge Reading (hr)			
		2	3	4	5	6	7	8	9	24	48	72	96
85		0	0	0	0	0	0	0	0	0	0	0	0
86		0	0	0	0	0	0	0	0	0	0	0	0
87		0	0	0	0	0	0	0	0	0	0	0	0
88		0	0	0	0	0	0	0	0	0	0	0	0
89		0	0	0	0	0	0	0	0	0	0	0	0
90		0	0	0	0	0	0	0	0	0	0	0	0
91		0	0	0	0	0	0	0	0	0	0	0	0
92		0	0	0	0	0	0	0	0	0	0	0	0
93		0	0	0	0	0	0	0	0	0	0	0	0
94		X	X	X	X	X	X	X	X	X	X	X	X
95		0	0	0	0	0	0	0	0	0	0	0	0
96		0	0	0	0	0	0	0	0	0	0	0	0
97		0	0	0	0	0	0	0	0	0	0	0	0
98		0	0	0	0	0	0	0	0	0	0	0	0
99		0	0	0	0	0	0	0	0	0	0	0	0
100		0	0	0	0	0	0	0	0	0	0	0	0
101		0	0	0	0	0	0	0	0	0	0	0	0
102		0	0	0	0	0	0	0	0	0	0	0	0
103		0	0	0	0	0	0	0	N9R	0	0	0	0
104		0	0	0	0	0	0	0	0	0	0	0	0
105		0	0	0	0	0	0	0	0	0	0	0	0
106		X	X	X	X	X	X	X	X	X	X	X	X
107		0	0	0	0	0	0	0	0	0	0	0	0
108		0	0	0	0	0	0	0	0	0	0	0	0
109		0	0	0	0	0	0	0	0	0	0	0	-
110		0	0	0	0	0	0	0	0	0	0	0	0
111		0	0	0	0	0	0	0	0	0	0	0	0
112		0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

	[redacted]	Induction Reading									Challenge Reading (hr)			
		1	2	3	4	5	6	7	8	9	24	48	72	96
113		0	0	0	0	0	0	0	0	0	0	0	0	0
114		0	0	0	0	0	0	0	0	0	0	0	0	0
115		0	0	0	0	0	0	0	0	0	0	0	0	0
116		0	0	0	0	0	X	X	X	X	X	X	X	X
117		0	0	0	0	0	0	0	0	0	0	0	0	0
118		0	0	0	0	0	0	0	0	0	0	0	0	0
119		0	0	0	0	0	0	0	0	0	0	0	0	-
120		0	0	0	0	0	0	0	0	0	0	-	0	0
121		0	0	0	0	0	0	0	0	0	0	0	X	X
122		0	0	0	0	0	0	0	0	0	0	0	0	0
123		0	0	0	0	0	0	0	0	0	0	0	0	0
124		0	0	0	0	0	0	0	0	0	0	0	0	0
125		0	0	0	0	0	0	0	0	0	0	0	0	0
126		0	X	X	X	X	X	X	X	X	X	X	X	X
127		0	0	0	0	0	0	0	0	0	0	0	0	-
128		0	0	0	0	0	0	0	0	0	0	0	0	0
129		0	0	0	0	0	0	0	0	0	0	0	0	0
130		0	0	0	0	0	0	0	0	0	0	0	0	0
131		0	0	0	0	0	0	0	0	0	0	0	0	0
132		X	X	X	X	X	X	X	X	X	X	X	X	X
133		0	0	0	0	0	0	0	0	0	0	0	0	0
134		0	0	0	0	0	0	0	0	0	0	0	0	0
135		0	0	0	0	0	0	0	0	0	0	0	0	-
136		0	0	0	0	0	0	0	0	0	0	0	0	-
137		0	0	0	0	0	0	0	0	0	0	0	0	-
138		0	0	0	0	0	0	0	0	0	0	0	0	0
139		0	0	0	0	0	0	0	0	0	0	0	0	0
140		0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

	[redacted]	Induction Reading									Challenge Reading (hr)			
		1	2	3	4	5	6	7	8	9	24	48	72	96
141		0	0	0	0	0	0	0	0	0	0	0	0	0
142		0	0	0	0	0	0	0	0	0	0	0	0	0
143		0	0	0	0	0	0	0	0	0	0	0	0	0
144		0	0	0	0	0	0	0	0	0	0	-	0	-
145		0	0	0	0	0	0	0	0	0	0	0	0	0
146		X	X	X	X	X	X	X	X	X	X	X	X	X
147		0	X	X	X	X	X	X	X	X	X	X	X	X
148		0	0	0	X	X	X	X	X	X	X	X	X	X
149		0	0	0	0	0	0	0	0	0	0	0	0	0
150		0	0	0	0	0	0	0	0	0	0	0	0	0
151		0	0	0	0	0	0	0	0	0	0	0	0	0
152		0	0	0	0	0	0	0	0	0	0	0	0	0
153		0	0	0	0	0	0	0	0	0	0	0	0	0
154		0	0	0	0	0	0	0	0	0	0	0	0	0
155		0	0	0	0	0	0	0	0	0	0	0	0	0
156		0	0	0	0	0	0	0	0	0	0	0	0	0
157		0	0	0	0	0	0	0	0	0	0	0	0	-
158		0	0	0	0	0	0	0	0	0	0	0	0	0
159		0	0	0	0	0	0	0	0	0	0	0	0	0
160		0	X	X	X	X	X	X	X	X	X	X	X	X
161		0	0	0	0	0	0	0	0	0	0	0	0	0
162		0	0	0	0	0	0	0	0	0	0	0	0	0
163		0	0	0	0	0	0	0	0	0	0	0	0	0
164		0	0	0	0	0	0	0	0	0	0	0	0	0
165		0	0	0	0	0	0	0	0	0	0	0	0	0
166		0	0	0	0	0	0	0	0	0	0	0	0	-
167		0	0	0	0	0	0	0	0	0	0	0	0	-
168		0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

	[redacted]	Induction Reading									Challenge Reading (hr)			
		1	2	3	4	5	6	7	8	9	24	48	72	96
169		0	0	0	0	0	0	0	0	0	0	0	0	0
170		0	0	0	0	0	0	0	0	0	0	0	0	0
171		0	0	0	0	0	0	0	0	0	0	0	0	-
172		0	0	0	0	0	0	0	0	N9R	0	0	0	-
173		0	0	0	0	0	0	0	0	N9R	0	0	0	-
174		0	0	0	0	0	0	0	0	0	0	0	0	0
175		0	X	X	X	X	X	X	X	X	X	X	X	X
176		0	0	0	0	0	0	0	0	0	0	0	0	0
177		0	0	0	0	0	0	0	0	0	0	0	0	0
178		0	0	0	0	0	0	0	0	0	0	0	0	0
179		0	0	0	0	0	0	0	0	0	0	0	0	0
180		0	0	0	0	0	0	0	0	0	0	0	0	0
181		0	0	0	0	0	0	0	0	0	0	0	0	0
182		X	X	X	X	X	X	X	X	X	X	X	X	X
183		0	0	0	0	0	0	0	0	0	±	0	0	0
184		0	0	0	0	0	0	0	0	0	0	0	0	0
185		0	0	0	0	0	0	0	0	0	0	0	0	0
186		0	0	0	0	0	0	0	0	0	0	0	0	0
187		0	0	0	0	0	0	0	0	0	0	0	-	0
188		0	0	0	0	0	0	0	0	0	0	0	0	0
189		0	0	0	0	0	0	0	0	0	0	0	0	0
190		0	0	0	0	0	0	0	0	0	0	0	0	0
191		0	0	0	0	0	0	0	0	0	0	0	0	0
192		0	0	0	0	0	0	0	0	0	0	0	0	0
193		0	0	0	0	0	0	0	0	0	0	0	0	0
194		0	0	0	0	0	0	0	0	0	X	X	X	X
195		0	0	0	0	0	0	0	0	0	0	0	0	0
196		0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted]

TABLE II: INDIVIDUAL SUBJECT DATA

	[redacted]	Induction Reading									Challenge Reading (hr)			
		1	2	3	4	5	6	7	8	9	24	48	72	96
197		0	0	0	0	0	0	0	0	0	0	0	0	0
198		0	0	0	0	0	0	0	0	0	0	0	0	0
199		0	0	0	0	0	0	0	0	0	0	0	0	0
200		0	0	0	0	0	0	0	0	0	0	0	0	0
201		0	0	0	0	0	0	0	0	0	0	0	0	0
202		0	0	0	0	0	0	0	0	0	0	0	0	0
203		0	0	0	0	0	0	0	0	0	0	0	0	-
204		0	0	0	0	0	0	0	0	0	0	0	0	0
205		0	0	0	0	0	±	0	0	0	0	0	0	0
206		1	X	X	X	X	X	X	X	X	X	X	X	X
207		X	X	X	X	X	X	X	X	X	X	X	X	X
208		0	0	0	0	0	0	0	0	0	0	0	0	0
209		X	X	X	X	X	X	X	X	X	X	X	X	X
210		0	0	0	0	0	0	0	0	0	0	0	0	0
211		0	0	0	0	0	0	0	0	0	0	0	0	0
212		0	0	0	0	0	0	0	0	0	0	0	0	0
213		0	0	0	0	0	0	0	0	0	X	X	X	X
214		0	0	0	0	0	0	0	0	0	0	0	0	-
215		X	X	X	X	X	X	X	X	X	X	X	X	X
216		0	0	0	0	0	0	0	0	0	0	0	0	0
217		0	0	0	0	0	0	0	0	0	0	0	0	0
218		0	0	0	0	0	0	0	0	0	0	0	0	0
219		0	0	0	0	0	0	0	0	0	0	0	0	-
220		0	0	0	0	0	0	0	0	0	0	0	0	0
221		0	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

[redacted]

[redacted]

SCORING SYSTEM

0	=	No visible reaction
±	=	Faint, minimal erythema
1	=	Erythema
2	=	Intense erythema, induration
3	=	Intense erythema, induration, vesicles
4	=	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	=	Edema
DR	=	Dryness
^	=	Hyperpigmentation
C	=	Change of test site
-	=	No reading
N9R	=	No 9th reading
X	=	Discontinued

[redacted]