
Safety Assessment of Fatty Ethers as Used in Cosmetics

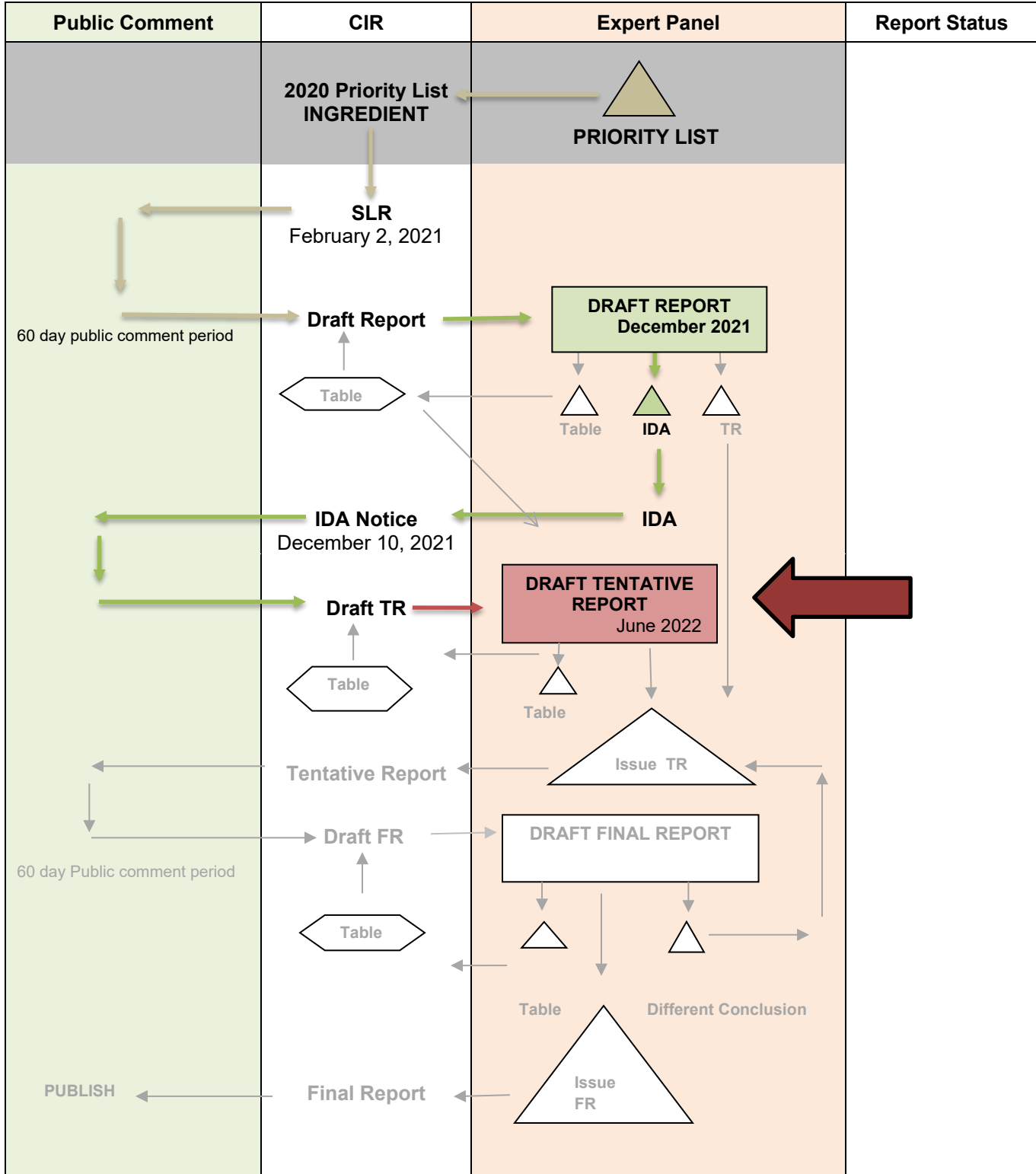
Status: Draft Tentative Report for Panel Review
Release Date: May 23, 2022
Panel Meeting Date: June 16-17, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D, and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Lisa A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi Raj, Senior Scientific Analyst/Writer, CIR.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Fatty Ethers

MEETING June 2022





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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst/Writer, CIR
Date: May 23, 2022
Subject: Safety Assessment of Fatty Ethers as Used in Cosmetics

Enclosed is a Draft Tentative Report of the Safety Assessment of Fatty Ethers as Used in Cosmetics (identified as *report_FattyEthers_062022* in the pdf). This is the second time the Panel is seeing a safety assessment of these 8 cosmetic ingredients. At the December 2021 meeting, a Draft Report was presented to the Panel. Upon review, the Panel issued an Insufficient Data Announcement (IDA) for:

- Method of manufacture data (specific to cosmetic ingredient production) for Dicaprylyl Ether and Distearyl Ether

Data were not received in response to this IDA.

Updated (2022) VCRP data were received from the FDA, and have been incorporated (*VCRP_FattyEthers_062022*). No significant changes in reported use categories or frequencies occurred. Changes to the VCRP and changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review.

Included in this package, for your review, are a flow chart (*flow_FattyEthers_062022*), literature search strategy (*search_FattyEthers_062022*), ingredient data profile (*datapofile_FattyEthers_062022*), ingredient history (*history_FattyEthers_062022*), and transcripts from the previous meeting (*transcripts_FattyEthers_062022*).

The Panel should carefully consider and discuss the data (or lack thereof), and the draft Abstract and draft Discussion presented in this report. A Tentative Report with a safe as used, safe with qualifications, insufficient, split, or unsafe conclusion should then be issued.

CIR History of:
Fatty Ether Ingredients

July 2019

-Concentration of use data submitted by Council

January 2021

-New VCRP data were received

February 2021

- SLR posted on the CIR website

February and April 2021

Data received:

- February 22, 2021: single occlusive patch test of sun tan oil product containing 15% Dicaprylyl Ether, in 11 subjects
- February 23, 2021: HRIPTs of a product containing 1.5% Distearyl Ether and a product containing 38.6% Dicaprylyl Ether
- April 12, 2021: Summary info for Cetyl Dimethylbutyl Ether (method of manufacture, dermal irritation and sensitization, and genotoxicity data)

December 2021

A Draft Report was presented to the Panel. The Panel issued an IDA, stating that the additional data needed to determine safety for these cosmetic ingredients is:

- Method of manufacture data (specific to cosmetic ingredient production) for Dicaprylyl Ether and Distearyl Ether

No further data or comments were received.

June 2022

A Draft Tentative Report is being presented for Panel review.

Fatty Ethers Data Profile* - June 16-17, 2022 - Preethi Raj

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization			Phototoxicity	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		In Vitro	Animal	Retrospective/Multicenter	Case Reports
Cetyl Dimethylbutyl Ether	X	X		X										X						X									
Dicaprylyl Ether	X		X	X	X		X	X			X			X						X	X			X		X			
Dicetyl Ether				X																									
Didecyl Ether				X																									
Diisononyl Ether				X																									
Dilauryl Ether				X																									
Dimyristyl Ether				X																									
Distearyl Ether	X		X	X			X	X						X						X		X	X			X			

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

Fatty Ethers

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Cetyl Dimethylbutyl Ether	185143-68-4	NR	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	
Dicaprylyl Ether	629-82-3	✓	NR	NR	NR	NR	NR	NR	✓*	✓	NR	NR	✓*	NR	NR	NR	✓*
Dicetyl Ether	4113-12-6	NR	NR	NR	NR	NR	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	
Didecyl Ether	2456-28-2	NR	NR	NR	NR	✓*	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	
Diisononyl Ether		NR	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	
Dilauryl Ether	4542-57-8	NR	NR	NR	NR	NR	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	
Dimyristyl Ether	5412-98-6	NR	NR	NR	NR	NR	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	
Distearyl Ether	6297-03-6	NR	NR	NR	NR	NR	NR	NR	✓*	✓	NR	NR	NR	NR	NR	NR	✓*

✓* - in database, but data not useful or available

NR – not reported

Search Strategy [total # of hits / # hits that were useful]**In Pubmed - Updated 5/2/2022**

((((((((((((dicaprylyl ether) OR 629-82-3) OR dicetyl ether) OR didecyl ether) OR 2456-28-2) OR dilauryl ether) OR 2456-28-2) OR dimyristyl ether) OR 5412-98-6) OR distearyl ether) OR 6297-03-6) OR cetyl dimethylbutyl ether) OR 185143-68-4) - 31 hits/ 0 useful

((((((((((cetyl dimethylbutyl ether) OR (dicaprylyl ether)) OR (629-82-3)) OR (dicetyl ether)) OR (didecyl ether)) OR (diisononyl ether)) OR (dilauryl ether)) OR (dimyristyl ether)) OR (distearyl ether)) OR (6297-03-6)) AND (toxicity) – 7 hits/ 0 useful

Dicaprylyl Ether – 2 hits/0 useful

Method of manufacture – 0/0

Impurities – 0/0

Dermal penetration – 3 hits/0 useful

Toxicokinetics – 3 hits/ 0 useful

Toxicity, acute toxicity, dermal toxicity, oral toxicity, inhalation toxicity, short term/subchronic/chronic toxicity- 3 hits/ 0 useful

Developmental toxicity – 0/0

Reproductive toxicity – 0/0

Genotoxicity – 0/0

Carcinogenicity – 0/0

Pigmentation – 2 hits/1 useful

Dermal irritation – 11 hits/0 useful

Dermal sensitization – 5 hits/ 0 useful

Photosensitization – 4 hits/ 0 useful

Ocular irritation – 7 hits/ 0 useful

Mucous membrane irritation – 5 hits/0 useful

Clinical studies/case reports – 9 hits/ 0 useful

Epidemiology – 15 hits/ 0 useful

Dicetyl Ether – 0/0 (found as dimethyl ether – not the same)

Method of manufacture – 5 hits/0 useful

Impurities- 5 hits/0 useful

Dermal penetration- 13 hits/0 useful
Toxicokinetics- 13 hits/ 0 useful
Toxicity – 57/0, acute toxicity – 6/0, dermal toxicity- 6/0, oral toxicity – 5/0, inhalation toxicity – 5/0, short term/subchronic/chronic toxicity – 4/0
Developmental toxicity – 2 hits/ 0 useful
Reproductive toxicity – 13 hits/ 0 useful
Genotoxicity – 1 hit/ 0 useful
Carcinogenicity – 18 hits/ 0 useful
Pigmentation – 5 hits/ 0 useful
Dermal irritation – 5 hits/ 0 useful
Dermal sensitization – 5 hits/ 0 useful
Photosensitization – 11 hits/ 0 useful
Ocular irritation – 0/0
Mucous membrane irritation – 0/0
Clinical studies/case reports – 4 hits/ 0 useful
Epidemiology – 2 hits/0 useful

Didecyl Ether -0/0 (found as dodecyl ether or dodecyl sulfate– not the same)

Method of manufacture – 3 hits/ 0 useful
Impurities- 3 hits/ 0 useful
Dermal penetration- 1 hit/0 useful
Toxicokinetics- 63 hits/ 0 useful
Toxicity, acute toxicity, dermal toxicity, oral toxicity, inhalation toxicity, short term/subchronic/chronic toxicity- 60 hits/ 0 useful
Developmental toxicity – 2 hits/ 0 useful
Reproductive toxicity – 1 hit/ 0 useful
Genotoxicity – 2 hits/ 0 useful
Carcinogenicity – 63 hits/ 0 useful
Pigmentation – 8 hits/ 0 useful
Dermal irritation – 0/0
Dermal sensitization – 0/0
Photosensitization – 6 hits/ 0 useful
Ocular irritation – 0/0
Mucous membrane irritation – 5 hits/ 0 useful
Clinical studies/case reports – 31 hits/ 0 useful
Epidemiology – 3 hits/ 0 useful

Diisononyl Ether – 9 hits/ 0 useful (not exact ingredient)

Method of manufacture – 21 hits/0 useful
Impurities- 2 hits/ 0 useful
Dermal penetration- 4 hits/ 0 useful
Toxicokinetics- 0/0
Toxicity, acute toxicity, dermal toxicity, oral toxicity, inhalation toxicity, short term/subchronic/chronic toxicity- 33 hits/0 useful
Developmental toxicity – 0/0
Reproductive toxicity – 0/0
Genotoxicity – 11 hits/ 0 useful
Carcinogenicity – 14 hits/ 0 useful

Pigmentation – 1 hit/ 0 useful
Dermal irritation – 0/0
Dermal sensitization – 0/0
Photosensitization – 0/0
Ocular irritation – 0/0
Mucous membrane irritation – 0/0
Clinical studies/case reports – 7 hits/0 useful
Epidemiology – 1 hit/0 useful

Dilauryl Ether – 5 hits/ 0 useful (not exact ingredient)

Method of manufacture – 0/0
Impurities- 1 hit/ 0 useful
Dermal penetration- 1 hit/ 0 useful
Toxicokinetics- 64 hits/ 0 useful
Toxicity, acute toxicity, dermal toxicity, oral toxicity, inhalation toxicity, short term/subchronic/chronic toxicity- 37 results/ 0 useful
Developmental toxicity – 0/0
Reproductive toxicity – 0/0
Genotoxicity – 0/0
Carcinogenicity – 1 hit/0 useful
Pigmentation – 1 hit/ 0 useful
Dermal irritation – 0/0
Dermal sensitization – 0/0
Photosensitization – 5 hits/ 0 useful
Ocular irritation – 2 hits/ 0 useful
Mucous membrane irritation – 5 hits/ 0 useful
Clinical studies/case reports – 22 hits/ 0 useful
Epidemiology – 2 hits/ 0 useful

Dimyristyl Ether – 3 hits/0 useful (not exact ingredient)

Method of manufacture – 16 hits/ 0 useful
Impurities- 2 hits/ 0 useful
Dermal penetration- 2 hits/ 0 useful
Toxicokinetics- 3 hits/0 useful
Toxicity, acute toxicity, dermal toxicity, oral toxicity, inhalation toxicity, short term/subchronic/chronic toxicity- 3 hits/0 useful
Developmental toxicity – 3 hits/0 useful
Reproductive toxicity – 2 hits/ 0 useful
Genotoxicity – 2 hits/ 0 useful
Carcinogenicity – 1 hit/ 0 useful
Pigmentation – 2 hits/ 0 useful
Dermal irritation – 2 hits/ 0 useful
Dermal sensitization – 2 hits/ 0 useful
Photosensitization – 1 hit/ 0 useful
Ocular irritation – 2 hits/ 0 useful
Mucous membrane irritation – 0/0
Clinical studies/case reports – 1 hit/ 0 useful

Epidemiology – 0/0

Distearyl Ether – 1 hit/0 useful (not exact ingredient)

Method of manufacture – 18 hits/ 0 useful

Impurities- 18 hits/ 0 useful

Dermal penetration- 10 hits/ 0 useful

Toxicokinetics- 2 hits/ 0 useful

Toxicity, acute toxicity, dermal toxicity, oral toxicity, inhalation toxicity, short term/subchronic/chronic toxicity- 1 hit/ 0 useful

Developmental toxicity – 0/0

Reproductive toxicity – 17 hits/ 0 useful

Genotoxicity – 8 hits/ 0 useful

Carcinogenicity – 5 hits/ 0 useful

Pigmentation – 6 hits/ 0 useful

Dermal irritation – 0/0

Dermal sensitization – 3 hits/ 0 useful

Photosensitization – 10 hits/ 0 useful

Ocular irritation – 3 hits/ 0 useful

Mucous membrane irritation – 4 hits/ 0 useful

Clinical studies/case reports – 7 hits/ 0 useful

Epidemiology – 0/0

Cetyl Dimethylbutyl Ether – 0/0

Method of manufacture – 0/0

Impurities- 0/0

Dermal penetration- 0/0

Toxicokinetics- 0/0

Toxicity, acute toxicity, dermal toxicity, oral toxicity, inhalation toxicity, short term/subchronic/chronic toxicity- 0/0

Developmental toxicity – 0/0

Reproductive toxicity – 0/0

Genotoxicity – 0/0

Carcinogenicity – 0/0

Pigmentation – 0/0

Dermal irritation – 0/0

Dermal sensitization – 0/0

Photosensitization – 0/0

Ocular irritation – 0/0

Mucous membrane irritation – 0/0

Clinical studies/case reports – 0/0

Epidemiology – 0/0

General Web Search – Most relevant results: Pubchem pages, for chemical properties

LINKS

Search Engines

- Pubmed (- <http://www.ncbi.nlm.nih.gov/pubmed>)
- Connected Papers - <https://www.connectedpapers.com/>

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

Pertinent Websites

- wINCI - <http://webdictionary.personalcarecouncil.org>
- FDA databases <http://www.ecfr.gov/cgi-bin/ECFR?page=browse>
- FDA search databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>;
- Substances Added to Food (formerly, EAFUS): <https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus>
- 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>
- FDA Orange Book: <https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm>
- (inactive ingredients approved for drugs: <http://www.accessdata.fda.gov/scripts/cder/iig/>)
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/opthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - <http://www.cdc.gov/niosh/>
- NTIS (National Technical Information Service) - <http://www.ntis.gov/>
 - technical reports search page: <https://ntrl.ntis.gov/NTRL/>
- NTP (National Toxicology Program) - <http://ntp.niehs.nih.gov/>
- Office of Dietary Supplements <https://ods.od.nih.gov/>
- FEMA (Flavor & Extract Manufacturers Association) GRAS: <https://www.femaflavor.org/fema-gras>
- 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/>
- 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
- AICIS (Australian Industrial Chemicals Introduction Scheme)- <https://www.industrialchemicals.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

DECEMBER 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT**Belsito Team – December 6, 2021**

DR. BELSITO: Okay, so we're moving on to Dicaprylyl Ether. So this is the first time we're looking at this, and we've got a bunch of data. So we need to determine whether the data is sufficient. We have method of manufacture for just one of them. We have impurities data for just two. Dan, does that cover the space of these or do we need more on that?

DR. LIEBLER: No, I wasn't really happy with this method of manufacture situation. This Cetyl Dimethylbutyl Ether is a straight chain, branch chain, hybrid ether. It's not representative of the two that have the highest uses, which are the Dicaprylyl or Distearyl, so we should get method of manufacture for the highest use ingredient Dicaprylyl Ether. Or for the Distearyl Ether, either of those would be fine, both would be preferable. We can still include this, but it's just not sufficient. We can still include the Cetyl Dimethylbutyl Ether, which is there. It's just by itself it's not sufficient.

DR. BELSITO: So method of manufacture for the Dicaprylyl and/or Distearyl Ether.

DR. LIEBLER: Right, because we've got the impurities for them right below it.

DR. BELSITO: Right.

DR. LIEBLER: And, you know, 99 plus percent on these, they're going to be -- they're going to sail right through, just we need method of manufacture for these.

DR. BELSITO: So, even though we have the impurities, you feel we need the method of manufacture?

DR. LIEBLER: Yep.

DR. BELSITO: Okay. That's one data insufficiency. So the in vitro dermal penetration?

DR. LIEBLER: Essentially nothing.

DR. BELSITO: Yeah, very low. So does that obviate the need for systemic tox?

DR. LIEBLER: I think it does, but I'd like to hear my colleagues. My point on this one I think is that these ethers are very non-polar molecules. They're not unabsorbed by virtue of just at their molecular weight because they're not that big.

DR. BELSITO: Right.

DR. LIEBLER: But they're so non-polar that they just don't get taken up, but all the tox data is consistent with that. Its low solubility would seem to be the driver of low toxicity. Essentially, we got data on data absorption, and it's just about nil. We have no chemical reactivity. They're not going to be easily metabolized. These are fairly inert without being that big.

DR. BELSITO: Right.

DR. KLAASSEN: I agree.

DR. BELSITO: Okay. We do have some limited sub-chronic and DART for the Dicaprylyl Ether.

DR. SNYDER: Yeah, and there's no signal there whatsoever, that NOAELs are at the maximum concentration, a thousand.

DR. BELSITO: Right.

DR. SNYDER: This developmental repro, same thing. It's negative for genotox.

DR. BELSITO: Yeah.

DR. SNYDER: Table 6, we got irritation sensitization data.

DR. BELSITO: Yeah.

DR. SNYDER: I had kind of a question.

DR. BELSITO: The max leave-on is 25 percent.

DR. SNYDER: Yes.

DR. BELSITO: We do have data to -- actually at 38.6, so I think we pretty much have the dermal covered. Go ahead, someone had a point, Paul?

DR. SNYDER: My point is, I meant to mention this earlier on, but the first word on the introduction says, "This is the safety assessment of the following eight fatty ethers as used in cosmetic formulations," but six of the eight are not used. So should we really say this is a safety assessment of eight fatty ethers and two as used? I mean, because it's kind of a -- these aren't used. I mean, six of the eight aren't even used. Or how do we deal with that?

I thought we used to say in the discussion that the safety would be supported if they were used in a similar concentration and uses as the ones reported or something. I don't recall seeing that wording lately.

DR. BELSITO: Yeah, that typically was in the discussion. You're right, Paul.

DR. SNYDER: Yeah, and I haven't seen that for a long time and, all of a sudden, we had a lot of reports this time. And the reason I should have mentioned it before, I put a sticky note saying six of the eight are not used. So it's not an assessment of them as used in cosmetics because they're not used. Not these of all eight, only two of them are.

DR. BELSITO: Well, if we just got rid of the number and said, as used, and then, in the discussion, the assumption that the ones not used would be used in a similar fashion?

DR. SNYDER: Well, I thought that same way. That's why we're -- this is a safety assessment of the following fatty ethers as potentially used in cosmetic formulation. Then have an asterisk with ones that are used, and then ones that are not used the other way.

DR. BELSITO: Right.

DR. SNYDER: Something like that.

DR. BELSITO: Yeah, we need to go back and look at all of these reports and make sure that that language that we used to have in the discussion -- or I think it typically was a footnote to the table that listed the ones not used, right?

DR. SNYDER: I can't remember, and I looked for it and looked for it, and I couldn't find it in any of these reports.

DR. BELSITO: I think it used to be a footnote to the table that came after concentration of use. There was a footnote that defined, that listed the ones not used and that's not here in this one.

DR. SNYDER: I don't think it's in any of them, Don. I was looking for it, but I think that's something we need to revisit.

DR. BELSITO: Yeah, so, Bart, could you ask the writers to go back and make that table with the footnote that we used to have for the ones not used, that our assumption would be that they'd be used in the same concentration and types of uses as described in the report, or whatever that language was?

DR. HELDRETH: Yes, but historically, at the draft report stage, since we don't have a conclusion, we don't include that information yet.

DR. BELSITO: Oh, okay.

DR. HELDRETH: Usually, it comes in at the next iteration, and typically, the conclusion will even have an asterisk on each ingredient that's not in use with some verbiage that says for those ingredients not in use, if they were to be used the expectation is that they'd be used at concentrations and formulations like others in the report that are used.

DR. BELSITO: Okay, so we'll expect to see it when it comes back to us.

DR. HELDRETH: That's correct.

DR. BELSITO: Okay.

DR. SNYDER: Thank you for that clarification.

DR. HELDRETH: Sure.

DR. BELSITO: Are we safe as used, but I guess, we need more data on manufacturing and impurities, is that what I'm hearing, Dan?

DR. LIEBLER: Yep, that's it for me.

DR. BELSITO: Well, I guess impurities we have. You want manufacturing for Caprylyl or Distearyl.

DR. LIEBLER: Right. Only method of manufacture is just the one gap, and it should be really easy to provide.

MS. RAJ: Does the Panel have any comments regarding inhalation boilerplate language anywhere in the report?

DR. LIEBLER: Scrolling down to the use table. It's a high concentration of use for inhalation spray, 10 and 24, and for powder, 2 and 25. So we can't say that it's very, very low. The only thing I think we can say is that there is very low systemic toxicity for multiple endpoints.

DR. BELSITO: Right.

DR. LIEBLER: There's no irritation with these, is that right?

DR. BELSITO: Well, we had HRIPT after 30 some odd percent that was negative without irritation during the induction phase.

DR. LIEBLER: Bingo.

DR. BELSITO: Yeah, for the discussion I had no systemic toxicity alerts and just the standard respiratory boilerplate.

DR. LIEBLER: Yeah. I think, Preethi, what you can say, you can use the respiratory boilerplate and you can say the Panel's concern was mitigated -- any concern about respiratory tox was mitigated by the very low toxicity of these ingredients and the lack of evidence for irritation, ocular or skin irritation, of its ingredients.

MS. RAJ: Okay. Thank you.

DR. BELSITO: Anything else on these ethers? Okay. Preethi, you got your marching orders?

MS. RAJ: Yes. Thank you, Dr. Belsito.

DR. BELSITO: Okay. We're going to conclude this with radish.

Cohen Team – December 6, 2021

DR. COHEN: Okay. So we have fatty ethers. Dicaprylyl ether. Preethi this is yours. This is a draft report. It's the first time we're reviewing it. There are eight derived ingredients. It's used as a skin conditioning agent. We have frequency of use. We have max use of dicaprylyl ether at up to 25 percent in a body and hand product and cetyl dimethylbutyl ether at a max concentration of 19.3 percent in a foundation. It's used around the eyes, and it's used in some cosmetic sprays.

We have some impurities, some method of manufacturing. We have irritation/sensitization at max use.

DR. SLAGA: Genotox.

DR. COHEN: Yeah, and neat dicaprylyl ether will produce some irritant reactions in animals and humans. So, I mean, that was much higher concentration, but the max use is pretty high -- something for us to consider in our final decision. So, I'll open it up. Lisa, you want to start.

DR. PETERSON: Sure, our needs are method of manufacturing on all but the cetyl dimethylbutyl ether, and we need impurities on all but the dicaprylyl ether and distearyl ether. I think this is the first time we asked for it and --

MS. RAJ: I'm sorry, Dr. Peterson, could you please repeat that again?

DR. PETERSON: So, method of manufacturing on everything except the cetyl dimethylbutyl ether and the distearyl ether. No, I'm sorry, method of manufacturing on everything but the cetyl dimethyl ether and then impurities on everything but dicaprylyl ether and distearyl ether.

MS. RAJ: Thank you.

DR. COHEN: Tom.

DR. SLAGA: Well, for sufficient data other than methods of manufacturing and then impurities, we have irritation/sensitization and genotox, which are negative, for three of the ingredients, and the rest of them we have very little data.

DR. SHANK: Can we read across?

DR. SLAGA: That's what I was --

DR. SHANK: Using dicaprylyl ether.

DR. SLAGA: We don't need any irritation/sensitization and genotox for the rest.

DR. SHANK: I agree.

DR. COHEN: Wouldn't you still want impurities on them?

DR. SLAGA: Well, it's the first time. I would go -- let's get the method of manufacturing for the one and the impurities for the other. You know, we'll see where it goes.

DR. COHEN: Ron?

DR. SHANK: I don't have any toxicology concerns. If you want to ask for impurities, that's fine. If there was a significant hazard, that impurity that had a toxic effect, I would think that the toxicity test would detect that.

DR. PETERSON: Yeah, so I'm I-dotting, T-crossing, and I would be perfectly comfortable saying that we might not need -- yeah, that we would be okay without having method of manufacturing and the impurities on the ones that we have. But I'm I-dotting, T-crossing, and I would expect that perhaps the other team is going to request those things.

DR. SHANK: Right.

DR. COHEN: Ron, had you had that, were you going with safe as used when formulated to be non-irritating or safe as used?

DR. SHANK: Safe as used.

DR. SLAGA: I would go with that, too.

DR. PETERSON: Yeah, I could support that.

DR. COHEN: Even when the neat dicaprylyl ether caused some irritant reactions in humans and animals, understanding that it's at a much higher concentration?

DR. SHANK: Right.

DR. SLAGA: Yeah, the data we have at a lower concentration is safe. No irritation.

DR. SHANK: It's not a sensitizer.

DR. SLAGA: Yeah.

DR. COHEN: Yeah. So, I have this one tomorrow. So are we going to go out with an IDA and be open for discussion, or are we going to go out as a safe as used?

DR. SLAGA: I would be bold. Let's go out as safe as used.

DR. COHEN: Draw a line in the sand, Tom.

DR. SLAGA: Ron, what do you think?

DR. SHANK: I would say safe as used, and you're the lead on this one, David?

DR. COHEN: Yes.

DR. SHANK: So, you can say we discussed a need for impurity and manufacturing data, but we're satisfied that the toxicity data was sufficient to not require further data.

DR. COHEN: Thank you.

DR. SHANK: And then if the other team says, oh, we have to have manufacturing and impurity, you've already covered that.

DR. COHEN: Yeah. I have room to move.

DR. SHANK: Yes.

DR. COHEN: Good, good. Just playing out the scenarios.

DR. COHEN: We'll move to radish. We're okay to move on from the ethers?

DR. SHANK: Yes.

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DR. COHEN: Okay. So this is a draft report for the fatty ethers, dicaprylyl ether. It's the first time we're reviewing this, and this safety assessment is for eight derived ingredients, which are used as skin conditioning agents. We have frequency of use reported. We have max use reported at up to 25 percent in body and hand lotions. It's used in baby lotions and lipsticks. It's in pump hairsprays, and we are making a motion for safe as used.

DR. BERGFELD: Is there a second or a discussion?

DR. BELSITO: Yes. We thought it was insufficient for manufacturing of either the dicaprylyl or the distearyl ether, which are the smallest of them. And I'll let Dan address that since this was his point. Otherwise, we would agree with you, David.

DR. LIEBLER: Yeah. I agree with you entirely, David, except we don't have method of manufacture on either of the two highest use. The dicaprylyl is the high use one, and we have it for this branch chain analog that's not used. So that's the only thing I think we need to ask for. Again, in the spirit of early stage report, that's a missing piece. Otherwise, these are going to be good to go.

DR. BERGFELD: Okay. Do you want to rescind your motion, David?

DR. COHEN: Yes. Dan, I'll rescind my motion and make a motion for an IDA and just ask Dan to repeat the needs to we're clear.

DR. LIEBLER: So method of manufacture for the dicaprylyl or the distearyl ether. Dicaprylyl is preferred because it's by far the most used. The distearyl would suffice. These are chemically very similar analogs. I suspect the methods are the same, so either of those would be fine.

DR. COHEN: That motion is made.

DR. BERGFELD: Yeah. Okay. And is there a second? Don, are you there?

DR. BELSITO: I second.

DR. BERGFELD: Okay. Any further discussion about the ether?

DR. COHEN: Yeah. Don, can I ask your advice on something? The neat material caused some irritant reactions I think in the animals and humans, so just going forward would you think about a formulate to be nonirritating on this one? Or do you think we have enough no to have that?

DR. BELSITO: Okay. Sorry, I thought we were done and went on to the radish.

DR. COHEN: You closed it.

DR. BELSITO: Let me go back to dicaprylyl.

DR. COHEN: We can come back to that. It's an IDA now.

DR. BELSITO: No, no. I've got it here. I did not ask for that.

DR. SNYDER: Page 24, table 6 -- or page 25, table 6.

MS. RAJ: So can I clarify the IDA is for -- sorry, go ahead.

DR. BELSITO: We have a lot of animal data. We have the dicaprylyl undiluted, TJ404, and really considered a nonirritant. I mean, what is the max use concentration?

DR. COHEN: 25 percent in body and hand lotions. I was really looking to you for advice on that. Just seeing some of those signals in animals and humans that neat material, there's just a couple of remarks about it.

DR. BELSITO: Yeah. But we have the distearyl ether TJ404 was put on for four hours on saved skin, semi-occlusive, and the score was zero for animals. So I think we have enough test data to clear that.

MS. RAJ: And I think one of the teams had discussed -- I think Dr. Belsito's team -- that there's very low dermal penetration, which is less likely to have any dermal tox.

DR. COHEN: Okay.

DR. BERGFELD: Okay? All right. Are we ready to move on?

MS. RAJ: If I could clarify the IDA is for the method of manufacture for both dicaprylyl ether and distearyl ether?

DR. BELSITO: And/or.

DR. LIEBLER: Either of them.

DR. COHEN: Well, we'll ask for both, right?

MS. RAJ: Thank you.

DR. LIEBLER: Yeah. That's fine. Thanks, David.

DR. COHEN: Thank you. That's good.

DR. BERGFELD: All right. Are you ready, Dr. Belsito, for radish?

Safety Assessment of Fatty Ethers as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: May 23, 2022
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D, and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Lisa A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi Raj, Senior Scientific Analyst/Writer, CIR.

ABBREVIATIONS

CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
<i>Dictionary</i>	<i>International Cosmetic Ingredient Dictionary and Handbook</i>
DMSO	dimethyl sulfoxide
ECHA	European Chemicals Agency
FDA	Food and Drug Administration
HRIPT	human repeated insult patch test
LD	lethal dose
N/A	not applicable
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NR	not reported/none reported
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
SDS	sodium dodecylsulfate
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 8 fatty ethers as used in cosmetic formulations. These ingredients are reported to function in cosmetics as skin conditioning agents. The Panel reviewed the available data to determine the safety of these ingredients, and concluded...[to be determined].

INTRODUCTION

This is a safety assessment of the following 8 fatty ethers as used in cosmetic formulations:

Cetyl Dimethylbutyl Ether	Diisononyl Ether
Dicaprylyl Ether	Dilauryl Ether
Dicetyl Ether	Dimyristyl Ether
Didecyl Ether	Distearyl Ether

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients are reported to function in cosmetics as skin conditioning agents (Table 1).¹

The ingredients reviewed in this safety assessment are all ethers, which comprise an oxygen atom bonded to two alkyl (fatty) chains. Thus, these ingredients are reviewed together in this report.

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 exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cirsafety.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.^{2,3} 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.

CHEMISTRY**Definition and Structure**

These organic compounds are fatty, dialkyl ethers, such as Dicaprylyl Ether (CAS No. 629-82-3), Diisononyl Ether (no CAS No.), and Distearyl Ether (CAS No. 6297-03-06), comprising an oxygen atom, bonded to two fatty alkyl chains.¹ The definitions and structures of all of the ingredients included in this review are provided in Table 1.

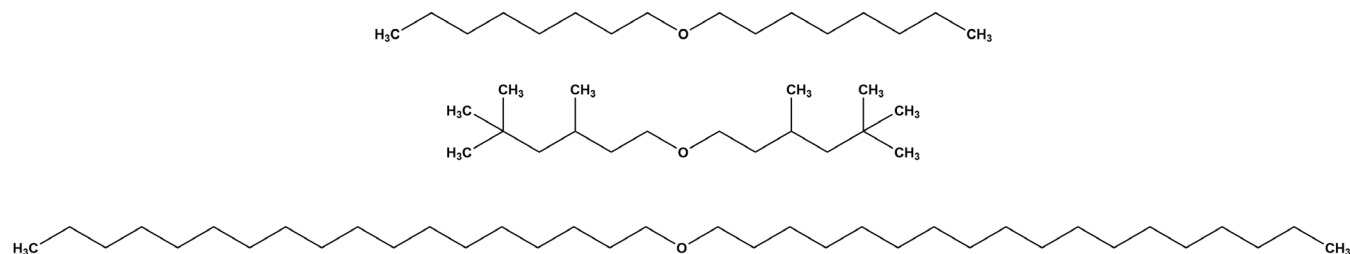


Figure 1. (from top to bottom) Dicaprylyl Ether, Diisononyl Ether, and Distearyl Ether

Chemical Properties

The smallest of these ingredients, Dicaprylyl Ether (2, 8-carbon chains bonded to 1 oxygen atom), has a molecular weight of 242.44 g/mol and an estimated log K_{ow} of 6.94,^{4,5} while the largest of these ingredients, Distearyl Ether (2, 18-carbon chains bonded to 1 oxygen atom), has a molecular weight of 523 g/mol and an estimated log K_{ow} of 16.76.^{3,5,6} Chemical properties for the ingredients in this report are further outlined in Table 2.

Method of Manufacture*Cetyl Dimethylbutyl Ether*

Cetyl Dimethylbutyl Ether is formed using cetyl alcohol and 4-methyl-2-pentanone, under hydrogen atmosphere in the presence of hydrogenation catalyst.⁷ After the reaction, it is separated by several processes, including filtration and distillation.

Impurities

ECHA data specifies that Dicaprylyl Ether was tested at either 99.1% or > 99.9% purity, and that Distearyl Ether was tested at 99.1% purity.^{2,3} No further impurities data were found in the published literature, and unpublished data were not submitted.

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, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Therefore, airbrush application of cosmetic products is not assessed by the Panel.

According to 2022 VCRP survey data, Dicaprylyl Ether is reported to be used in 255 formulations, the majority of which are leave-on products (Table 3).⁸ The results of the concentration of use survey, conducted in 2019 by the Council, indicate Dicaprylyl Ether also has the highest reported concentration of use; it is used at up to 25% in body and hand products.⁹ Cetyl Dimethylbutyl Ether is not reported to be in use according to the VCRP, but it is reported to be used in 3 product categories according to the Council survey; accordingly, it should be presumed there is at least 1 use in each product category. The 5 fatty ethers that are not reported to be in use, according to the VCRP and industry survey, are listed in Table 4.

Distearyl Ether has reported uses in products that may come in contact with the eyes; for example, it is used at up to 0.05% in eye lotions. Dicaprylyl Ether is used at up to 0.45% in baby lotions, oils, and creams, and has reported use in lipsticks (concentration not reported) which may lead to exposure to mucous membranes and incidental ingestion.

Some of these ingredients are reported to be used in cosmetic spray formulations and could possibly be inhaled; for example, Dicaprylyl Ether is reported to be used at 10% in pump hair spray products and Dicaprylyl Ether has reported use in 2 face powder formulations (concentration not reported). 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.

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

All of the fatty ethers named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.¹⁰

Non-Cosmetic

Non-cosmetic uses were not found in the published literature, and unpublished data were not submitted.

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Dicaprylyl Ether

Dermal penetration of Dicaprylyl Ether (99.1% pure) was examined in vitro, in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 428, using full-thickness human abdominal skin samples from 3 donors, in duplicate (n = 6).^{2,3} The Dicaprylyl Ether content in the test article was determined prior to the study by liquid chromatography- mass spectrometry (LC-MS); methanol was used as the extraction medium. The content of Dicaprylyl Ether in the test solution was determined to be 108.0 %. Undiluted test article (30 µl) was then applied for 24 h to

skin sections in diffusion cells. (Details regarding the diffusion cell portion of the experiment were not provided.) Subsequently, the remaining Dicaprylyl Ether content at the skin surface was determined by first removing the residual emollient by washing using the extraction medium, followed by tape-stripping the corneous layer and cryo-sectioning the residual skin. The amount of Dicaprylyl Ether in a filter placed under the skin was measured. Mass recovery was used to determine the mass balance and local distribution of Dicaprylyl Ether in the different skin compartments by ascertaining the total mass of Dicaprylyl Ether on the skin surface, in the stratum corneum, epidermis/dermis, and the used filter at the end of the study versus the applied amount of Dicaprylyl Ether in the test item at the start of the study. The mean recovery of Dicaprylyl Ether from the skin surface ranged from 103.90% to 120.51% of the applied dose, and the mean recovery of Dicaprylyl Ether in the first two tape strips and all 18 tape strips was $0.20\% \pm 0.09\%$ and $0.52\% \pm 0.27\%$, respectively. The mean absorbed dose of Dicaprylyl Ether (i.e., amounts found in the viable epidermis, dermis, and filter) was determined to be $0.30\% \pm 0.15\%$.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Toxicokinetic studies were not found in the published literature, and unpublished data were not submitted. However, the following presumptions regarding absorption, distribution, metabolism and excretion are based on physical and chemical properties of Dicaprylyl Ether and Distearyl Ether.

Given that both ingredients have a water solubility < 1 mg/l at 20 °C, low volatility, and a lipophilic character ($\log K_{ow}$ is estimated as 6.94 for Dicaprylyl Ether, and 16.76, for Distearyl Ether), the likelihood of gastrointestinal absorption is unlikely.^{2,3,5} Similarly, both ingredients are not easily soluble in mucus, and do not easily pass through aqueous pores or epithelial barriers.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute toxicity studies summarized below are described in Table 5.

The acute dermal LD₅₀ of both Dicaprylyl Ether and Distearyl Ether was determined to be > 2000 mg/kg, in Wistar and Sprague-Dawley rats, respectively.^{2,3} The acute oral LD₅₀ of Dicaprylyl Ether in Wistar rats was determined to be > 2000 mg/kg,² while the acute oral LD₅₀ of Distearyl Ether was determined to be > 5000 mg/kg in Sprague-Dawley rats.³

Subchronic Toxicity Studies

Oral

Dicaprylyl Ether

In accordance with OECD TG 408, groups of 10 male and 10 female Sprague-Dawley rats were exposed to 0 (controls: sunflower oil), 100 (low), 300 (mid-), or 1000 (high-dose) mg/kg bw/d Dicaprylyl Ether (99.1% pure) in sunflower oil, via gavage, for 90 d, and then killed.^{2,3} Two additional groups of 5 males and 5 females, which were dosed with 0 and 1000 mg/kg bw/d Dicaprylyl Ether during the 90-d period, were used as recovery animals and were observed, without dosing, for 6 wk before being killed (results for recovery animals not provided). No mortality occurred during the study. No treatment-related changes were seen in food consumption and body weight, or in urinalysis, hematological, or clinical chemistry parameters. No treatment related changes in gross pathology (examined in all animal groups) or histopathology (examined in the control and 1000 mg/kg groups) was observed. Treatment with 1000 mg/kg bw/d caused an increase in absolute and relative liver weights, and absolute kidney weight, by up to 280%; however, the increase was considered to be a non-specific adaptive change to the high work load of the liver caused by the high-dose level. Based on these findings, the no-observed-effect-level (NOEL) for liver and kidney weights and organ to body weight ratios was determined to be 300 mg/kg bw/d. The no-observed-adverse-effect-level (NOAEL) was determined to be > 1000 mg/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Dicaprylyl Ether

In accordance with OECD TG 414, groups of 25 gravid female Sprague-Dawley rats were used to evaluate the effects of Dicaprylyl Ether (99.1% pure) upon maternal toxicity, embryonic, and fetal development.^{2,3} Dams were dosed from day 6 to 19 of gestation, via gavage, with 0, 100, 300, or 1000 mg/kg bw/d of Dicaprylyl Ether, in sunflower oil. Body weight, appearance and behavioral changes were examined daily during pregnancy, and dams were killed on day 20 of gestation. No adverse effects on maternal reproductive parameters, body weight and food consumption, and no abnormal post-mortem findings, were observed. No test-item related malformations or changes were observed in fetuses, upon external and internal examination. No microscopic changes were observed in either the liver or kidneys. The NOEL was determined to be ≥ 1000 mg/kg bw/d for maternal and fetal toxicity.

GENOTOXICITY

Details of in vitro genotoxicity studies summarized below are described in Table 6.

In the Ames test, Cetyl Dimethylbutyl Ether and Dicaprylyl Ether, both tested at up to 5000 µg/ml, were not mutagenic.^{2,7} The mutagenicity of Dicaprylyl Ether (99% pure) was evaluated using Chinese hamster lung fibroblast (V79) cell lines, in accordance with OECD TG 473, at concentrations of up to 10 µg/ml, in 2 separate chromosome aberration tests.^{2,3} No positive increases in the mean number of revertants per plate were observed, either in the presence or absence of metabolic activation. In a mammalian cell gene mutation test, mouse lymphoma L5178Y cells were tested at concentrations of 1.56 – 25 µg/ml Dicaprylyl Ether.² The test article was not genotoxic, in the presence or absence of metabolic activation; cytotoxicity was observed at the highest concentration. Distearyl Ether, tested at up to 150 and 500 µl/plate in 2 bacterial reverse mutation assays, using *S. typhimurium* strains and *E. coli* WP2 uvr A, was not genotoxic, in the presence or absence of metabolic activation.³

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION

Details of dermal irritation and sensitization summarized below are described in Table 7.

A semi-occlusive application of 0.5 ml undiluted Dicaprylyl Ether was applied to 3 New Zealand white rabbits for 4 h; mild edema and erythema disappeared by day 21.² In a maximization test using 20 female Pirbright Dunkin-Hartley guinea pigs, a 2% intracutaneous, followed by a 10% epicutaneous, administration of Dicaprylyl Ether (in paraffin oil) was made during induction.² An initial challenge application of 5% Dicaprylyl Ether, followed by a 2nd challenge application of 3% Dicaprylyl Ether, (both in paraffin oil) were then made for 24 h. Of the 20 test animals, 14 and 9 animals had positive reactions at 24 and 48 h after the 1st challenge, respectively, while 10 and 3 test animals had positive reactions at 24 and 48 h after the 2nd challenge. All 10 negative controls had positive reactions 24 h following the 1st challenge, while 5 controls had positive reactions at 48 h; 3 and 1 controls had positive reactions at both time points following the 2nd challenge. The observed reactions were attributed to irritation and no distinct dermal effects were observed after re-challenge; the test article was considered non-sensitizing. Distearyl Ether was applied to 3 male New Zealand white rabbits in a single application of 0.5 g, under a semi-occlusive patch for 4 h; the test article was deemed non-irritating.³ In a Buehler test, 0.5 ml of 50% Distearyl Ether (in mineral oil) was applied during induction to 20 female Hartley guinea pigs, while challenge applications of 0.5 ml, 20% and 50% Distearyl Ether were made for 6 h under occlusion; the test article was a non-sensitizer.³

No dermal irritation or sensitization was observed in 99 subjects tested with an occlusive application of a leave-on product containing 19.3% Cetyl Dimethylbutyl Ether for 24 h.⁷ No dermal irritation was observed in 11 subjects tested with a 48-h, single patch, occlusive application of a suntan oil containing 15% Dicaprylyl Ether.¹¹ Dicaprylyl Ether, tested undiluted and at 50% in 2-hexyl decanol, caused “single occurrences of slight erythema” in 8 and 2 subjects, respectively, when reactions were scored following a 4-h occlusive patch in 19 subjects.² An overall irritation score of 1.39 was fully reversible within 72 h. A leave-on, face care formulation containing 38.6% Dicaprylyl Ether was not sensitizing when tested, undiluted, in an human repeated insult patch test (HRIPT) of 107 subjects.¹² A shampoo formulation containing 1.5% Distearyl Ether was tested in an occlusive HRIPT of 108 subjects at a concentration of 1%, in water.¹³ Thirty-six subjects experienced weak erythematous reactions during induction, with only 1 of these subjects exhibiting a similar reaction in the challenge phase; the test article was considered non-sensitizing.

OCULAR IRRITATION STUDIES

Animal

Dicaprylyl Ether

The ocular irritation potential of Dicaprylyl Ether (> 99.9% pure) was evaluated in the eyes of 3 Kleinrussen rabbits, in accordance with OECD TG 405.² An undiluted dose of 0.1 ml Dicaprylyl Ether was instilled into the eye for 24 h, with the contralateral eye as the control. The treated eyes were scored at 24, 48, and 72 h after application. The average conjunctival erythema and edema scores were 0.33 and 0.11, respectively; the conjunctiva reactions reversed completely within 72 h. The test article was deemed slightly irritating.

Distearyl Ether

The ocular irritation potential of Distearyl Ether was evaluated in the eyes of 3 female New Zealand white rabbits, in accordance to OECD TG 405.³ Each rabbit received a 0.1 g dose of the undiluted test article instilled into the conjunctival sac of one eye, while the other eye remained untreated and served as the corresponding control for each animal. Test and control eyes were examined for signs of irritation for up to 72 h following dosing. After 1 h, an outbreak of diffuse purple enanthemae with lacrimations was observed in all animals. Slight redness (mean conjunctivae score of 0.3, out of a

maximum score of 3) remained visible in all animals after 24 h, which resolved within 48 h. Slight chemosis was observed in one animal (score 0.3), which was also reversible within 48 h. The test item was considered non-irritating to rabbit eyes.

SUMMARY

According to the *Dictionary*, the 8 fatty ethers included in this safety assessment are reported to function in cosmetics as skin conditioning agents. According to 2022 VCRP data and a 2019 Council survey, Dicaprylyl Ether is reported to be used in 255 formulations at a maximum concentration of 25% in body and hand products, which is the highest reported concentration of use for the fatty ethers.

In an in vitro study, the dermal penetration of Dicaprylyl Ether was measured using full-thickness human abdominal skin samples. Undiluted test article (30 µl) was first applied for 24 h to skin sections in diffusion cells; the amount that remained at the skin surface was then determined by washing with methanol, and the content in the upper layers of the skin was determined via tape stripping. The mean recovery of Dicaprylyl Ether from the skin surface ranged from 103.90% to 120.51% of the applied dose, and the mean recovery of Dicaprylyl Ether in the first two tape strips and all 18 tape strips was 0.20 % ± 0.09% and 0.52 % ± 0.27 %, respectively. The mean absorbed dose of Dicaprylyl Ether was determined to be 0.30 % ± 0.15%.

The acute dermal LD₅₀s of Dicaprylyl Ether and Distearyl Ether were determined to be > 2000 mg/kg bw in Wistar and Sprague-Dawley rats, respectively. The acute oral LD₅₀ of Dicaprylyl Ether was determined to be > 2000 mg/kg in Wistar rats, while the acute oral LD₅₀ of Distearyl Ether was determined to be > 5000 mg/kg in Sprague-Dawley rats.

In an oral study, groups of 10 male and 10 female Sprague-Dawley rats received 0, 100, 300, or 1000 mg/kg bw/d Dicaprylyl Ether via gavage for 90 d and were necropsied. Two additional groups of 5 males and 5 females, dosed with 0 and 1000 mg/kg bw/d during the original 90-d period, were observed as recovery animals for an additional 6 wk, and were killed (recovery animal results not provided). No mortality occurred during the study and no treatment-related effects were seen in the animals; the NOEL for liver and kidney weights was determined to be 300 mg/kg bw/d and the NOAEL was determined to > 1000 mg/kg bw/d.

In a developmental toxicity study, groups of 25 gravid female Sprague-Dawley rats were dosed with up to 1000 mg/kg bw/d of Dicaprylyl Ether, via gavage, from days 6 to 19 of gestation. Dams were killed on day 20 of gestation. No adverse effects on maternal reproductive parameters, or post-mortem findings for dams and the fetuses were observed; the NOEL was determined to be ≥ 1000 mg/kg bw/d for both maternal and fetal toxicity.

Cetyl Dimethylbutyl Ether and Dicaprylyl Ether were not mutagenic in the Ames test when tested at up to 5000 µg/l in *S. typhimurium* and *E.coli* WP2 uvr A strains, with or without metabolic activation. Dicaprylyl Ether was not mutagenic when tested using Chinese hamster lung fibroblast cell lines at up to 10 µg/ml in two separate chromosome aberration tests. In a gene mutation test, Dicaprylyl Ether tested at up to 25 µg/ml in mouse lymphoma L5178Y cells was not genotoxic; cytotoxicity was observed at the highest concentration. Distearyl Ether was not genotoxic, when tested at up to 150 and 500 µl/plate in two bacterial reverse mutation assays using *S.typhimurium* and *E.coli* WP2 uvr A strains.

In a dermal irritation test using New Zealand white rabbits, a semi-occlusive application of 0.5 ml undiluted Dicaprylyl Ether produced mild edema and erythema reactions within 72 h after exposure; the reactions resolved within 21 d. An initial challenge application of 5% Dicaprylyl Ether, followed by a 3% Dicaprylyl Ether re-challenge, was applied to Pirbright Dunkin-Hartley guinea pigs for 24 h in a guinea pig maximization test. Positive reactions were observed in both test and negative control animals at 24 and 48 h following the 1st and 2nd challenge applications; these reactions were attributed to irritation, and no distinct dermal effects were observed after re-challenge. The test article was considered non-sensitizing. Distearyl Ether, at a dose of 0.5 g, did not cause dermal irritation when applied semi-occlusively to New Zealand white rabbits for 4 h; 20% and 50% Distearyl Ether was also non-sensitizing when applied to Hartley guinea pigs for 6 h, occlusively, in a Buehler test. No dermal irritation was observed in a 24-h occlusive patch test of 99 subjects using a leave-on product containing 19.3% Cetyl Dimethylbutyl Ether, or in a 48-h occlusive patch test of 11 subjects using a suntan oil containing 15% Dicaprylyl Ether. Dicaprylyl Ether, undiluted and at 50% in 2-hexyl decanol, caused “single occurrences of slight erythema” in 8 and 2 subjects, respectively, during a 4-h, occlusive patch test of 19 subjects; the overall irritation score of 1.39 was fully reversible within 72 h. An HRIPT was performed in 107 subjects on a face care formulation containing 38.6% Dicaprylyl Ether; no signs of irritation or sensitization were observed. In an HRIPT of 108 subjects, using a 1% aqueous dilution of a shampoo formulation containing 1.5% Distearyl Ether, 36 subjects experienced weak erythematous reactions during induction, with only 1 subject experiencing the same during the challenge phase. The test article was not considered irritating or sensitizing.

Dicaprylyl Ether was deemed slightly irritating to the eyes of Kleinrussen rabbits when instilled at an undiluted dose of 0.1 ml for 24 h. The average conjunctival erythema and edema scores were 0.33 and 0.11, respectively; the conjunctiva reactions reversed completely within 72 h. Distearyl Ether was instilled at a 0.1 g dose to New Zealand white rabbit eyes and observed for up to 72 h for eye irritation. Redness in all animal eyes, chemosis in 1 animal, and an average conjunctiva score of 0.3 (maximum score of 3) were fully reversible within 48 h. The test article was deemed non-irritating.

DRAFT DISCUSSION

[Note: This Discussion is in draft form, and changes will be made following the Panel meeting.]

This assessment reviews the safety of 8 fatty ether ingredients, as used in cosmetic formulations. The Panel concluded [TBD].

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients; for example, Dicaprylyl Ether is reported to be used at 10% in pump hair spray products and Dicaprylyl Ether has reported use in 2 face powder formulations (concentration not reported). 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. As indicated in the respiratory exposure resource document and in the Cosmetic Use section of this report, airbrush application of cosmetic products is not assessed by the Panel. 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>.

CONCLUSION

To be determined.

TABLES**Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.**^{1, CIR Staff}

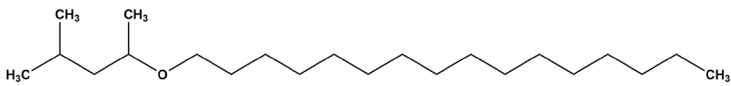
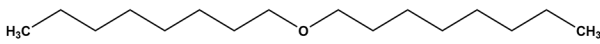
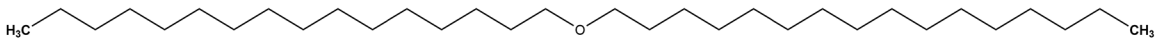
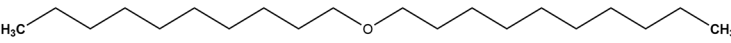
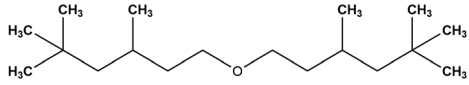
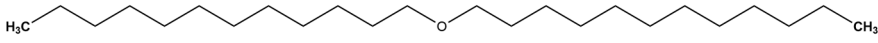
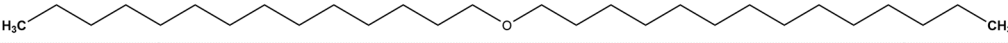
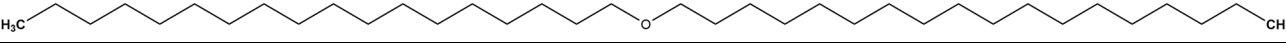
Ingredient/ CAS No.	Definition	Function(s)
Cetyl Dimethylbutyl Ether 185143-68-4	Cetyl Dimethylbutyl Ether is the organic compound that conforms to the structure:	Skin-Conditioning Agents- Miscellaneous
		
Dicaprylyl Ether 629-82-3	Dicaprylyl Ether is the ether that conforms to the structure:	Skin-Conditioning Agents- Emollient
		
Dicetyl Ether 4113-12-6	Dicetyl Ether is the ether that conforms to the structure:	Skin- Conditioning Agents- Occlusive
		
Didecyl Ether 2456-28-2	Didecyl Ether is the organic compound that conforms to the structure:	Skin- Conditioning Agents- Miscellaneous
		
Diisononyl Ether	Diisononyl Ether is the organic compound that conforms to the structure:	Skin-Conditioning Agents- Humectant
		
Dilauryl Ether 4542-57-8	Dilauryl Ether is the organic compound that conforms to the structure:	Skin-Conditioning Agents- Miscellaneous
		
Dimyristyl Ether 5412-98-6	Dimyristyl Ether is the organic compound that conforms to the structure:	Skin-Conditioning Agents - Miscellaneous
		
Distearyl Ether 6297-03-6	Distearyl Ether is the ether that conforms to the structure:	Skin-Conditioning Agents- Occlusive
		

Table 2. Chemical properties

Property	Value	Reference
Cetyl Dimethylbutyl Ether		
Molecular Weight (g/mol)	326.6	14
Topological Polar Surface Area (Å ²)	9.2	14
log K _{ow}	9.74 (estimated)	5
Dicaprylyl Ether		
Physical Form (@ 20 °C & 1013 hPa)	liquid	2
Molecular Weight (g/mol)	242.44	4
Specific gravity (@ 20 °C)	0.807	2
Viscosity (kg/(m x s) @ 20 °C)	0.0037	2
Vapor pressure (mmHg @ 20 °C)	< 0.3	2
Melting Point (°C)	-8	2
Water Solubility (mg/l @ 20 °C)	< 0.1 (estimated)	2
Topological Surface Area (Å ²)	9.2	4
log K _{ow}	6.94 (estimated)	5
Dicetyl Ether		
Molecular Weight (g/mol)	466.9	15
Topological Surface Area (Å ²)	9.2	15
log K _{ow}	14.80 (estimated)	5

Table 2. Chemical properties

Property	Value	Reference
Didecyl Ether		
Molecular Weight (g/mol)	298.5	16
Topological Surface Area (Å ²)	9.2	16
log K _{ow}	8.91 (estimated)	5
Diisononyl Ether		
Molecular Weight (g/mol)	270.5	17
Topological Surface Area (Å ²)	9.2	17
log K _{ow}	7.56 (estimated)	5
Dilauryl Ether		
Molecular Weight (g/mol)	354.7	18
Topological Surface Area (Å ²)	9.2	18
log K _{ow}	10.87 (estimated)	5
Dimyristyl Ether		
Molecular Weight (g/mol)	410.8	19
Topological Surface Area (Å ²)	9.2	19
log K _{ow}	12.84 (estimated)	5
Distearyl Ether		
Physical Form (@ 20 °C & 1013 hPa)	solid	3
Color	yellowish	3
Odor	odorless	3
Molecular Weight (g/mol)	523	3,6
Specific Gravity (@ 20 °C)	0.955	3
Viscosity (kg/(m x s) @ 70 °C)	0.0084	3
Vapor pressure (mmHg @ 20 °C)	0.00000975	3
Melting Point (°C)	-49 to 67	3
Boiling Point (°C)	401	3
Water Solubility (mg/l @ 20 °C)	< 0.05	3
log K _{ow}	16.76 (estimated)	5

Table 3. Frequency (2022)⁸ and concentration (2019)⁹ of use according to duration and exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Cetyl Dimethylbutyl Ether		Dicaprylyl Ether		Distearyl Ether	
Totals*	NR	10 -19.3	255	0.0019 - 25	6	0.05 - 0.23
Duration of Use						
Leave-On	NR	10 -19.3	210	0.005 - 25	2	0.05
Rinse-Off	NR	13.3	44	0.0019 - 14.2	4	0.23
Diluted for (Bath) Use	NR	NR	1	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	7	NR	NR	0.05
Incidental Ingestion	NR	NR	8	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	14; 83 ^a ; 69 ^b	10; 24 ^a	NR	NR
Incidental Inhalation-Powder	NR	NR	2; 69 ^b	2-25 ^c	NR	NR
Dermal Contact	NR	10 - 19.3	213	0.0019 - 25	2	0.05
Deodorant (underarm)	NR	NR	13 ^a	not spray: 10.3	2 ^a	NR
Hair - Non-Coloring	NR	NR	34	0.06 - 24	4	0.23
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	11	NR	NR	NR
Baby Products	NR	NR	NR	0.45	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

^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

NR – not reported

Table 4. Fatty Ether ingredients not reported to be in use^{8,9}

Dicetyl Ether
Didecyl Ether
Diisononyl Ether
Dilauryl Ether
Dimyristyl Ether

Table 5. Acute toxicity studies

Ingredient	Species	No./Group	Vehicle	Dose/Protocol	LD₅₀/Results	Reference
<i>Dermal</i>						
Dicaprylyl Ether, 99.1%	Wistar rats	5/sex	N/A	OECD TG 402. An undiluted, single occlusive application of 2000 mg/kg test substance was made for 24 h. Animals were observed for 14 d and necropsied.	LD ₅₀ > 2000 mg/kg No mortality, significant weight gain or adverse effects were observed.	²
Distearyl Ether, 99.1%	Sprague-Dawley rats	5/sex	N/A	OECD TG 402. An undiluted, single occlusive application of 2000 mg/kg test substance was made for 24 h. Animals were observed for 14 d and necropsied.	LD ₅₀ > 2000 mg/kg No mortality, gross, clinical, or pathological changes occurred.	³
<i>Oral</i>						
Dicaprylyl Ether, >99.9%	Wistar rats	5/sex	arachis oil	OECD TG 401. Animals were administered 2000 mg/kg of the test substance, via gavage. Animals were observed for 14 d and necropsied.	LD ₅₀ > 2000 mg/kg No mortality or adverse effects occurred.	²
Distearyl Ether	Sprague-Dawley rats	5/sex	mineral oil	OECD TG 401. Animals were administered 5000 mg/kg of the test substance, via gavage. Animals were observed for 14 d and necropsied.	LD > 5000 mg/kg No mortality or adverse effects occurred.	³

N/A – not applicable

Table 6. Genotoxicity studies

Test Article	Concentration	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Cetyl Dimethylbutyl Ether	Up to 5000 µg/plate, with or without metabolic activation	NR	<i>Salmonella typhimurium</i> TA98, TA100	Ames test	Not genotoxic	7
Dicaprylyl Ether, (99.9% pure)	Up to 5000 µg/plate, with or without metabolic activation	Tween 80/ distilled water	<i>S. typhimurium</i> strains TA 98, TA 100, TA 1535, TA 1537, TA 1538	OECD 471. Bacterial reverse mutation assay	No reverse mutations were induced, either in the presence or absence of metabolism.	2
Dicaprylyl Ether	Up to 5000 µg/plate, with or without metabolic activation	acetone	<i>Escherichia coli</i> WP2 uvr A	OECD 471. Bacterial reverse mutation assay. In the presence of metabolic activation, 2-aminoanthracene dissolved in DMSO was used as a positive control, while 4-nitroquinoline-N-oxide, dissolved in DMSO was used as a positive control without metabolic activation.	No significant increases in the number of revertants were observed in the presence or absence of metabolism. In a related preincubation assay, a slight increase in back mutations from tryptophan independence was observed, in the absence of metabolic activation. However, these results were not reproducible and were considered biologically irrelevant.	2
Dicaprylyl Ether (99% pure)	2.5, 5, or 10 µg/ml, with or without metabolic activation	acetone	Chinese hamster lung fibroblast cell lines	OECD TG 473. Two separate chromosome aberration tests were performed. Untreated cell lines were used as negative controls and cyclophosphamide and ethylmethanesulphonate were used as positive controls.	No positive increases in the mean number of revertants per plate were observed.	2,3
Dicaprylyl Ether, (99.1% pure)	1.56 – 25 µg/ml, with or without metabolic activation	acetone	Mouse lymphoma L5178Y cell lines	OECD TG 476. Mammalian cell gene mutation test. Two exposure times were employed for the cells cultured without metabolic activation (3 and 24 h). Cells cultured with metabolic activation were exposed for 3 h. Methylmethanesulfonate was used a positive control in the absence of metabolic activation, while methylcholanthrene was used as a positive control in the presence of metabolic activation.	The test article was not genotoxic, in the presence or absence of metabolic activation. Cytotoxicity was observed at the highest dose, immediately after treatment.	2,3
Distearyl Ether (99% pure)	Up to 500 µl/plate (1 st assay) and up to 150 µl/plate (2 nd assay), with or without metabolic activation	tetrahydrofuran	<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537, and <i>E.coli</i> WP2 uvr A	OECD 471. Two separate bacterial reverse mutation assays were performed (all doses were used in triplicates). Appropriate positive controls were used.	The test article was considered non-genotoxic. Precipitate was observed during the 1 st assay, at the 500 µl/plate concentration, which prompted lowering of the concentration in the 2 nd assay.	3

DMSO – dimethyl sulfoxide; NR – not reported

Table 7. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL					
Dicaprylyl Ether (99.9% pure)	0.5 ml, undiluted	3 New Zealand white rabbits	OECD TG 404. A semi-occlusive patch of the undiluted test substance was applied for 4 h to shaved skin, and observed for up to 21 d.	Mean scores of readings taken at 24, 48, and 72 h after exposure, for edema and erythema were 2.3 and 2.7, respectively. Reactions disappeared completely within 21 d.	²
Dicaprylyl Ether (99.9% pure)	2% intracutaneous followed by 10% epicutaneous at induction; 5% and 3% during challenge and re-challenge, respectively; in paraffin oil	20 female Pirbright Dunkin-Hartley guinea pigs; 10 negative controls	OECD TG 406. In a guinea pig maximization test, animals received 2% intracutaneous and 10% epicutaneous administration of Dicaprylyl Ether during induction, in paraffin oil. Challenge applications were made at a concentration of 5% in the vehicle for 24 h. Re-challenge applications were made 24 h after challenge at a concentration of 3%. Reactions were scored 24 and 48 h after challenge.	Of the 20 test animals, 14 had positive reactions at 24 h, while 9 animals had positive reactions at 48 h, following the 1 st challenge. All 10 of the negative control animals had positive reactions, at 24 h following the 1 st challenge, while 5 negative controls had positive reactions at 48 h. For readings following the 2 nd challenge, 10 test animals had positive reactions at 24 h, which reduced to 3 animals at 48 h; 3 and 1 negative control animal had positive reactions at 24 h and 48 h post the 2 nd challenge, respectively. These reactions were attributed to irritation, and following re-challenge no distinct dermal effects were observed. The test article was considered non-sensitizing.	²
Distearyl Ether	0.5 g; in distilled water	3 male New Zealand white rabbits	OECD TG 404. The test article was applied for 4 h to 2.5 cm ² of shaved skin using a semi-occlusive patch. The test sites were washed with distilled water, and observed for up to 14 d following patch removal.	Erythema and edema scores were 0 for all animals.	³
Distearyl Ether	50% at induction; 20% and 50% during challenge; in mineral oil	20 female Hartley guinea pigs; 10 negative controls	OECD TG 406. In a Buehler test, animals were patched with a 4 cm ² cotton pad containing 0.5 ml of 50% test article, in mineral oil, for the topical induction, using an occlusive dressing, for 6 h on days 1, 8, and 15. Challenge consisted of 2 topical applications of 0.5 ml of the test article, diluted at 20% and 50%, each on a 4 cm ² cotton pad, held in place by an occlusive dressing for a 6-h exposure period on day 29. Reactions were scored 24 and 48 h after challenge.	One animal from the treated group died on day 4; the death was unrelated to the test article. All dermal scores were 0.	³
HUMAN					
leave-on formulation containing 19.3% Cetyl Dimethylbutyl Ether	19.3% in a leave-on product	99 subjects	In an HRIPT, the test article was applied via 24-h occlusive patches. No further details were provided.	No dermal irritation or sensitization were observed.	⁷
suntan oil containing 15% Dicaprylyl Ether	0.02 ml; undiluted	11 subjects	An occlusive application was made for 48 h on a 68 mm ² area of the back.	No dermal irritation was observed.	¹¹
Dicaprylyl Ether; 99.9% pure	70 µl; undiluted, and 50% in 2-hexyl decanol	19 subjects	Subjects were treated with the undiluted test substance and with a 50% concentration in 2-hexyl decanol, under occlusion, for 4 h. SDS (2%) was used as a positive control; all subjects were observed 72 h for reactions.	The undiluted test substance caused a "single occurrence of slight erythema" in 8 out of 19 subjects, while the 50% concentration of the test substance caused a "single occurrence of slight erythema" in 2 out of the 19 subjects. SDS caused slight to very strong reactions in 16 out of the 19 subjects. The overall irritation score, of 3 scores taken at 24, 48, and 72 h after exposure, was 1.39, and was fully reversible by the last reading (maximum possible score not provided).	²

Table 7. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
face care formulation containing 38.6% Dicaprylyl Ether	40 µl; applied neat	107 subjects	In an HRIPT (modified Marzulli-Maibach protocol), the test material was applied occlusively, for 48 h, via 9 induction applications made using 8 mm Finn chambers, to a 0.5cm ² area of the upper back, over a 3-wk period. After a 2-wk non-treatment period, a 48-h challenge application was made to the induction site, as well as an untreated site in the same manner as the induction applications. Reactions were scored 15-35 min after patch removal at both induction and challenge phases.	No participants withdrew due to adverse reactions, and the test material did not induce dermal irritation or sensitization.	¹²
shampoo formulation containing 1.5% Distearyl Ether	20 µl; tested at 1% in water	108 subjects	In an HRIPT, the test material was applied occlusively, for 48 to 72 h via 9 induction applications, made using 8 mm Finn chambers, to the upper back, over a 3-wk period. After a 2-wk non-treatment period, a 48-h challenge application was made to the induction site, as well as an untreated site in the same manner as the induction applications. Reactions were scored 15-30 min after patch removal during the induction phase, and from 30 min up to 48 h after patch removal for the challenge phase.	Although 36 subjects experienced weak erythematous reactions during induction, only 1 of these subjects exhibited a weak erythematous reaction during challenge. The test material was considered non-sensitizing.	¹³

SDS – sodium dodecylsulfate

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2022 VCRP Frequency of Use Data – Fatty Ethers

INGREDIENT_NAME	CATEGORY	CPIS_COUNT
Dicaprylyl Ether		
Total Uses: 255		
Dicaprylyl Ether	02A - Bath Oils, Tablets, and Salts	1
Dicaprylyl Ether	03D - Eye Lotion	4
Dicaprylyl Ether	03E - Eye Makeup Remover	1
Dicaprylyl Ether	03G - Other Eye Makeup Preparations	2
Dicaprylyl Ether	04B - Perfumes	6
Dicaprylyl Ether	04E - Other Fragrance Preparation	8
Dicaprylyl Ether	05A - Hair Conditioner	9
Dicaprylyl Ether	05E - Rinses (non-coloring)	1
Dicaprylyl Ether	05F - Shampoos (non-coloring)	18
Dicaprylyl Ether	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
Dicaprylyl Ether	05I - Other Hair Preparations	5
Dicaprylyl Ether	07B - Face Powders	2
Dicaprylyl Ether	07C - Foundations	2
Dicaprylyl Ether	07E - Lipstick	8
Dicaprylyl Ether	10A - Bath Soaps and Detergents	1
Dicaprylyl Ether	10B - Deodorants (underarm)	13
Dicaprylyl Ether	10E - Other Personal Cleanliness Products	1
Dicaprylyl Ether	11E - Shaving Cream	1
Dicaprylyl Ether	11G - Other Shaving Preparation Products	2
Dicaprylyl Ether	12A - Cleansing	8
Dicaprylyl Ether	12B - Depilatories	1
Dicaprylyl Ether	12C - Face and Neck (exc shave)	40
Dicaprylyl Ether	12D - Body and Hand (exc shave)	29
Dicaprylyl Ether	12F - Moisturizing	65
Dicaprylyl Ether	12G - Night	12
Dicaprylyl Ether	12H - Paste Masks (mud packs)	1
Dicaprylyl Ether	12J - Other Skin Care Preps	8
Dicaprylyl Ether	13A - Suntan Gels, Creams, and Liquids	1
Dicaprylyl Ether	13B - Indoor Tanning Preparations	2
Dicaprylyl Ether	13C - Other Suntan Preparations	2
Distearyl Ether		
Total Uses: 6		
Distearyl Ether	05F - Shampoos (non-coloring)	4
Distearyl Ether	10B – Deodorants (underarm)	2