Safety Assessment of Fatty Ethers as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	November 10, 2022
Panel Meeting Date:	December 5-6, 2022

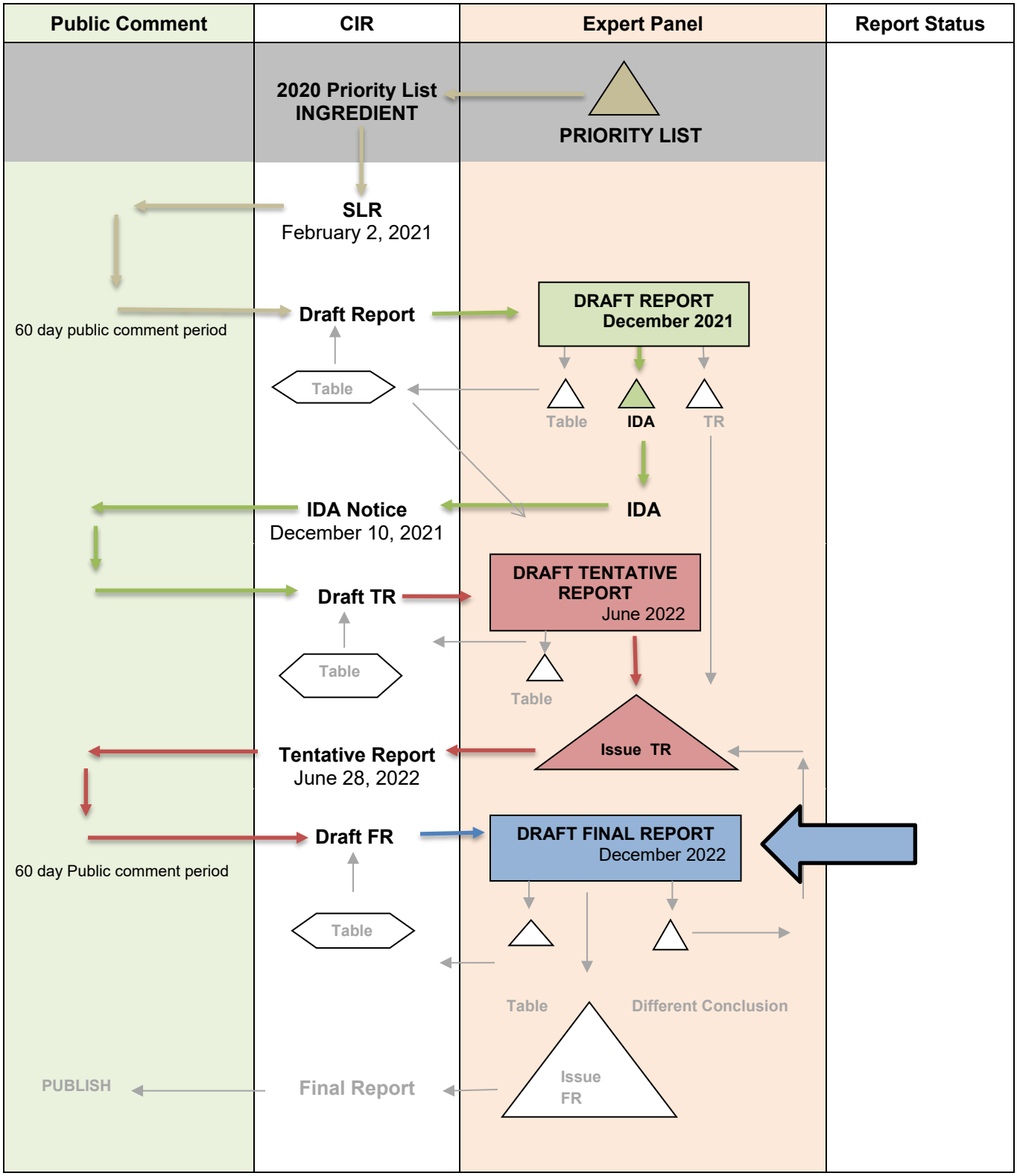
The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; and Ronald C. Shank, 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.

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

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Fatty Ethers

MEETING December 2022



Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst/Writer, CIR

Date: November 10, 2022

Subject: Safety Assessment of Fatty Ethers as Used in Cosmetics

Enclosed is a Draft Final Report of the Safety Assessment of Fatty Ethers as Used in Cosmetics (identified as *report_FattyEthers_122022* in the pdf). This is the third time the Panel is seeing a safety assessment of these 8 cosmetic ingredients. At the June 2022 meeting, a Draft Tentative Report was presented to the Panel. Upon review, the Panel issued a Tentative Report for public comment with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Included in this package, for your review, are a flow chart (*flow_FattyEthers_122022*), literature search strategy (*search_FattyEthers_122022*), ingredient data profile (*dataprofile_FattyEthers_122022*), ingredient history (*history_FattyEthers_122022*), 2022 VCRP data (*VCRP_FattyEthers_122022*), and transcripts from the previous meetings (*transcripts_FattyEthers_122022*).

No data have been submitted since the last review. Comments on the Tentative Report that were received from the Council (*PCPCcomments_FattyEthers_062022*) have been addressed. A comments response checklist is included (*response-PCPCcomments_FattyEthers_062022*).

The Panel should carefully consider the updated data and the Abstract, Discussion, and Conclusion, and be prepared to issue a Final Report.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: July 11, 2022

SUBJECT: Tentative Report: Safety Assessment of Fatty Ethers as Used in Cosmetics (release date: June 28, 2022)

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

Dermal Irritation and Sensitization; Summary; Table 7 – In the human irritation study in which 19 subjects were patched with undiluted and a 50% dilution of Dicaprylyl Ether (reference 2), only one irritation score (1.39) is stated. It should be made clear that this score was for undiluted Dicaprylyl Ether. A score for the 50% dilution was not stated in the reference.

Table 6 – The results column for the bacterial reverse mutation assay of Dicaprylyl Ether (reference 2). States: "No reverse mutations were induced, either in the presence or absence of metabolism". This is misleading as a low number of reverse mutations are observed even in untreated controls. The results section of the study (reference 2) states: "According to the results of the present study, the test substance did not lead to a biologically relevant increase in the number of revertant colonies either without S9 mix or after adding a metabolizing system in several experiments carried out independently of each other (standard plate test and preincubation assay)." Please revise the current statement.

Fatty Ethers - December 5-6, 2022 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: July 11, 2022 (Comments on TR posted on June 28, 2022)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Table 7 - Indicate that the provided irritation score (1.39) is for undiluted Dicaprylyl Ether (score for 50% dilution was not in the reference)	Indicated	
2	Table 6 – Revise statement of 'no reverse mutations were induced' to statement that there "were not any biologically relevant increases in the number of revertant colonies"	Revised	

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 was presented for Panel review. After reviewing the available data, the Panel issued a Tentative Report for public comment with the conclusion that the following 8 ingredients are safe as used in the present practices of use and concentration described in the safety assessment. The Panel discussed the absence of method of manufacturing data for ingredients with the highest reported frequencies of use and noted, however, the data stating that Dicaprylyl Ether and Distearyl Ether were tested at ≥ 99.1% purity. Negative DART data, as well as negative genotoxicity data, a lack of structural alerts, and data demonstrating lack of dermal absorption, mitigated systemic toxicity concerns. Irritation and sensitization study data results further assured the Panel of the dermal safety of these ingredients.

July 2022

Comments on the Tentative Report were received from Council.

December 2022

A Draft Final Report is being presented to the Panel for review.

Fatty Ethers Data Profile* – December 5-6, 2022 – Preethi Raj																															
				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
Cetyl Dimethylbutyl Ether	X	X		X											X						X			X					
Dicaprylyl Ether	X		X	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 10/12/2022

((((((((((((dicaprylyl either) 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 Dimethybutyl 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/oppthpv/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 Dimethyl Butyl 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 Dicaprylyl 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.

Full Panel – December 7, 2021

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?

JUNE 2022 PANEL MEETING -SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – June 16, 2021

DR. BELSITO - OK. Then Fatty Ethers I guess is next. And.

DR. LIEBLER - So this one. I think it's still insufficient for method of I think it's still insufficient for method of manufacture for either the dicaprylyl ether or the distearyl ether. This is one where we needed to draw a line in the sand -- you got to give us one of these. They got a method of manufacture for the cetyl dimethyl butyl, which is hardly used. And the major use ingredients are, you know, are not covered. And Allan and I chatted about this yesterday and we both agreed that the synthesis of these should be relatively straightforward and you know we pointed out this was an insufficiency. We got no response. And this isn't, you know, that this shouldn't be some proprietary magic synthetic method that is, you know, totally unique is probably involves some pretty garden variety chemistry. And what we just don't have a response to this. And I think it remains an insufficiency.

DR. BELSITO - I agree.

DR. RETTIE - Should be simple right? As you say, it's sort of fairly trivial for these symmetrical ethers that the reaction that they probably use and it's different from the one that's reported for the sea tile compound. So be nice to know that.

DR. KLAASSEN - Carol has her hand up.

CAROL EISEMANN (PCPC) - I understand it would be nice to know, but we haven't gotten it and I ask, and in this case though, in the ECHA dossier the purity is listed. So, in other words the materials that were tested were 99.1 or 99.9% pure for both the dicaprylyl or and distearyl ether. So, I don't know why you can't say that your conclusion is for the material as it was tested. Which is that purity.

DR. LIEBLER - Carol, I agree with you about the impurities, but we don't use impure. We don't use purity level to impute a method of manufacture and method of manufacture is one of our criteria and I know that you've asked. I completely trust your ability to pry information out of industry, but we don't have the data despite your request. And so as far as I'm concerned, it's still insufficient.

DR. BELSITO - No, I mean I agree. OK, anyone disagree? Paul?

DR. SNYDER - No, I'm fine. I'm fine. I think we had any submission announcement, we didn't get the data, it still stands.

DR. BELSITO - OK. Very good. So, it's it stays insufficient. And any other discussions on this?

PREETHI RAJ (CIR) - To doctor Belsito, could you clarify what the consensus of your conclusion is?

DR. BELSITO - That the data are insufficient because we don't have method of manufacturing data for either dicaprylyl ether or distearyl ether one or the other.

PREETHI RAJ (CIR) - So is it insufficient for just those two ingredients or the whole group?

DR. BELSITO - Those two ingredients are the lead ingredients for the group, so it's insufficient for the whole group. Right then.

CAROL EISEMANN (PCPC) - But you have method of manufacture for cetyl dimethyl butyl ether and you have data on it so that one should be safe?

DR. RETTIE - Yeah, that is the one we have method of manufacture on.

DR. LIEBLER - Correct.

DR. BELSITO - Did, but did we have use concentrations?

CAROL EISEMANN (PCPC) - Yes, 19.3 and foundation is the maximum use concentration.

DR. LIEBLER - Yeah. We just have a use concentrations couple and no reported uses. So yeah, as far as it goes, we could, you know, we could I mean I think our sense is that the data package for these was probably OK. But we are stuck on this method of manufacture for the two major use ingredients. I don't know that we have. So, we have a HRIPT for 19.2. 3% cetyl dimethyl butyl ether. On PDF 21. In the toxicity, these is, I think these are minimal with high NOELs. No genotox, I mean no genotox or carcinogenicity concerns and I think if we're OK on the skin endpoints, it's just that it's the method of manufacture is the missing piece. This is where I as a chemist have been consistently drawn my line in the sand about this stuff. And I'm not willing to accept the cetyl dimethyl butyl method of manufacturers covering the main ingredients cause it's, I think Allan and I is we discussed it, it's kind of a quirky method of synthesis for the cetyl dimethyl butyl and maybe that's how maybe there's an analogous process for the others, but it's not something that's disclosed to us, and this is just not acceptable.

DR. BELSITO - OK, but Carol's proposing that we go with the a safe as used for dicaprylyl ether and insufficient for the remainder.

DR. LIEBLER - No.

DR. BELSITO - Or method of manufacture of one or the other.

DR. LIEBLER - Yeah, it's it's cetyl dimethyl butyl. That could be safe as used. Because we do have method of manufacture for that, we don't have the impurities, but we do have method of manufacture which I think would probably be fine. You know, we don't have impurities for cetyl dimethyl butyl. It's like we've got method of manufacture for that one. No impurities. And then for the other two we've got impurities. But no method of manufacture.

DR. SNYDER - It's. Is it likely there would be significant differences? Because I mean we have these are not absorbed if I'm not mistaken and we have HRIPT data for the C look, 19 percent is negative. So, I think it kind of clears our major tox concerns with systemic toxicity and--

DR. BELSITO - OK.

DR. SNYDER – sensitization, so. Are we being? You really think that there's a significant difference in the method manufacturer or impurity content because I mean. Yeah, we don't have impurities on all of them anyway. And, so, we're saying.

DR. LIEBLER - This is 1 this is my.

Dr. Klaassen - Well, we know that basically no impurities I say.

Dr. Liebler - All we've had a couple of these in my history on the panel. Where they've just stiffed us on something and I think is important. And I've just sort of decided not for me now. You know there was one where I think I simply would not vote to support it, but it ended up being approved safe as used. You know I'm a big boy. I can take that but this is how I feel about this particular issue. I don't think we should let 'em stiff us.

Dr. Snyder - OK.

Dr. Rettie - And I'm just listening and learning.

Dr. Belsito - OK.

Dr. Belsito - What I'm hearing then, if and correct me if I'm wrong, that we're fine saying cetyl dimethyl butyl ether is safe as used and the others are the remaining are insufficient for method of manufacture specific to the cosmetic ingredient either dicaprylyl ether or distearyl ether. Is that correct?

Dr. Liebler - Right. And I would be happy to settle for one of those.

Dr. Belsito - Right. One of the other.

Dr. Rettie - So Dan, can I ask you if you were looking at let's see what is it? The cetyl dimethyl butyl ether? If that was just a straightforward synthesis that you know this Williamson one that's easier. SN two reaction and that was in there and that had been given, but method of manufacture wasn't there for the other two, but the but you had a different type of method of manufacture. What? What would you be? What would you think about that would, would that be sufficient for you? I'm just trying to get a handle on. How to draw this line?

Dr. Liebler - I guess my concern was really less about the about the synthesis method per se, because that's really a judgment call and more about the fact that the most widely used ingredients which should have relatively straightforward information. I mean, the information about how they're made is available. They're just not giving it. And I just think that that's not, that's not something we should accept.

Dr. Rettie - And because they're the greatest use ingredients in the in the list of three.

Dr. Liebler -

Dr. Rettie - OK.

Dr. Liebler - Uh, which should have relatively straightforward information. I mean, the information about how they're made is available. They're just not giving it. And I just think that that's not, that's not something we should accept.

Dr. Rettie -And because they're the greatest use ingredients in the in the list of three.

Dr. Liebler - Yeah. I mean, it's OK for a lesser use ingredient without method of manufacture to be dragged along in the report by others that are more widely used with which have sufficient information. We do that all the time.

Dr. Rettie - OK. Thanks.

Dr. Klaassen - Allan, I'd like to say that Dan has very strong feelings on this and I'm not against that, although not all of us feel quite at that strongly as Dan does so. That's I kind of leave that up to the chemist to decide, but I mean, if I was doing this chemical all by myself and didn't have to agree with anybody, I would say safe as used. But just to say that, you know, we compromise in these committees, and we don't always agree 100%, even within the one of our committees, so. There are no absolutes except Dan's one absolute that he wants the method of manufacture, and that's OK. I don't fight it.

Dr. Rettie - Yeah. I tend philosophically to agree with Dan. Certainly at this point. But who knows over the years, if I stay on this panel, then maybe things will change. But I'm just trying to get a road map of sorts here.

Dr. Belsito - Right, OK, so cetyl dimethyl butyl ether is safe as used and the others are insufficient for method of manufacturing for either dicaprylyl ether or distearyl ether? Is that OK? Very good.

Dr. Liebler - Yep.

Dr. Belsito - OK. So, then we're moving on to Polyacrylamides.

Preethi Raj (CIR) – To Doctor Belsito, may I ask on since this is a draft tentative, what kind of language would the panel want in the discussion because I noticed there isn't carcinogenicity data for this report and then based on their conclusion you just came to what would you like in the discussion?

Dr. Belsito - Umm.

Dr. Liebler - So there is genotox data and it's the cetyl dimethyl methylbutyl is clean, as is the dicaprylyl ether in a mammalian cell test. In other words, there are negative genotox data.

And that these molecules we've started referring to this, if we've got clean genotox and these lacked any structural alerts for carcinogenicity we don't have a concern about a lack of carcinogenicity studies data.

Preethi Raj (CIR) - OK. Thanks.

Dr. Belsito - And we have, we have DART, Dieter (?) on dicaprylyl ether. I mean, we really have and we have the HRIPT data. I mean I think we really have all the data we need except for what we're asking for. So, I mean in the discussion, I think just point out that there was you know that there was data to support or that I don't know how you want to phrase it. And you're we had DART data. We had negative genotox data to support systemic toxicity because we don't have absorption, right? But I've heard someone say before that they did not feel that this would be absorbed. That's something that's beyond my ability to look at a structure and make a decision on. So that might be something you could all.

Dr. Klaassen - I'm pretty sure we have. I think there is data in the report that is that it was like .3% absorbed or am I getting my chemicals mixed up?

Dr. Liebler - You got right, Curt, on PDF 20.

Dr. Snyder - No, I had. Yeah, I had. Yeah, I head down, not absorbed, so it's not absorbed.

Dr. Liebler - Yeah.

Dr. Belsito - Yeah, the tape stripping. You're right, Kurt. I'm sorry. Yeah -- So, we updated that it's not absorbed, you know, which limits our concern about, you know, systemic topics endpoints and on top of it we had negative dart and we have negative genotox. And we have.

Dr. Liebler - Those are all discussion points.

Dr. Belsito - Yeah, we have. Good. We have data supporting the dermal safety, so.

And we even have ocular irritation studies. So really the only thing we're lacking, I mean the is the method manufacturer. OK.

Dr. Rettie - As so, could I ask a question about, you know what? Might have happened in the past for something like this, where you had a pretty clean looking package, but there was just some piece that was that was messing around method of manufacture. When you issue an IDA and then nothing came back. Perhaps a little surprisingly, because it could have been easy to get. Does anyone remember how that way to go on in the past is it is it probably fairly uncommon thing to issue a second IDA is it?

Dr. Belsito - No, once I mean at this stage this comes back and if we don't have the report.

It would go out as final right Monice?

Monice Fiume (CIR) (CIR) - Right. So, from the IDA it will go out as a tentative report with this insufficient data conclusion. The only time a second IDA is issued is if the needs are changed because the need has to be identified for the report to be insufficient for that reason. So that is the only time a second IDA is issued. So, this goes out as a tentative report as insufficient, and nothing comes in. Then it goes as a final with the insufficient conclusion except for the one ingredient.

Dr. Belsito - And we would see it again? And then I think they're probably have been instances where we don't get the data and then we change our mind at the last minute.

And then it has to go out again as another final.

Monice Fiume (CIR) - Well, and that would a lot of times, yes. But if it becomes less restrictive, it can go forward as a final.

Dr. Belsito - That's right.

Dr. Snyder - So Allan, part of this process will also be determined by the discussions tomorrow, because we're only one half of the decision. So, so Allan may or Ron Shank may want to go out in flames. So, he may he may burn down on the way out. We don't know. We'll see.

Dr. Belsito - No.

Dr. Rettie - Right.

Dr. Liebler - You would you would love that.

Dr. Klaassen - And vice versa.

Dr. Liebler - Right.

Dr. Belsito - OK, so I think we've beaten this down. So now we're moving on to polyacrylamide which is a re review. And I don't think we need to reopen this, we just need to add our new respiratory boiler plate.

DR. COHEN - OK. Can we move on to fatty ethers? OK so, we've reviewed this in December, we issued an IDA for method of manufacturing for the dicaprylyl ether and the distearyl ether. Hold on.

DR. BERGFELD - Nothing was received.

DR. COHEN - I don't know. Yeah. Nothing was received. I want to recap by indicating when we went out to the last meeting that this group came out with safe as used. And the Belsito group wanted some more information. About the method of manufacturing.

DR. ROSS - I think the you when I read it was sorry. Go ahead Ron.

DR. SHANK - Well, if we if we. If we assume the method of manufacture is similar to that stated for cetyl dimethyl butyl ether. And I don't think we need it for everything. And we were right. All of them are safe as used. There's going to be little penetration of the stratum corneum. We have data like that for dicaprylyl ether page 19. The toxicity test show a little toxicity. So, we can read across the other ingredients, assuming the method of manufacture is the same as cetyl dimethyl butyl. So, all are safe. Which is where we were.

DR. COHEN - The first time.

DR. SHANK - In March.

DR. ROSS - Yeah, they absorption with *(inaudiable), as you said, David, for the two methods of manufacture. You didn't get it. So, the question is what do you do now? And that was my question.

DR. COHEN - Well, the, I think we've some of the question has partially been answered is there sufficient comfort with the data we have for method of manufacturing for cetyl dimethyl butyl ether. That we couldn't move ahead because the rest of the data is reassuring. And I guess the question back to you, David, is, is there anything in the chemistry here that you might suspect? That knowing more method of manufacturing would raise concerns about impurities or toxicities from that?

DR. SLAGA - Not for me. I didn't have any further concerns.

DR. ROSS - Certainly looks.

DR. SLAGA - I agree with Ron. I think there is a degree of we have enough method of manufacturing from another similar compound that I think that we could use that.

DR. ROSS - I think the only concern Tom was that the two were the most frequent in use, right?

DR. COHEN - Yes.

DR. ROSS - And I think the common in the transcript that I read was that. You know the method of manufacture for the most common to should be very easy to get. And that was in the transcript.

DR. COHEN - Yeah, Dan. Dan brought that up.

DR. ROSS - Yeah, maybe true. What Ron says, you might be able to.

DR. SLAGA - Yeah.

DR. ROSS - Read across but seems to me that probably still needed if they're the most frequently ones you.

DR. COHEN - It should be easy to get cause it's use far exceeds a lot of the others and this is a this is a tentative report. So, we can go out. Listen, this is going to be presented first by the Belsito team who brought up this specific issue, Dan articulated it. I think the team in general's comfortable with safe as used if there's a greater discussion about additional needs from method of manufacturing we could flex with that discussion because we're not at a final report yet. I wouldn't want to go to a split conclusion if we didn't have this further on and maybe it lights a fire.

DR. SLAGA - Right.

DR. COHEN - Under some of the manufacturers to get this in or not. Is that OK?

DR. SLAGA - Yeah.

DR. ROSS - Yeah, it works for me.

DR. BERGFELD - So you actually have two issues.

DR. ROSS - 2.

DR. BERGFELD - Uh, the first one being. You asked that you didn't get and it's easy to get and the 2nd is there read across.

DR. COHEN - We didn't answer the second question.

DR. BERGFELD - I mean, I mean.

DR. ROSS - I'm not good manufacturing that we haven't answered.

DR. BERGFELD - Well, you were going to piggyback. On the other ingredient.

DR. SLAGA - Right.

DR. COHEN - We we're comfortable. Yeah, I, retract that. We were comfortable reading across with the method of manufacturing because of the similarities to the other ones.

DR. BERGFELD - I think in the presentation that has to be stated.

DR. COHEN - Will do.

DR. BERGFELD - OK.

DR. COHEN - I'm just taking notes. Hold on.

DR. BERGFELD - Glad to see you're writing them. I do write myself.

DR. COHEN - Ohh no. I yeah. And then I have to sit with this afterwards and organize it for the another several hours. OK. Any other comments on Fatty ethers?

PREETHI RAJ (CIR) - Umm, so Doctor Cohen could clarify your vision once again.

DR. ROSS - The better chance verify your then once again.

DR. COHEN - Uh, yeah, I'm sorry, Preethi. I couldn't hear you.

PREETHI RAJ (CIR) - I just would like to hear your conclusion once again.

DR. COHEN - OK.

PREETHI RAJ (CIR) - Yeah, please.

DR. COHEN - I it team, is it safe for us to go with safe as used? As we originally came out last time. Ron, Tom, David. We're going to affirm our original safe as used and.

DR. SLAGA - Right.

DR. COHEN - We will be open to the discussion about the method of manufacturing our thoughts on read across and hear. The Belsito team further or deeper or lesser concerns about it.

DR. BERGFELD - Sounds good.

DR. COHEN - Yeah, I mean. The full team meetings are I think are for us to talk through things, not just to I have a whose will is stronger to get a point across, right? So, I think we do get to do that and we should do it particularly in this situation.

PREETHI RAJ (CIR) - Thank you.

Full Panel – June 17, 2022

Dr. Bergfeld - All right, we're going to call the question all those opposing a split decision on this ingredient. Abstaining. Unanimous approval of this ingredient as it stands. Thank you. All right. We're moving on to the next set of ingredients called reports Advancing. The first is Fatty ethers. Doctor Belsito.

Dr. Belsito - So this is the second time we're looking at this safety assessment of these eight cosmetic products and the December meeting we had a draft report and on review we issued an IDA for method of manufacture specific to cosmetic ingredient production for *(Inaudiable) ether and sterile ether. We didn't receive the data. We did get updated VCRP data from the FDA which was incorporated nothing really major there. And, so, we took another good look at this. And after reviewing all the material we had, we felt that cetyl dimethyl butyl ether was safe as used and the others were insufficient for method of manufacturing.

Dr. Cohen – So, but--

Dr. Bergfeld - I'm sorry, Don. That was a motion?

Dr. Belsito - That was my motion, yes.

Dr. Bergfeld - Yeah.

Dr. Cohen - Before, before I second, we discussed the method of manufacturing with the cetyl dimethyl butyl ether. And the panel thought maybe we could read across. And give the safe as used and we would we wanted to have further discussion with your team over that.

Dr. Belsito - OK. Well, Dan was the most vehement about not letting that pass. So, I'll let him comment.

Dr. Liebler - Well, you guys have people have served with me on the panel, know that I've been a stickler about this issue when we've got nothing on method of manufacture for the major ingredients in use. We can't let 'em get away with that. And it when this I made this point when this report was at it in his draft stage, now we've got it, a tentative stage. And we didn't get a response. Sometimes we've held out and gotten a response, you know, on the in the last in the last home stretch but Alan and I have had a little bit of a dialogue about this and I invite Alan to air his comments here because I think it's worth sharing with the panel so.

Dr. Rettie - Yes. So, Don and I talked a little bit about this last night and I hear Dan's line in the sand. And I guess I'm learning as I go here. And philosophically and the agreement with that and that's what I said, yes. It was kind of. I was kind of wavering a little bit. Because I could see on their chemistry. That uh, while we didn't have method of manufacture, it's kind of an older one for making these ethers. So, wouldn't you agree, Dave?

Dr. Ross - Yeah.

Dr. Rettie - And then reading across, I mean I'm sure you could probably end up making them both the same way, but my gut feeling was that they weren't, so that's why I was mostly in line with Dan. But then thinking more about it and reading the paragraph, it tells us that the major ingredients of purities in excess of 99%. So, I kind of started the wonder, what does it matter how they made it, even if it was a different way around? If you have that high degree of. Purity. So those that was my only comment.

Dr. Liebler - So I can, having heard that and then slept on it, I woke up this morning and I realized, you know, when you say you draw a line in the sand, the virtue of that is that you draw the line in sand, not is a rock. So, having said that, I think I'm amenable to removing my objection to this, and I realize I'm the one who's been driving it. So, Don, I don't mean to ambush you with this, but.

Dr. Belsito - Dan you don't ambush me. You just continue to surprise me.

Dr. Liebler - Yeah.

Dr. Ross - Dan. Could I just ask you a question that don't know, could it you know this one is it was an interesting one because they're using a hydrogenation catalyst in the synthesis and you know, so if you're using read across, I mean do you think there would always use the hydrogenation catalysts?

Dr. Liebler - There are, you know, it would be a prelim question for early organic students there a dozen ways you could make these ethers. And I don't know why they did it that way for the seal, but you know it, I think the key point is there are well established methods for doing this. It's not a mystery. And the purity kind of makes the point. And, so and we do have, you know, we have in the past, accepted method of manufacture for one ingredient that we felt was at least a reasonably representative of the group to cover for that. So, you know, I felt like I felt that. Yeah, you know. That we could I could. Let the water wash over my line in the sand.

Dr. Belsito – So, you would have to put in the discussion that we were although we lack method of manufacturing for the two, those prominently used members of this group, we were provided with data that the product, the ingredient itself, was quite pure or something to that extent.

Dr. Liebler - Yeah.

Dr. Belsito - That we were assured by the purity of the file ingredient used in cosmetic preparations. So, we'll have to tweak the discussion a little bit.

Dr. Bergfeld - So Don is.

Dr. Cohen - Don.

Dr. Bergfeld - Are you restating your conclusion then?

Dr. Belsito - I believe this was David's conclusion.

Dr. Bergfeld - Yeah. OK.

Dr. Cohen - No.

Dr. Bergfeld - Ohh. That's yours.

Dr. Cohen - Now this this is yours, but before you go there.

Dr. Belsito - OK.

Dr. Cohen - Can you just run through for me? What are the consequences or issues of leaving Dan's sand line in it until the next reiteration of this?

Dr. Belsito - Well, this would go out as a tentative final, right, Bart?

Dr. Bergfeld - Yeah.

Dr. Cohen - Yeah.

Dr. Belsito - Yeah. So, if we did that and then it came back in September and we decided to no longer exclude those that we didn't have method of manufacturing and we didn't get it and we decided that all of them could go ahead because of the purity of the two major ones. We would then have to reissue another Tentative report--

Dr. Cohen - Ah. OK.

Dr. Belsito - So we either do it now, or if we change subsequently, we have to look at it again.

Dr. Klaassen - Let's do it now.

Dr. Bergfeld - Alright, this is your ingredient Don.

Dr. Belsito - OK. Yeah. Thought it was David's. So safe as used.

Dr. Cohen - Second.

Dr. Bergfeld - And don't give it your second.

Dr. Cohen - 2nd.

Dr. Bergfeld - Any further, any further comments then?

Dr. Belsito - Again, just in the discussion that despite the fact we lack method of manufacturing, we're assured by the purity of the individual ingredients.

Dr. Bergfeld - That's a good addition and I think that's the first time we've done that. Thank you. I'm going to call the question then those opposing. Abstaining ? Unanimously approved, Thank you very much. Moving on then, from that safe conclusion to the fatty acid Ester end capped alkoxylates Dr Cohen.

Safety Assessment of Fatty Ethers as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: November 10, 2022
Panel Meeting Date: December 5-6, 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.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; and Ronald C. Shank, 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.

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

ABBREVIATIONS

CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMSO	dimethyl sulfoxide
ECHA	European Chemicals Agency
FDA	Food and Drug Administration
HRIPT	human repeated insult patch test
LC-MS	liquid chromatography – mass spectrometry
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

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 that these ingredients are safe in cosmetics in the present practices of use and concentrations described in this safety assessment.

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 (Figure 1).[1] The definitions and structures of all of the ingredients included in this review are provided in Table 1.

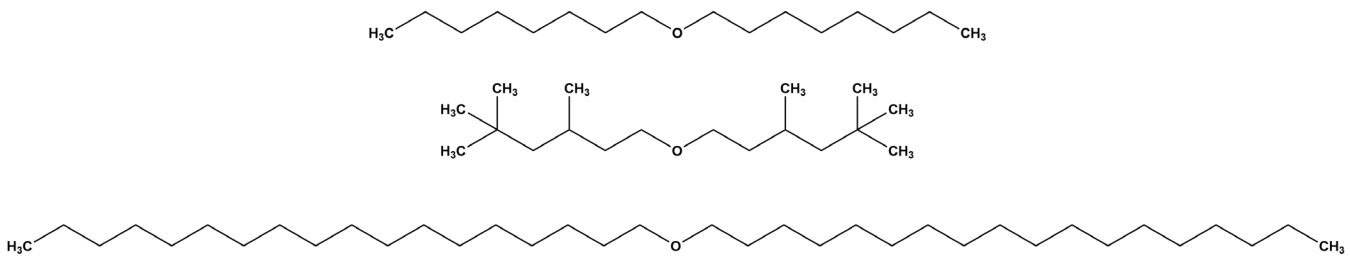


Figure 1. (from top to bottom) Dicaprylyl Ether, Diisononyl Ether, and Distearyl Ether

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.

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. It also has reported use in lipsticks (concentration not reported), which may lead to incidental ingestion and mucous membrane exposure.

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 % ± 0.09% and 0.52 % ± 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 % ± 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 LD_{50} 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 LD_{50} of Dicaprylyl Ether in Wistar rats was determined to be > 2000 mg/kg,[2] while the acute oral LD_{50} 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 STUDIES

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 *Salmonella typhimurium* strains and *Escherichia 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 STUDIES

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 erythemal 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 LD_{50}s of Dicaprylyl Ether and Distearyl Ether were determined to be > 2000 mg/kg bw in Wistar and Sprague-Dawley rats, respectively. The acute oral LD_{50} of Dicaprylyl Ether was determined to be > 2000 mg/kg in Wistar rats, while the acute oral LD_{50} 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 erythemal 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.

DISCUSSION

This assessment reviews the safety of 8 fatty ether ingredients as used in cosmetic formulations. The Panel concluded that these ingredients are safe in cosmetics in the present practices of use and concentrations described in this safety assessment.

The Panel considered the absence of method of manufacturing data for Dicaprylyl Ether and Distearyl Ether, which are the ingredients with the highest reported frequencies of use. The Panel noted, however, that the toxicity studies on Dicaprylyl Ether and Distearyl Ether reported that the purity of the test article was ≥ 99.1%, indicating that the amount of possible impurities was negligible; accordingly, the need for method of manufacture data for these ingredients was mitigated. The Panel also reasoned that these are non-polar molecules with low solubility, and that these ingredients are not expected to absorb into the skin. Additionally, the Panel noted that in oral toxicity studies, the NOAEL (subchronic toxicity study) and NOEL (developmental and reproductive toxicity study) for Dicaprylyl Ether were ≥ 1000 mg/kg bw/d, which was the maximum test dose. Negative genotoxicity data and

a lack of structural alerts mitigated the need for carcinogenicity data. Furthermore, results from irritation and sensitization study data further reassured the Panel of the dermal safety of these ingredients.

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. 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, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 8 fatty ethers are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

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

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.[1, CIR Staff]

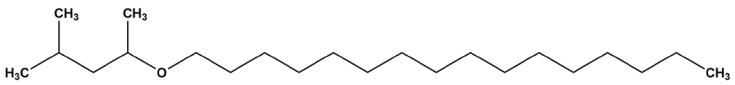
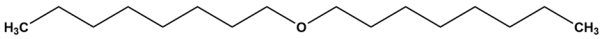
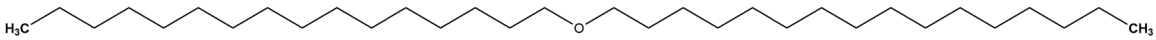
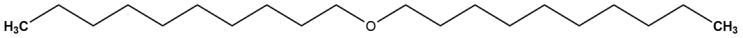
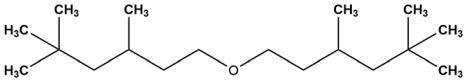
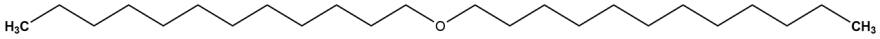
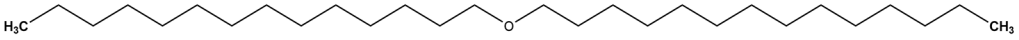
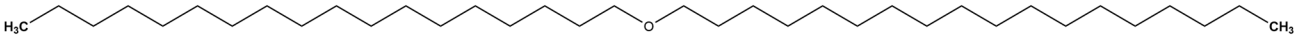
Ingredient/ CAS No.	Definition	Function(s)
Cetyl Dimethylbutyl Ether 185143-68-4	Cetyl Dimethylbutyl Ether is the organic compound that conforms to the structure: 	Skin-Conditioning Agents-Miscellaneous
Dicaprylyl Ether 629-82-3	Dicaprylyl Ether is the ether that conforms to the structure: 	Skin-Conditioning 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 ºC)	0.807	2
Viscosity (kg/(m x s) @ 20 ºC)	0.0037	2
Vapor pressure (mmHg @ 20 ºC)	< 0.3	2
Melting Point (ºC)	-8	2
Water Solubility (mg/l @ 20 ºC)	< 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

Table 2. Chemical properties

Property	Value	Reference
log K_{ow}	14.80 (estimated)	[5]
	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 ºC)	0.955	[3]
Viscosity (kg/(m x s) @ 70 ºC)	0.0084	[3]
Vapor pressure (mmHg @ 20 ºC)	0.00000975	[3]
Melting Point (ºC)	-49 to 67	[3]
Boiling Point (ºC)	401	[3]
Water Solubility (mg/l @ 20 ºC)	< 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	LD_{50}/Results	Reference
			Dermal			
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]
			Oral			
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	*Salmonella typhimurium* 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	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538	OECD 471. Bacterial reverse mutation assay	The test substance did not lead to a biologically relevant increase in the number of revertant colonies, either in the presence or absence of metabolism.	[2]
Dicaprylyl Ether	Up to 5000 µg/plate, with or without metabolic activation	acetone	*Escherichia coli* 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 (1st assay) and up to 150 µl/plate (2nd assay), with or without metabolic activation	tetrahydro-furan	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E.coli* 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 1st assay, at the 500 µl/plate concentration, which prompted lowering of the concentration in the 2nd 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 1st challenge. All 10 of the negative control animals had positive reactions, at 24 h following the 1st challenge, while 5 negative controls had positive reactions at 48 h. For readings following the 2nd 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 2nd 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 for the undiluted test substance 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 erythemal reactions during induction, only 1 of these subjects exhibited a weak erythemal reaction during challenge. The test material was considered non-sensitizing.	[13]

SDS – sodium dodecylsulfate

REFERENCES

1. Nikitakis J., Kowcz A. Web-based International Cosmetic Ingredient Dictionary and Handbook (wINCI Dictionary). http://webdictionary.personalcarecouncil.org/jsp/IngredientSearchPage.jsp. Last Updated: 2022. Accessed: May 2, 2022.

2. European Chemical Agency (ECHA). REACH registration dossier: Dioctyl ether (CAS No. 629-82-3; INCI name, Dicaprylyl Ether). https://echa.europa.eu/registration-dossier/-/registered-dossier/2013/1. Last Updated: June 30, 2021. Accessed: May 2, 2022.

3. European Chemical Agency (ECHA). REACH registration dossier: Dioctadecyl ether (CAS No. 6297-03-6; INCI name, Distearyl Ether). https://echa.europa.eu/registration-dossier/-/registered-dossier/10944/1. Last Updated: November 21, 2017. Accessed: May 2, 2022.

4. National Center for Biotechnology Information. PubChem Database CID= 12399. https://pubchem.ncbi.nlm.nih.gov/compound/Dioctyl-ether. U.S. National Library of Medicine. Last Updated: April 29, 2022. Accessed: May 2, 2022.

5. EPI Suite (for Windows)., Environmental Protection Agency. 4.0. Washington, DC.: 2012.

6. National Center for Biotechnology Information. PubChem Database CID= 80526. https://pubchem.ncbi.nlm.nih.gov/compound/Dioctadecyl-ether. U.S. National Library of Medicine. Last Updated: April 29, 2022. Accessed: May 2, 2022.

7. Anonymous. 2021. Summary information Cetyl Dimethylbutyl Ether. (Unpublished data submitted by Personal Care Products Council on April 12, 2021.)

8. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). 2022. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients (VCRP). (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2022; received January 11, 2022.)

9. Personal Care Products Council. 2019. Concentration of Use by FDA Product Category: Dialkyl Ethers. (Unpublished data submitted by Personal Care Products Council on July 24, 2019.)

10. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated: 2020. Accessed: November 02, 2020.

11. Anonymous. 2009. Assessment of skin tolerance of a cosmetic product after single application under occluded patch during 48 hours on 11 volunteers (suntan oil containing 15% Dicaprylyl Ether). (Unpublished data submitted by Personal Care Products Council on February 22, 2021.)

12. Anonymous. 2018. Modified Marzulli-Maibach protocol human repeat insult patch test with challenge (product contains 38.6% Dicaprylyl Ether). (Unpublished data submitted by Personal Care Products Council on February 23, 2021.)

13. Anonymous. 2006. Human repeat insult patch test with challenge (product contains 1.5% Distearyl Ether). (Unpublished work submitted by the Personal Care Products Council on February 23, 2021.)

14. National Center for Biotechnology Information. PubChem Database CID= 9883836. https://pubchem.ncbi.nlm.nih.gov/compound/Cetyl-dimethylbutyl-ether. U.S. National Library of Medicine. Last Updated: April 29, 2022. Accessed: May 2, 2022.

15. National Center for Biotechnology Information. PubChem Database CID= 77757. https://pubchem.ncbi.nlm.nih.gov/compound/Dihexadecyl-ether. U.S. National Library of Medicine. Last Updated: April 29, 2022. Accessed: May 2, 2022.

16. National Center for Biotechnology Information. PubChem Database CID= 17152. https://pubchem.ncbi.nlm.nih.gov/compound/Decyl-ether. U.S. National Library of Medicine. Last Updated: April 29, 2022. Accessed: May 2, 2022.

17. National Center for Biotechnology Information. PubChem Database CID= 13603457. https://pubchem.ncbi.nlm.nih.gov/compound/Diisononyl-ether. U.S. National Library of Medicine. Last Updated: April 29, 2022. Accessed: May 2. 2022.

18. National Center for Biotechnology Information. PubChem Database CID= 20667. https://pubchem.ncbi.nlm.nih.gov/compound/Dodecyl-ether. U.S. National Library of Medicine. Last Updated: April 29, 2022. Accessed: May 2, 2022.

19. National Center for Biotechnology Information. PubChem Database CID= 79433. https://pubchem.ncbi.nlm.nih.gov/compound/Tetradecyl-ether. U.S. National Library of Medicine. Last Updated: April 29, 2022. Accessed: May 2, 2022.

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