Safety Assessment of Fatty Ethers as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (i.e., August 27,2022) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to the Cosmetic Ingredient Review (CIR) will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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

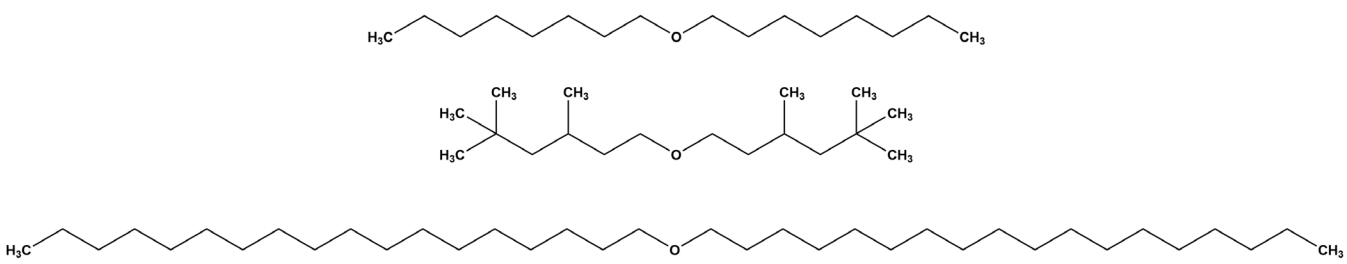


Figure 1. (from top to bottom) Dicaprylyl Ether, Diisononyl Ether, and Distearyl Ether

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, and has reported use in lipsticks (concentration not reported) which may lead to incidental ingestion.

Some of these ingredients are reported to be used in cosmetic spray formulations and could possibly be inhaled; for example, Dicaprylyl Ether is reported to be used at 10% in pump hair spray products and Dicaprylyl Ether has reported use in 2 face powder formulations (concentration not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e. they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

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

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

Non-Cosmetic

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

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Dicaprylyl Ether

Dermal penetration of Dicaprylyl Ether (99.1% pure) was examined in vitro, in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 428, using full-thickness human abdominal skin samples from 3 donors, in duplicate (n = 6).[2,3] The Dicaprylyl Ether content in the test article was determined prior to the study by liquid chromatography- mass spectrometry (LC-MS); methanol was used as the extraction medium. The content of Dicaprylyl Ether in the test solution was determined to be 108.0 %. Undiluted test article (30 µl) was then applied for 24 h to skin sections in diffusion cells. (Details regarding the diffusion cell portion of the experiment were not provided.) Subsequently, the remaining Dicaprylyl Ether content at the skin surface was determined by first removing the residual emollient by washing using the extraction medium, followed by tape-stripping the corneous layer and cryo-sectioning the residual skin. The amount of Dicaprylyl Ether in a filter placed under the skin was measured. Mass recovery was used to determine the mass balance and local distribution of Dicaprylyl Ether in the different skin compartments by ascertaining the total mass of Dicaprylyl Ether on the skin surface, in the stratum corneum, epidermis/dermis, and the used filter at the end of the study versus the applied amount of Dicaprylyl Ether in the test item at the start of the study. The mean recovery of Dicaprylyl Ether from the skin surface ranged from 103.90% to 120.51% of the applied dose, and the mean recovery of Dicaprylyl Ether in the first two tape strips and all 18 tape strips was 0.20 % ± 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 $\geq$ 99.1%, indicating that there should be no impurities of concern; 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) values for Dicaprylyl Ether were $\geq$ 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]

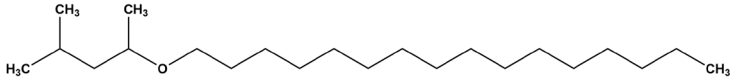
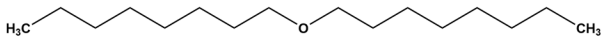
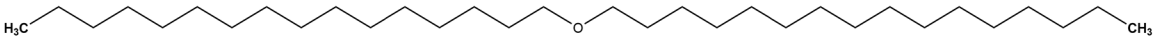
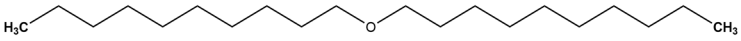
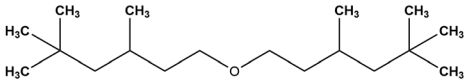
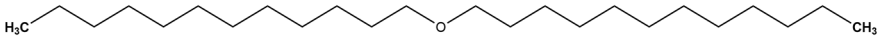
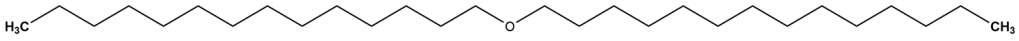
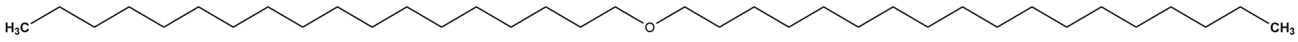
Ingredient/ CAS No.	Definition	Function(s)
Cetyl Dimethylbutyl Ether 185143-68-4	Cetyl Dimethylbutyl Ether is the organic compound that conforms to the structure: 	Skin-Conditioning Agents-Miscellaneous
Dicaprylyl Ether 629-82-3	Dicaprylyl Ether is the ether that conforms to the structure: 	Skin-Conditioning 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	No reverse mutations were induced, either in the presence or absence of metabolism.	[2]
Dicaprylyl Ether	Up to 5000 µg/plate, with or without metabolic activation	acetone	*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. Methyl-methanesulfonate 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, 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

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