Safety Assessment of Fatty Ethers as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	November 10, 2021
Panel Meeting Date:	December 6-7, 2021

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

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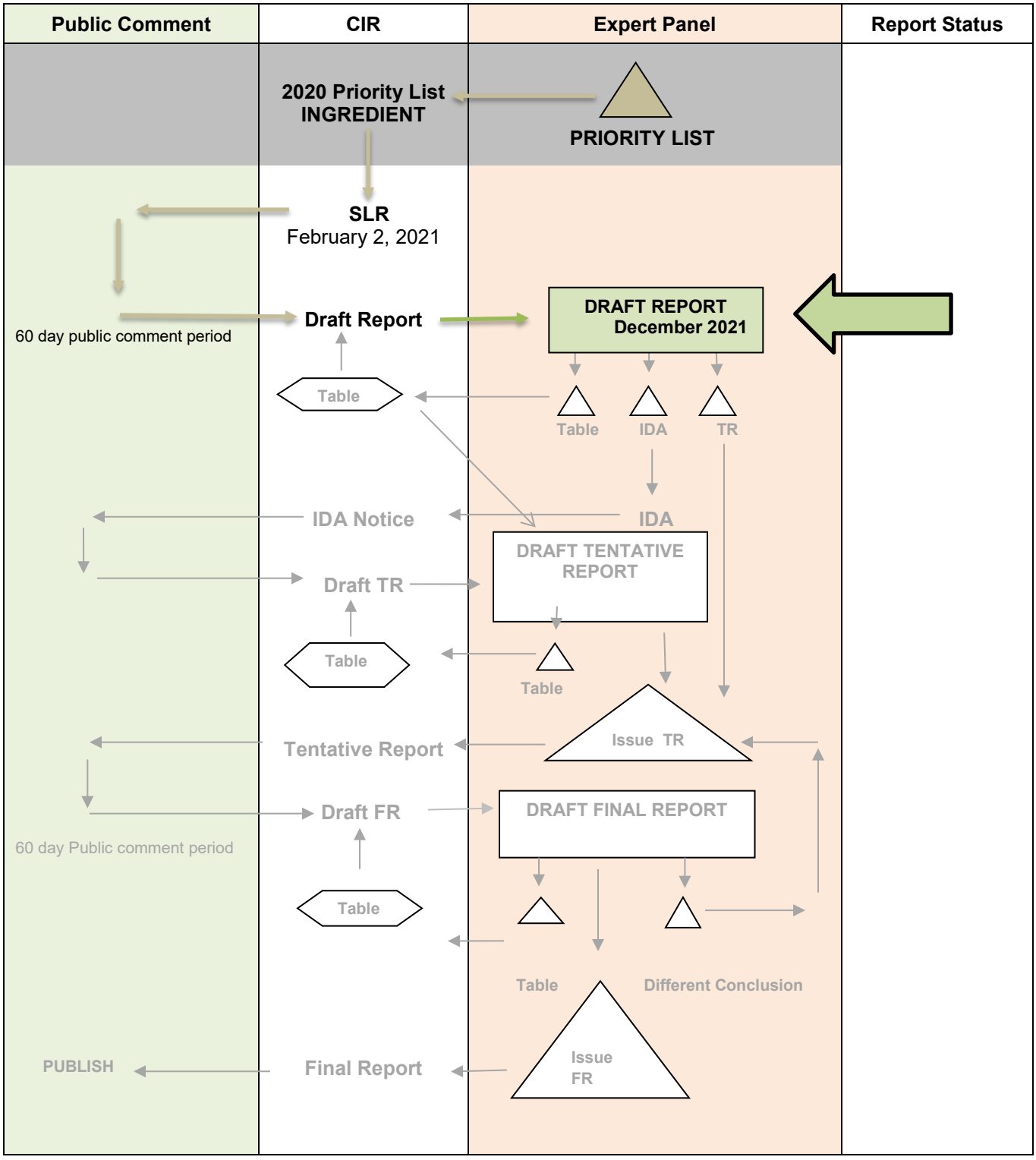
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Fatty Ethers

MEETING December 2021



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

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

Date: November 10, 2021

Subject: Safety Assessment of Fatty Ethers as Used in Cosmetics

Enclosed is the Draft Report of the Safety Assessment of Fatty Ethers as Used in Cosmetics (identified as *report_FattyEthers_122021* in the pdf). This is the first time the Panel is seeing a safety assessment of these 8 cosmetic ingredients. A Scientific Literature Review (SLR) was announced on February 2, 2021. Following the announcement of the SLR, the following data were received:

data1_FattyEthers_122021

- Anonymous. (2009) Assessment of skin tolerance of a cosmetic product after single occlusive application of suntan oil product containing 15% Dicaprylyl Ether

data2_FattyEthers_122021

- Anonymous. (2018) Modified Marzulli-Maibach protocol HRIPT of a product containing 38.6% Dicaprylyl Ether
- Anonymous. (2006) HRIPT of a product containing 1.5% Distearyl Ether

data3_FattyEthers_122021

- Anonymous. (2021) Summary information for Cetyl Dimethylbutyl Ether

Comments on the SLR (*PCPCcomments_FattyEthers_122021*) that were received from the Council have been addressed, and follow this memo. A comments response checklist is also included (*response-PCPCcomments_FattyEthers_122021*).

Also included in this package, for your review, are:

- a flow chart (*flow_FattyEthers_122021*)
- literature search strategy (*search_FattyEthers_122021*)
- data profile (*dataprofile_FattyEthers_122021*)
- ingredient history (*history_FattyEthers_122021*)
- 2021 FDA VCRP data (*VCRP_FattyEthers_2021*),
- 2019 concentration of use data (*data4_FattyEthers_122021*)

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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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: February 9, 2021

SUBJECT: Scientific Literature Review: Safety Assessment of Fatty Ethers as Used in Cosmetics (release date February 2, 2021)

The Personal Care Products Council has no suppliers listed for Cetyl Dimethylbutyl Ether, Dicetyl Ether, Didecyl Ether, Diisononyl Ether, Dilauryl Ether and Dimyristyl Ether.

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

Ingredient subheadings are used in some sections but not others. The ingredient subheadings should either not be used or should be used consistently throughout the report.

Impurities – Although specific impurities are not stated, the ECHA dossier indicates that the Dicaprylyl Ether tested was either 99.1% or 99.9% pure. This should be stated in the Impurities section.

Dermal Penetration – Please state the purity of the Dicaprylyl Ether that was tested in the *in vitro* dermal penetration study (99.1%).

Subchronic – Please state the purity of the Dicaprylyl Ether tested in the 90-day rat study (99.1%) and add that sunflower oil was the vehicle, which was also used to treat the control rats.

Please revise: “caused an increase in absolute and related liver kidney weights”. Absolute and relative liver weights were increased, but only absolute kidney weights were increased. It would also be helpful to state that no microscopic changes were observed in either the liver or kidneys.

Genotoxicity – It should be stated that increases in gene mutation were not observed in the mammalian cell gene mutation test in mouse lymphoma L5178Y cells (currently just effects on cell survival are stated in the text).

Dermal Irritation and Sensitization – The descriptions of sensitization tests in the text should include descriptions of both the induction and challenge treatments as both are important. The vehicle control also needs to be stated.

Dermal Irritation and Sensitization; Table 6 – The conclusion of the guinea pig maximization study of Dicaprylyl Ether should be clearly stated in both the text and Table 6. The ECHA dossier states that both control (paraffin oil) and treated guinea pigs showed weak reactions attributed to irritation. Following re-challenge, no distinct dermal effects were observed. Dicaprylyl Ether was considered non-sensitizing.

Summary – In the description of the guinea pig maximization study of Dicaprylyl Ether, it should be stated that the observed reactions were attributed to irritation and that the conclusion was that Dicaprylyl Ether was considered non-sensitizing.

Table 4 – Both positive controls state that they were “with metabolic activation”. This is not correct as 4-nitroquinoline-N-oxide in DMSO was use as a positive control without metabolic activation.

Table 6 – All of the treatment concentrations (induction and challenge) should be included in the Concentration/Dose column for the guinea pig maximization study of Caprylyl Ether (as was done for the Buehler test of Distearyl Ether).

Fatty Ethers - December 6-7, 2021 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: February 9, 2021 (Comments on SLR posted on February 2, 2021)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
	General statement: "The Personal Care Products Council has no suppliers listed for: Cetyl Dimethylbutyl Ether, Dicetyl Ether, Didecyl Ether, Diisononyl Ether, Dilauryl Ether, and Dimyristyl Ether."	Have noted	
1	General: Inconsistent usage of ingredient subheadings	Currently written in accord with CIR format	
2	Impurities – state purity of Dicaprylyl Ether (99.1-99.9%) in ECHA studies	Have added	
3	Dermal Penetration – state purity of Dicaprylyl Ether in the in vitro dermal penetration study (99.1%)	Have added	
4	Subchronic – state purity of Dicaprylyl Ether (99.1%) and sunflower oil (vehicle) in 90 d rat study	Have added	
5	Subchronic – revise wording of increase in liver and kidney weights	Have revised	
6	Genotoxicity – state that increases in gene mutation were not observed in mouse lymphoma cells	Have revised	
7	Dermal Irr and Sens – include descriptions of both induction and challenge treatments and the vehicle control in the text body	Have included	
8	Dermal Irr and Sens – clearly state conclusion in the guinea pig maximization study of Dicaprylyl Ether in the text and Table 6 (non-sensitizing)	Have revised/included	
9	Summary – reiterate conclusion of Dicaprylyl Ether being non-sensitizing in the guinea pig test	Have revised/included	
10	Table 5 (says Table 4 in comments) – indicate that 4-nitroquinoline-N-oxide was used as a positive control without metabolic activation	Have revised	
11	Table 6 – include all treatment concentrations for induction and challenge in the Conc/Dose column for the guinea pig maximization study of Dicaprylyl Ether	Have included	

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 is being presented to the Panel.

Fatty Ethers Data Profile* – December 6-7, 2021 – 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

((((((((((((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) - 1984 hits/ 15 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

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ABBREVIATIONS

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

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.

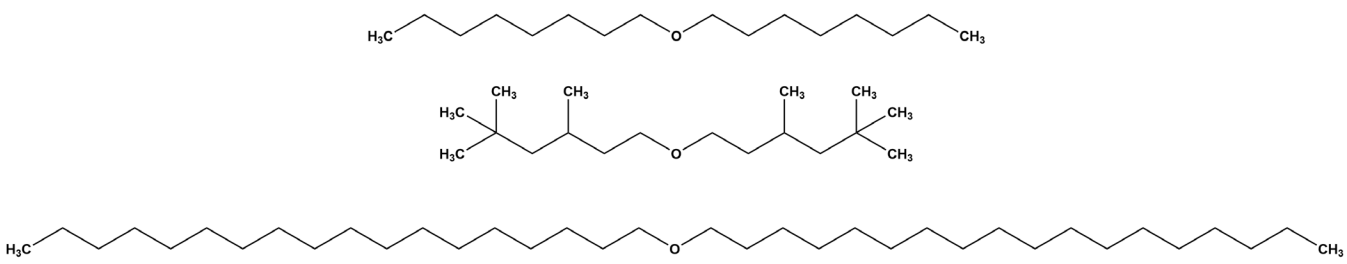


Figure 1. (from top to bottom) Dicaprylyl Ether, Diisononyl Ether, and Distearyl Ether

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. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2021 VCRP survey data, Dicaprylyl Ether is reported to be used in 239 formulations, the majority of which are leave-on products (Table 3).[8] The only other ingredient with use reported in the VCRP is Distearyl Ether, with 4 reported uses. 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.[7] Cetyl Dimethylbutyl Ether is reported to be used at a maximum concentration of 19.3% in foundations. Dicetyl Ether, Didecyl Ether, Diisononyl Ether, Dilauryl Ether, and Dimyristyl Ether are not reported to be in use, according to the VCRP and industry survey.

Additionally, 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 5 reported uses in lipsticks (concentration not reported) which may lead to exposure to mucous membranes and incidental ingestion.

Some of these ingredients are reported to be used in cosmetic spray formulations and could possibly be inhaled; for example, Dicaprylyl Ether is reported to be used at 10% in pump hair spray products and Dicaprylyl Ether has 1 reported use in a face powder formulation (concentration not reported). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 μm, with propellant sprays yielding a greater fraction of droplets/particles < 10 μm compared with pump sprays.[9,10] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[11,12] 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 air.[13-15]

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.[16]

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 4.

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

Details of in vitro genotoxicity studies summarized below are described in Table 5.

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

CARCINOGENICITY STUDIES

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

DERMAL IRRITATION AND SENSITIZATION

Details of dermal irritation and sensitization summarized below are described in Table 6.

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.[17] 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 HRIPT of 107 subjects.[18] A shampoo formulation containing 1.5% Distearyl Ether was tested in an occlusive HRIPT of 108 subjects at a concentration of 1%, in water.[19] 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. Data from 2021 VCRP and the 2019 Council survey indicate that Dicaprylyl Ether is reported to be used in 239 formulations at a maximum concentration of 25% in body and hand products, the highest reported concentration of use in a dermal leave-on formulation.

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

To be developed.

CONCLUSION

To be determined.

TABLES

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

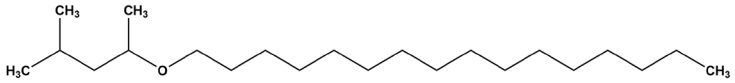
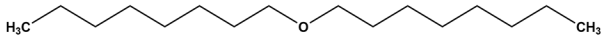
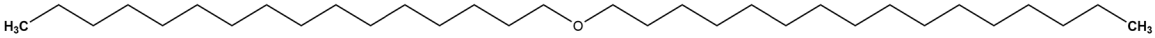
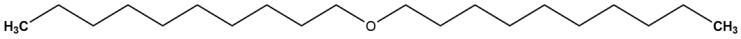
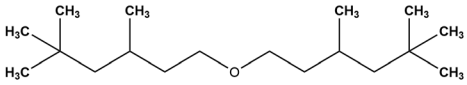
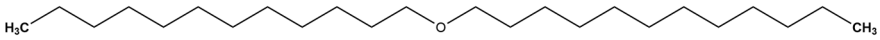
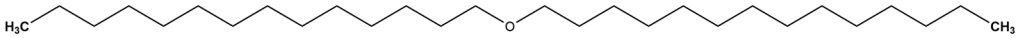
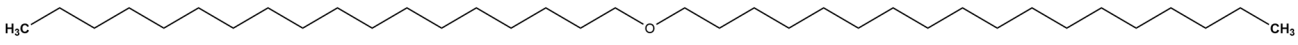
Ingredient/ CAS No.	Definition	Function(s)
Cetyl Dimethylbutyl Ether 185143-68-4	Cetyl Dimethylbutyl Ether is the organic compound that conforms to the structure: 	Skin-Conditioning Agents-Miscellaneous
Dicaprylyl Ether 629-82-3	Dicaprylyl Ether is the ether that conforms to the structure: 	Skin-Conditioning 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	[20]
Topological Polar Surface Area (Å^2)	9.2	[20]
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	[21]
Topological Surface Area (Å^2)	9.2	[21]
log K_{ow}	14.80 (estimated)	[5]

Table 2. Chemical properties

Property	Value	Reference
	Didecyl Ether	
Molecular Weight (g/mol)	298.5	22
Topological Surface Area (Å^2)	9.2	22
log K_{ow}	8.91 (estimated)	5
	Diisononyl Ether	
Molecular Weight (g/mol)	270.5	23
Topological Surface Area (Å^2)	9.2	23
log K_{ow}	7.56 (estimated)	5
	Dilauryl Ether	
Molecular Weight (g/mol)	354.7	24
Topological Surface Area (Å^2)	9.2	24
log K_{ow}	10.87 (estimated)	5
	Dimyristyl Ether	
Molecular Weight (g/mol)	410.8	25
Topological Surface Area (Å^2)	9.2	25
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 (2021)[8] and concentration (2019)[7] 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**	**239**	**0.0019 - 25**	**4**	**0.05 - 0.23**
Duration of Use						
Leave-On	*NR*	*10 -19.3*	*200*	*0.005 - 25*	NR	*0.05*
Rinse-Off	*NR*	*13.3*	*38*	*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	5	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	15; 81[a]; 64[b]	10; 24[a]	NR	NR
Incidental Inhalation-Powder	NR	NR	1; 64[b]; 1[c]	2-25[c]	NR	NR
Dermal Contact	NR	10 - 19.3	207	0.0019 - 25	NR	0.05
Deodorant (underarm)	NR	NR	10[a]	not spray: 10.3	NR	NR
Hair - Non-Coloring	NR	NR	27	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	3	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. 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 5. 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. 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	tetrahydrofuran	*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 6. 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.	[17]
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 6. **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.	[18]
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.	[19]

SDS – sodium dodecylsulfate

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 22, 2021

SUBJECT: Dicaprylyl Ether

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).

STUDY REPORT

These results concern only the samples tested in the laboratory and defined here after.
The samples will be kept in our premises during 2 months from the date below mentioned.

[redacted]

04/05/2009

ASSESSMENT OF SKIN TOLERANCE OF A COSMETIC PRODUCT AFTER SINGLE APPLICATION UNDER OCCLUDED PATCH DURING 48 HOURS ON 11 VOLUNTEERS: *patch test method*

Study sponsor: [redacted]

Client reference: **Your e-mail dated on April the 15th 2009**

Quotation N°: **2009/18991/2**

Tested product:

- Name: REF 6B 1001 SUNTAN OIL FACE & BODY WALNUT & COCONUT SPF 10 150 ML [redacted]
- Client reference: 6B 1001 BATCH 902091
- Sample N°: [redacted]
- Brand:
- Product type: suntan oil face and body

contains 15% Dicaprylyl Ether

Study code: [redacted]

[redacted]

STUDY SUMMARY

ASSESSMENT OF SKIN TOLERANCE OF A COSMETIC PRODUCT AFTER A SINGLE APPLICATION UNDER OCCLUDED PATCH DURING 48 HOURS ON 11 VOLUNTEERS: *48 hours occluded patch tests*

- **Product tested**: REF 6B 1001 SUNTAN OIL FACE & BODY WALNUT & COCONUT SPF 10 150 ML / [redacted]
- **Study sponsor**: [redacted]
- **Objective**: Assessment of the skin local tolerance of the studied product after an epicutaneous test performed in occluded conditions, during 48 hours on healthy adult volunteers.
- **Place of the study:** [redacted]
- **Investigator**: Doctor [redacted] dermatologist
- **Dates of study:** from 28/04/2009 to 30/04/2009
- **Method:**

✓ ***Application:***

Area: on the back
Quantity of product: 0.02 ml
Frequency and duration: single application during 48 hours
Conditions of application: product applied pure under occluded patch.

✓ ***Assessment method:***

A dermatologist performs the clinical observation after the removal of the patches. The quantification of the skin irritation is given through a numeric scale (erythema, oedema, dryness/desquamation, vesicles). The average irritant score of the product to be tested is calculated from the average of the quotations obtained for each volunteer, allowing to rank the product from "non irritant to very irritant". The assessment is always made by comparison with the "negative" control.

- **Panel:** 11 healthy adult volunteers.
- **Result:** The average irritant score of the product is 0.00.
- **Conclusion:**

According to the experimental conditions of the study, **the product REF 6B 1001 SUNTAN OIL FACE & BODY WALNUT & COCONUT SPF 10 150 ML / [redacted] referenced 6B 1001 BATCH 902091**, can be considered as **non irritant regarding its primary skin tolerance.**

[redacted]

RESULTS AUTHENTICITY

The study concerned by this report was carried out under my responsibility, according to the experimental protocol and the quality plan of the [redacted] and follows the good clinical practices.

All the observations and data recorded during this test are reported in this study report.

I certify the rereading of this report and do agree with its content,

Study Manager, [redacted]

TABLE OF CONTENTS

[redacted]

1 OBJECTIVE

The objective of the study is to assess the local skin tolerance of the REF 6B 1001 SUNTAN OIL FACE & BODY WALNUT & COCONUT SPF 10 150 ML / [redacted] product, after single application on the skin of the back and under occluded patch, during 48 hours, on healthy adult volunteers.

2 PRINCIPLE

The principle of the study is based on the single application of 0.02ml of tested product, on the skin of the back of adult volunteers. The product is kept in contact with the skin for 48 hours under occluded patch.

The products are tested pure or diluted depending on their type and their use. Mostly, the products are tested pure. Rinse-off products are tested diluted at 5%.
Hydrophilic products are diluted in demineralised water; lipophilic products are diluted in mineral oil.

Powders are put pure in the patch small cavity and then a drop of mineral oil is added in order to avoid the product dispersion while applying the patch.

The clinical observation of effects caused is carried out by a dermatologist after withdrawal of the patch. The assessment is always made by comparison with a "negative" control: patch without any product and applied in the same conditions as the product to be tested:

- if the product is tested pure: empty patch.
- if the product is tested diluted: patch with 0.02ml of the solvent used (demineralised water or mineral oil).

The clinical marking is given according to a numerical scale determined according to the intensity of the irritation phenomena observed (erythema, oedema, dryness, blister, etc.).

The Average Irritation Index (or Primary Skin Irritation) is calculated doing the average of markings obtained for the whole of the volunteers.

3 REGULATORY, CONFIDENTALITY AND ARCHIVING

3.1 Regulatory

The law relative to the public health n° 2004-806 dated August 9th 2004 (articles from 88 to 97) modified by the law n° 2006-450 dated April 18th 2006 for the research (articles from 31 to 33) integrates the dispositions regarding the biomedical researches modifying the law dated December 20th 1988 relative to the protection of persons who take part in biomedical researches called "loi Huriet" (JO dated August 11th 2004). All the tests carried out within [redacted] even if they are not included in the application field of this law, are carried out according to this law.
The studies are realised according to the most recent recommendations of the World Medical Association (Helsinki Declaration 1964, 48e General Assemble Somerset West, October 1996), and to the AFSSAPS recommendations relative to the biomedical researches on cosmetic products entering in the application field of the law relative to the public health n° 2004-806 dated August 9th 2004 (Version dated September 7th 2006).
No information is sent to the national folder of people who takes part in biomedical research and the opinion of the "Comité de Protection des Personnes" is not asked.

The studies follow the « Guidelines for the Assessement of Skin Tolerance of Potentially Irritant Cosmetic Ingredients », COLIPA, 1997.

The ethic requirements, necessary to the studies on Human, are respected:

- ✓ The volunteers are selected according to the inclusion and non inclusion criteria (see chapter 4).
- ✓ All volunteers are informed of the aim and the type of the study, of the possible risks taken participating in this study and give their free and informed consent before the beginning of the study.
- ✓ Before the volunteers be exposed to the product to be tested, minimum information regarding the safety of the products is asked to the sponsor.
- ✓ All care is taken in order to avoid excessive skin reactions or undesired effects on the volunteers' health during the study.
- ✓ Safety procedures are taken in the case of bad reactions.
- ✓ The volunteers are paid in compensation for the time spent and the risks due to the study.

3.2 Confidentiality

The complete data regarding the health of the volunteers, collected during their final admittance in the volunteers data of [redacted] and necessary when recruiting and selecting them for the studies are strictly confidential and submitted to the medical secret according to the article 378 of the "Code Pénal" and to the "Code de déontologie Médical" (decree dated 18th June 1979, articles 11, 12 and 13). The anonymity of the volunteers is respected within all studies carried out in our laboratories. However, each volunteer can be easily identified by the Investigator, the doctors and all the persons in charge of the study, thanks to his personal volunteer's code.
According to the article R. 5121-13 of the « Code de la Santé Publique », the product type studied, the trials, the volunteers and the results are strictly confidential and the secret is respected by the Doctors and all the persons working with him.
[redacted] ensures not to divulge all the data and results collected during a study.

3.3 Archiving

The laboratory book which contains all the information (raw data and results) regarding the study and the study reports are kept in [redacted] archives [redacted] during 10 years.

4 PANEL STUDIED

4.1 Number of volunteers

The product was tested on 11 volunteers.

4.2 Panel characteristics

The volunteers are people stemming from [redacted] the volunteers' database. All volunteers registered in this database were recruited according to the inclusion and non-inclusion criteria described in paragraphs 4.4 and 4.5 and had a medical examination (health certificate) and a dermatological examination with [redacted] dermatologist.

4.3 Recruitment, selection and final admittance for a study

The volunteers recruited in this study are all extracted from the volunteers' data base of [redacted] and answer the inclusion and non inclusion criteria presented in the paragraphs 4.4 and 4.5.

Their final admittance was determined by the study manager from the answers given in a pre-study questionnaire and after a preliminary interview. During this interview, the following information is explained to the volunteers: title, objective, protocol, planning of the study, payment methods, as well as the possible effects expected and the study constraints. The admittance of the volunteers is validated by the signature by the investigator and the volunteers of the Information Note and a free and informed consent.

4.4 Inclusion criteria

The volunteers answering the following criteria were included:

- ✓ Age: 18-70 years old.
- ✓ Sex: female and/or male.
- ✓ Social insurance: the volunteers must have a social insurance number.
- ✓ Free from dermatological lesions on the area studied.
- ✓ Volunteers with a proof of home address.
- ✓ Able to understand French and the study requirements.
- ✓ Volunteers who answer the specific criteria of the study (example: sensitive skin, etc.).

4.5 Non inclusion criteria

- ✓ Volunteers who does not answer the inclusion criteria (4.4).
- ✓ Volunteers within an exclusion period between two tests.
- ✓ Minors or majors protected by the law and people admitted in a sanitary or social institution for other purpose than research (article L209-6).
- ✓ Persons deprived of liberty by legal or administrative decision, patients in emergency situation (article
- ✓ Pregnant or breastfeed women.
- ✓ Volunteers presenting an evolutive skin pathology or a known contact allergy to one of the ingredients of the tested
- ✓ Volunteers who refused to give their free and informed consent.
- ✓ Volunteers under antihistaminic, corticoids, de-sensibilising treatment and/or under any treatment which could interfere with the skin metabolism.
- ✓ Volunteers showing a skin recently exposed to sun or to PUVA therapy sessions.

4.6 Study constraints

During the length of the study, the volunteers are asked:

- ✓ Not to put any product, also water on the patches area.
- ✓ Not to have a bath, neither expose themselves to UV.
- ✓ To avoid all intense sportive activities which could remove the patch.
- ✓ Not to take aspirin, anti-histaminics, corticoids, anti-inflammatories and any other treatment decreasing or avoiding inflammations or allergies or interfering with the skin metabolism.

4.7 Volunteers withdrawals

A volunteer can be excluded from the study for the following reasons:

- ✓ The volunteer not longer follows the requirements and constraints linked to the study and explained when signing the free and informed consent.
- ✓ The volunteer suffers illness developed during the study and which could interferes with the study aim.
- ✓ The volunteer does not want to participate to the study anymore.

5 PRODUCT TESTED

- ✓ Product name: REF 6B 1001 SUNTAN OIL FACE & BODY WALNUT & COCONUT SPF 10 150
- ✓ Client reference: [redacted]
- ✓ Sample number: [redacted]
- ✓ Galenic form : liquid
- ✓ Storage conditions: away from heat and light.

A sample of the tested product is kept in [redacted] laboratories for 2 months after the end of the study. After this date and unless contrary requirement from the study sponsor, the product will be destroyed.

[redacted]

6 CLINICAL STUDY

6.1 Description of the equipment

The equipment used is the IQ ULTRA patch test, made of a 68 mm² polyethylene plastic moss chamber with a filter paper incorporated. IQ ULTRA is supplied in units of 10 chambers on a hypoallergenic non woven adhesive tape.

6.2 Application method

Application area: back
Amount of product: 0.02 ml
Frequency and duration: single application during 48 hours.
Application conditions: product put pure under occluded patch.

The area on which the patch is applied is previously cleaned up with demineralised water and dried with cellulose cotton wool tissue.

The patches are put on the back of the volunteer. A specific examination of the contact zone is carried out just before starting the study in order to apply the product on a surface free from macroscopic irritation marks, scars or any abnormalities which could interfere with the reading of the results.

In parallel to the application of products to be studied, an empty patch "negative" control is applied.

The patches thus prepared are left in contact 48 hours.

6.3 Observations and clinical examination

The withdrawal of the patches and the reading are made by the dermatologist. The analysis of epidermic reaction markings is descriptive for each volunteer, according to the following scale:

ERYTHEMA:	
None	0
Slight erythema, hardly noticeable	1
Moderate and uniform redness	2
Significant and uniform redness	3
DRYNESS / DESQUAMATION:	
No dryness	0
Dry with desquamation, smooth and stretched aspect, slight and fine desquamation	1
Moderate desquamation	2
Severe desquamation with large scales	3
OEDEMA	
None	0
Slight	1
Noticeable	2
Significant	3
VESICLE	
None	0
Slight	1
Noticeable	2
Significant	3

The results obtained are compared to those obtained on the control zone. The primary irritation index is calculated doing the average of markings obtained for the whole of the panellists and according to the following formula:

$$\frac{[(\Sigma \text{Marks T48}) \text{ vol 1 to vol n}] / \text{ number of readings}}{\text{Number of volunteers}}$$

6.4 Data analysis and results interpretation

The results interpretation is carried out according to the irritation index obtained, the number of volunteers who reacted to the product and the importance of the reactions, the experimental conditions adopted and the type of product studied.

The ranking of the irritant potential is determined according to the index obtained as described in table 1:

Table 1: classification of the irritant potential

Average index	Classification
[0 - 0.08]	Non irritant
]0.08 - 0.16]	Very slightly irritant
]0.16 – 0.56]	Slightly irritant
]0.56 – 1]	Moderately irritant
]1 – 1.6]	Irritant
> 1.6	Very irritant

7 RESULTS

7.1 Panel description

This study includes 11 healthy adult volunteers whom characteristics are described in table 2.

Table 2: Volunteers characteristics

Inclusion N°	Vol. code	Sex	Age (years)	Characteristics	Events occurred during the study
8	BARMA	F	50	Normal skin	-
13	BONRE1	H	52	Normal skin	-
14	BOSPA	F	57	Normal skin	-
17	CERRA	F	39	Normal skin	-
20	COUEM	F	21	Normal skin	-
31	GILWI	H	39	Normal skin	-
34	HOMDA	F	66	Normal skin	-
35	IDJZA	F	64	Normal skin	-
39	MIRMA	F	24	Normal skin	-
43	RENMI	F	59	Normal skin	-
44	SAALE	F	28	Normal skin	-
Average			**45**		

None of the volunteers selected took a treatment contraindicated with the study.

7.2 Study withdrawals

No withdrawal of the study happened.

7.3 Results analysis

Table 3 presents the results obtained for each volunteer as well as the corresponding irritation index.

No skin reaction was noticed by the dermatologist on the reference area for all the volunteers.

Table 3: Results

Study code: [redacted]

Product	15	Number of readings:	1
Code	265509	Number of vol.:	xx
VOL	VOL CODE	Total readings 48 hours	Total irritation / number of readings
8	BARMA	0	0
13	BONRE1	0	0
14	BOSPA	0	0
17	CERRA	0	0
20	COUEM	0	0
31	GILWI	0	0
34	HOMDA	0	0
35	IDJZA	0	0
39	MIRMA	0	0
43	RENMI	0	0
44	SAALE	0	0
IRRITATION INDEX			0.00
CLASSIFICATION			Non irritant

After 48 hours of application, no skin reaction was observed by the dermatologist on the area treated by the REF 6B 1001 SUNTAN OIL FACE & BODY WALNUT & COCONUT SPF 10 150 ML / [redacted]

The average irritation index obtained is equal to 0.00.

8 DISCUSSION AND CONCLUSION

In the experimental conditions, after a single application of 0.02 ml of pure product under occluded patch and during 48 hours, on 11 healthy adult volunteers and according to the scale used for the interpretation of the results, **the REF 6B 1001 SUNTAN OIL FACE & BODY WALNUT & COCONUT SPF 10 150 ML / [redacted] product, referenced 6B 1001 BATCH 902091, can be considered as non irritant regarding its primary skin tolerance.**

[redacted]

APPENDIX 1: List of the persons who took part in the study

Investigator doctor:
Name: Doctor [redacted]
Address: [redacted]
Phone:

Operator:
Name:
Address: [redacted]
Phone:

Study Manager:
Name:
Address: [redacted]
Phone:

APPENDIX 2: Results authenticity

AUTHENTICITE DES RESULTATS

L'étude [redacted] a été conduite en conformité avec le protocole expérimental, le plan qualité du laboratoire [redacted] et dans le respect des bonnes pratiques cliniques.

The study [redacted] has been carried out in appliance with the experimental protocol, the quality plan of [redacted] laboratory and in respect with the good clinical practices.

MEDECIN INVESTIGATEUR
Dermatologue / *Dermatologist*

Date, signature

30.04.09

[redacted]

[redacted]

TECHNICIEN / *Technician*

Date, signature

[redacted]

[redacted]

[redacted]

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 23, 2021

SUBJECT: Dicaprylyl Ether and Distearyl Ether

Anonymous. 2018. Modified Marzulli-Maibach protocol human repeat insult patch test with challenge (product contains 38.6% Dicaprylyl Ether).

Anonymous. 2006. Human repeat insult patch test with challenge (product contains 1.5% Distearyl Ether).

MODIFIED MARZULLI-MAIBACH PROTOCOL
HUMAN REPEAT INSULT PATCH TEST WITH CHALLENGE
TCFS PSC

Study report – version n°1 of 20/09/2018

STUDY REFERENCES [redacted]

INVESTIGATIONAL PRODUCT	contains 38.6% Dicaprylyl Ether
Denomination	**FACE CARE**
Formula number	[redacted]
Batch number	

SPONSOR	[redacted]
MAIN STUDY MONITOR	
COORDINATING CENTRE	
INVESTIGATING CENTRE	
INVESTIGATOR	

Initiation date of study performance	**25/06/2018**
Completion date of study performance	**03/08/2018**

MODIFIED MARZULLI-MAIBACH PROTOCOL
HUMAN REPEAT INSULT PATCH TEST WITH CHALLENGE
TCFS PSC

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MODIFIED MARZULLI-MAIBACH PROTOCOL
HUMAN REPEAT INSULT PATCH TEST WITH CHALLENGE
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Synopsis

STUDY OBJECTIVES	Mainly to confirm that the application of the investigational product under maximized conditions of exposure in a panel of healthy human adult subjects, did not induce delayed contact sensitization. Secondarily to assess the skin compatibility of the investigational product during the study.
SPONSOR	[redacted]
COORDINATING CENTRE	
INVESTIGATING CENTRE	
INVESTIGATOR	
TYPE OF THE STUDY	Monocentric randomized study performed in simple blind
DATES OF STUDY PERFORMANCE	From June 25th to August 03rd 2018
INVESTIGATIONAL PRODUCT	**FACE CARE FORMULA** [redacted] **Modalities of application in the study:** Occlusive patch: Finn Chamber Standard® - as supplied - 20 µl – 8 mm diameter: 0.5cm², shake before use Switch to semi-occlusive patch if reactions ≥ 2 occurs

Synopsis (continuation)

STUDY POPULATION	**Number of test subjects: 100 valid cases** **Specific inclusion criteria: test subjects** ▪ aged from 18 to 70 (the 60-70 year age bracket not exceeding 10% of the total number of subjects) ▪ female and male ▪ with a phototype (Fitzpatrick): I, II, III or IV ▪ with all types of skin on body **Specific non-inclusion criteria: test subjects** ▪ with personal history of adverse reaction to: ethanol, colophony, rubber, nickel, aluminium, patch materials, adhesive plaster, ▪ with sensitive (declarative) / reactive skin on body ▪ with personal or familial history of atopy
METHODOLOGY [redacted]	**Application of the investigational product**, in healthy human subjects, by a technician, at the investigating centre, to a skin site on the upper back, under maximising conditions of exposure (occlusive patch) for a defined time Repeated applications 9 times to the same site (induction site) over a period of 3 consecutive weeks, period necessary to induce a possible allergy (induction phase) After a minimal 2-week rest phase, with no product application, single application of the investigational product, under patch, to the induction site and to a virgin site and for a defined time, enabling to reveal a possible induced allergy (challenge phase) **Application in parallel of physiological saline** under occlusive patch at the same defined times as the investigational product = control site Skin examination of the application site, before the 1st product application of the induction phase and the application of the challenge phase and after each patch removal by the test subjects by the same investigator / technician, supervised by the investigator Reporting of the sensations of discomfort directly by the test subjects to the investigator / technician, during the study Assessment of the allergic potential - checking of the skin compatibility: • Accurate description of the skin reactions observed • Evaluation of the allergic reaction according to the ICDRG scale: ?+, (+), (++), (+++) • Calculation of the percentage of reactive test subjects during the challenge phase and the induction phase

RESULTS

Characteristics of the included panel

Number of included subjects: 109
Number of exclusions: None
Number of withdrawals (reason): 2 (ref. 17b and 29b for personal reasons independent of the study)
Number of valid cases: 107

- Age: 19 to 70 (Mean: 45)
- Sex: F/M
- Phototype: II to IV
- Skin type on the application site: all types of skin - ATS (100 %; n=107)

Synopsis (continuation)

Checking of the skin compatibility

For the control product

No reaction was noted on the control site.

For the investigational product:

Induction period			
Type of reaction	**Description of the reaction on the induction site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

Challenge phase			
Type of reaction	**Description of the reactions on the induction site and the virgin site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

OVERALL CONCLUSION

Under the experimental conditions adopted:

- During the induction phase, the repeated applications of the product **FACE CARE FORMULA** [redacted] under occlusive patch, on a panel of 107 test subjects, with all types of skin on body induced no reaction of irritation.

- During the challenge phase, the single application of the investigational product to the induction site and virgin site induced no allergic reaction.

Based on these results, the product has a very good skin compatibility and does not show a sensitizing effect.

MODIFIED MARZULLI-MAIBACH PROTOCOL
HUMAN REPEAT INSULT PATCH TEST WITH CHALLENGE
TCFS PSC

Signatures and dates

[redacted]

MODIFIED MARZULLI-MAIBACH PROTOCOL
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I – INITIAL PROTOCOL DESIGN

PREAMBLE

The Sponsor provided to the investigating centre standard protocol ref. [redacted] containing general information and requirements to be respected when this type of clinical study is carried out.

Information related to the study was given by the Sponsor before the beginning of the study.
A specific study protocol referring to this standard protocol was then established.

Therefore, the study protocol was constituted by the standard protocol and the specific protocol.

I.1. INTRODUCTION

Different versions of the Human Repeat Insult Patch Test had been used by the cosmetic industry for some 60 years. The test consisted in the repeated dermal application of the Investigational Product to healthy human volunteer subjects under conditions which exaggerated the normal conditions of product use.

It was carried out on cosmetic product which safety has been assured by a toxicologist, with the aim to further confirm safety of this product which will be used by a large number of consumers under normal and reasonably foreseeable use conditions.

The maximization of exposure under the test conditions (occlusion, extended contact time etc.) made it possible to identify substances whose weak allergenic potential may have been expressed only in the finished product matrix.

I.2. STUDY OBJECTIVES

The main objective of this study was to confirm that the application of the investigational product to healthy volunteer subjects, under maximized conditions of exposure, did not induce delayed contact sensitization.

Secondarily, skin compatibility of the Investigational Product was evaluated during the study.

I.3. ETHICS AND GOOD CLINICAL PRACTICES

I.3.1. Regulatory requirements

The study was carried out in accordance with the following regulatory requirements:

- Regulatory requirements in force in the country of the test
- In the spirit of International Conference on Harmonization (ICH) Topic E6 Guidelines for Good Clinical Practices and Topic E3.

I.3.2. Protocol adherence

The Investigator had to read the protocol in its entirety and scrupulously respect it. Any anticipated modification to the protocol had to be agreed with the Sponsor and had to be recorded as a protocol amendment, signed by the Sponsor and the Investigator.

Any protocol deviations to the approved protocol had to be documented and explained.

I.3.3. Ethics Committees

An Institutional Ethics Committee was involved in the study, formed with members belonging to the staff of the investigating centre, but not directly implicated in the study.

I.3.3.1. Before the beginning of the study

The Institutional Ethics Committee had to review the following documents concerning the study:

- The standard protocol and the specific study protocol
- The written informed consent form and the subject information sheet
- The Case Report Form (CRF)
- Qualitative composition of the Investigational Product, only upon request
- Any relevant and available safety data concerning the Investigational Product

If needed, the Institutional Ethics Committee could ask for additional information (i.e. Investigator's current CV etc.).

The Institutional Ethics Committee gave the approval on June 22nd 2018.

The study only began after the approval of the Institutional Ethics Committee.

I.3.3.2. After the beginning of the study

- Any amendment to the study protocol was reviewed by the Institutional Ethics Committee before being implemented, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involved only logistical or administrative aspects of the study.
- Any Serious Adverse Events had to be promptly reported to the Institutional Ethics Committee.

The points described above were carried out according to the SOPs of the Investigating Centre.

I.3.4. Subjects' informed Consent Form / Subject Information Sheet

I.3.4.1. Principles

As requested in the declaration of Helsinki (1964) and its subsequent modifications and/or in the International Conference on Harmonization (ICH) Topic E6 Guidelines for Good Clinical Practices:

- All subjects participating in this study had to be adequately informed of the objectives, methods, the potential risks of the study and the discomfort it could entail. The language used should have been as non-technical as possible and understandable to the subject or the subject's legally acceptable representative(s).

- Neither the Investigator nor the study staff, in their oral and written communication, should have coerced or unduly influenced a subject to participate or to continue to participate in a study.

I.3.4.2. Content

The informed consent discussions with the subjects (written in a subject information sheet and/or the written informed consent form) included the following items as a minimum:

- That the study involved research
- That the subject did not participate in another study throughout the whole period of the current study
- That the subject was covered by Social Security Scheme (Private medical aid, social welfare, government health service…)
- That the subject had a fixed abode
- The purpose of the study
- The expected duration of the study
- The approximate number of subjects involved in the study
- The study design, experimental aspects and test constraints
- The subject's compliance to the study protocol
- Any restrictions concerning activities and medications
- Dates, locations, times and duration of visits
- The reasonable foreseeable risks or inconveniences to the subjects
- The person to contact for further information regarding the study and the rights of subjects and who to contact in the event of study-related injury with the corresponding 24/24 hours and 7/7 days contact telephone number
- That in the event of a significant reaction occurring during the course of the study the subject had to immediately contact the investigating centre which carried out a clinical examination as quickly as possible
- That photograph(s) could be taken (avoiding as much as possible the subject to be identifiable) and used in connection with the study. In the case where he could be recognizable, the subject or the subject's legally acceptable representative(s) was/were asked to give a written authorization
- That the subject could be asked to take part in a follow-up test to complete the study
- Indemnity for participation, if any
- That the subject's participation in a study was voluntary and that the subject or the subject's legally acceptable representative(s) could refuse to participate or withdraw from the study, at any time, without any legal consequences
- That records identifying the subject was kept confidential and, to the extent permitted by the applicable laws and/or regulations, was not made publicly available
- That the Monitors, the Auditors, the Ethics Committee and the Regulatory Authorities were granted direct access to the subject's original data without violating the confidentiality of the subject, to the extent permitted by the laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative(s), was/were authorizing such access.

I.3.4.3. Process

Prior to a subject's participation in a study:

- The Investigator or a person designated by the Investigator provided the subject or the subject's legally acceptable representative(s) sufficient time and opportunity to inquire about details of the study and to decide whether or not to participate in the study

- Two original copies of the written informed consent form were signed and personally dated by the subject or by the subject's legally acceptable representative(s) and by the person who conducted the informed consent discussion

- The subject or the subject's legally acceptable representative(s) received one original copy of the signed and dated written informed consent form and any other information provided to the subject. The Investigator retained in the study records the other original copy of the subject's signed and dated written informed consent form.

I.3.5. Subject's Identification / Confidentiality

Before inclusion of the subject in the panel of the investigating centre, subject identity had to be verified (presentation of an official document) by the staff of the investigating centre.

All information concerning the subjects' health condition and the results of clinical examination carried out before the study for their recruitment, selection and admission were subject to the rules of medical confidentiality, in compliance with the local regulation. In no case this information was communicated to the Sponsor with the identity of the subjects.

To preserve the anonymity of the subjects:

- During pre-study screening, a subject's code was used
- When eligibility criteria have been confirmed, the subject was assigned a unique identification in the study.

The investigating centre should have had SOPs covering these aspects.

I.4. INVESTIGATIONAL PRODUCT

I.4.1. Investigational Product information

The Investigational Product was a cosmetic product.

The number of investigational product(s) tested simultaneously should not have exceeded 12 per study (12 sites for investigational products and some sites for control sites).

The Sponsor manufactured, packaged, labelled and supplied the Investigational Product with the following information:

	On the label	On documentation
Formula Number	[redacted]	
Batch Number (including manufacturing date)		
Test demand (DT) Number		
Investigational product category	Face care	Face care
Expiry Date	[redacted]	
Physical form		
Colour		
Storage conditions		
Sealed envelope with the qualitative composition of the Investigational Product		

Quantity supplied: Sufficient and necessary for the number of specified subjects (mentioned in the specific study protocol) and Investigational Product sample storage in the investigating centre.

Safety certificate, signed by one or several Study Monitor(s) as clinical safety assessor(s), confirming investigational product safety in the study and where requested sealed envelope with investigational product qualitative composition was/were sent to the investigating centre

I.4.2. Control at receipt

Upon receipt the investigating centre will check and record:

- Date of receipt, quantity supplied, condition of the container etc.
- Information on the label (identification) compared to the documentation supplied
- Appearance of the investigational product (colour, physical form)
- Storage conditions: unless otherwise specified, investigational product was stored at room temperature (between +15°C to +25°C).

The investigational product was stored in a locked area especially dedicated to this purpose.

An acknowledgment of receipt was then sent to the Sponsor (according to agreed procedures) signalling any non-compliances.

I.4.3. Investigational Product Use

The investigating centre maintained records concerning the use of the investigational product in the study.

In any case, the archiving of samples respected the local regulations in that matter.
At minimum the investigating centre maintained sufficient quantity of investigational product used in the study during a 6-month period after the issue of the final study report. The location where sample was archived was mentioned in the study report.

The remaining containers (unused and used) of the investigational product was destroyed by the investigating centre (unless otherwise requested by the Sponsor) according to its standard operating procedures (SOPs).

I.4.4. Investigational Product conditions of application

For the investigational product, the Sponsor indicated the following information:

- Conditions of use of the Investigational Product: as supplied, shake before use
- The type of patch: occlusive Finn Chamber standard® (aluminium chambers mounted on Scanpor tape) of 8 mm diameter: 0.5cm²
- Quantity put on the patch: 20 µl (corresponding to 40 µl /cm²)
- Time-lapse between application of the investigational product to the patch and the application of the patch to the test site (a maximum of 20 min. except if evaporation was needed (between 15 to 30 min. in that case): not more than 20min.
- The duration of patch application: 48h-72h

For that purpose the Sponsor provided to the Investigating laboratory 2 documents called respectively "Summary chart / conditions of application" and "Dilution of Investigational Products" annexed to the specific study protocol.

If the study included several investigational products containing perfumes or alcohol or ingredients subject to cross-reactivity these products should not have to be applied to adjacent sites.

On occasions, during challenge, an extra test material such as a formula's perfume could be added at the request of the Sponsor and with the Investigator's agreement.

I.5. STUDY DESIGN

I.5.1. Selection, withdrawal and follow-up of subjects

The Investigating centre should have maintained a global panel with regular subjects' enrolment.
This panel should have been large enough and managed in order to guarantee an acceptable turn-over to ensure that the sample used in the study was as representative as possible of the population.

The required number of subjects depended on the risk considered as acceptable to wrongly conclude that the product did not cause delayed contact allergy reaction (α) though it was sensitizing and on the prevalence in the appearance of delayed contact allergy reactions in the considered population (p).

Should no reaction have been observed for all the subjects of the study, the number of required subjects (n) would have been:

$$n = \frac{\log(\alpha)}{\log(1-p)}$$

- The number of 50 subjects was used to obtain, for a value of p equivalent to 0.058, a risk α of 5% (or for p = 0.045, a risk of 10%)
- The number of 100 subjects was used to obtain, for a value of p equivalent to 0.030, a risk α of 5% (or for p = 0.023, a risk of 10%)
- The number of 200 subjects was used to obtain, for a value of p equivalent to 0.015, a risk α of 5% (or for p = 0.012, a risk of 10%)

The number of subjects included in the study had to be sufficient to obtain **100 valid cases.** It was chosen between 50, 100 or 200 on the basis of experience, according to the Investigational Product and the study conditions (type of patch and patch duration) implying more or less maximizing conditions.

The number of valid cases in the study was mentioned in the specific study protocol. At the end of the study, if the number of valid cases was less than the number requested by the Sponsor, this was mentioned in the deviation paragraph in the study report.

Unless specific cases discussed with the Sponsor and mentioned in the study report whatever the type of study, a **"valid case"** was defined as a subject who respected the following:

- Application of the investigational product all along the study in respect with the frequency
- Subject participation to all the visits and clinical examinations as requested in the study protocol
- Absence of any concomitant treatment interfering with the results of the study, according to the Investigator.

The suitability of each potential subject was confirmed before inclusion in the study on the basis of a study-specific questionnaire containing detailed inclusion and non-inclusion criteria and of a clinical examination.

The inclusion and non-inclusion criteria should have been mentioned in the study-specific questionnaire (CRF), in the same order as in the protocol to avoid any missing.

This study was carried out on an exclusive panel.

Note: any new inclusion and/or non-inclusion criteria, if not specified in the standard protocol was mentioned in the specific study protocol.
Any modification concerning inclusion and/or non-inclusion criteria had to be also mentioned in the specific study protocol.

I.5.1.1. Inclusion criteria

To be eligible, each subject had to satisfy the following:

a. Healthy subjects aged between 18 and 70 years. The 60-70 age range should not have exceeded 10% of the total number of subjects
b. Subjects with phototypes I, II, III and IV
c. Males and females
d. Females of childbearing age had to declare to use effective contraception for at least 3 months before the beginning of the study and had to maintain it throughout the study
e. Subjects whose medical examination confirmed their suitability for participation in the study
f. The wash-out period for each subject was 4 months minimum time-lapse from any other HRIPT study (no more than 3 participations per year in HRIPT studies). In addition, wash-out period for each subject was 1 month minimum time-lapse from the last participation in any clinical study involving patch on the back
g. Subjects covered by social security scheme (Private medical aid, social welfare, government health service…)
h. Providing a signed informed consent.

I.5.1.2. Non inclusion criteria

To be eligible, each subject had to not satisfy the following:

a. Current use of immunosuppressive drugs and/or an organ transplant
b. Current use of topical or systemic anti-inflammatory drugs for a defined medical condition; e.g. aspirin, ibuprofen, corticosteroids,
c. Intensive treatment with retinoids less than 3 months before the current HRIPT
d. Immune deficiency or autoimmune disease
e. Vaccination within 3 weeks preceding the study or intention to be vaccinated during the course of the study
f. Subjects with history of cancer (ex.: history of skin cancer, treatment for malignancy of any kind, mastectomy…)
g. Insulin-dependent diabetes
h. Asthma sufferers
i. Lactating or known to be pregnant
j. Application within the last two months of any anti-inflammatory drug to the skin area used in testing
k. Clinically significant active dermatitis or skin disease anywhere on the body (excluding facial acne)
l. Subjects with background of allergy (drugs, cosmetics, food…) that made the subject ineligible or placed him/her at undue risk
m. Skin disorders (scars, moles or other blemished / abnormalities) affecting the test area which, in the investigator's / designee's judgement, could interfere with grading / assessment of skin responses
n. Intensive exposure to sunlight (natural or artificial) the month preceding the study
o. Subjects with clinically significant dermographism that could compromise evaluation of skin reactions
p. Subjects with known excessive skin reactivity to patch materials
q. A condition or medication which, in the Investigator's judgement, made the subject ineligible or placed the subject at undue risk (if the potential subject was under the care of a physician, approval to participate could be sought from that physician, at the Investigator's discretion and/or in accordance with regulatory requirements)

r. Current participation in another clinical study of any kind
s. Unwillingness or inability to comply with protocol requirements
t. Subjects who had been deprived of their freedom by administrative or legal decision or who were under guardianship
u. Subjects who could not be contacted in case of emergency
v. Subjects who could not justify of a fixed abode
w. Subjects who were CRO's employees.

I.5.1.3. Test constraints

- Subjects were instructed not to change as far as possible their routine lifestyle, eg food, smoking, exercise, etc.
- The subjects were required to visit the investigating centre 13 times. Additional sessions could be envisaged if necessary.
- During the induction and challenge phases, the subjects had to not wet the patches sites, they had to refrain from practicing sport which could induce excessive perspiration, they were not allowed to apply product(s) to the test area and had to inform the Investigator in the event of any use of medication or vaccination.
- Throughout the entire test and for two weeks after the test, the subjects had to avoid UV exposure (natural or artificial).
- The subjects were instructed not to take part in any other study in the course of this study and should not have to be included in any other HRIPT study during 4 months following the end of the current HRIPT. In addition subjects should not have to be included in any other study involving patch on the back during a 1-month period following the end of the current HRIPT.

I.5.1.4. Subject withdrawal criteria

I.5.1.4.1. Premature discontinuation

A discontinuation took place:

- At the request of the Investigator for reasons of a subject's well-being (for example, onset of severe cutaneous reactions) or at the request of the subject (he/she was free to leave the study at any time without having to give a reason),
- When the protocol requirements had not been respected,
- When a concomitant medication likely to interfere with the results of the study was taken by the subject.

The Investigator had to record all relevant information on the Case Report Form and had to decide whether or not the subject should have been withdrawn from the study.

The Investigator had to carefully document all premature discontinuations and their reasons in the Case Report Form and if necessary in an "Adverse Event Form

I.5.1.4.2. Subjects lost to follow-up

In the case where the subject did not present for a visit, the Investigator or designee had to attempt to contact the subject by telephone on two occasions. These attempts had to be recorded in the Case Report Form. In the absence of any response, the subject was considered as "lost to follow-up" and this decision was documented in the Case Report Form.

If the number of subjects dropping out of the study prevented the required number of valid cases being achieved, taking into account the stage of the study, new subjects were included to replace them when required by the Sponsor.

The data concerning subjects who dropped out was not been included in the evaluation, unless they withdrew or were withdrawn for a reason linked to the study. This was specified in the study report.

I.5.1.5. Subject follow-up after the study

Subjects having presented an allergic type reaction during the study should have been withdrawn from the panel of the Investigating centre. If not, subjects would never be included again in Safety L'Oréal studies of any type.

At a minimum the Investigating centre gave to these subjects a document mentioning:

- Substance(s) concerned or "suspected" (if the relationship between the reactions linked to the finished product and breakdown substances was not established with certainty): INCI name and nature (function).
- Recommendations, prudence advice concerning the use of some categories of cosmetic products and action to be taken in case of reaction (consultation of the attending physician and/or of a dermatologist and/or of an allergist).

Any additional follow-up described in the Investigating centre procedures was ensured.

I.5.2. Type of patch and patch application time

I.5.2.1. Rationale for choosing the patch system

For a given Investigational Product, the same type of patch had to be used during the entire study except when decided otherwise jointly by the Sponsor and the Investigator during the course of the study.

Different types of patches could be used in the same study for different Investigational products (see I.5.2.2.). The patches had to be applied at least 1 cm apart.

The patch system **insured:**

- a **product dose** of 40 to 50 µl or mg/cm²
- an **acceptable** level of irritation

Occlusive patches applied for 48 hours should have been used whenever possible as they provided the maximum exaggeration of exposure.

However investigational products with higher irritation potential (surfactant-based matrices, mascaras, styling products and highly perfumed and/or alcohol-containing products for example) could be patched under semi-occlusion for 48 hours or occlusion/semi-occlusion for 24 hours.

In each case, the type of patch was selected by the Sponsor in agreement with the Investigator and was reported.

I.5.2.2. Type of patch used and quantities applied of Investigational Product

- **Occlusive patch:**
    - **Finn Chamber® on Scanpor®** (Aluminium chambers mounted on Scanpor tape):
        - ✓ **20 µl (or mg)** on 8 mm diameter Finn chambers (0.5 cm²) (corresponding to 40 µl or mg/cm²)

      Note: For liquids, the Investigational product(s) was/were on the Whatman paper provided by the Manufacturer and placed into the Finn Chamber.
    - **For perfumes and alcoholic products, Webril cotton square** covered with Blenderm occlusive type:
        - ✓ **110 µl (or mg)** on Webril cotton 1.5 cm x 1.5 cm = 2.25 cm² (corresponding to approximately 50 µl or mg/cm²)

          or
        - ✓ **200 µl (or mg)** on Webril cotton of approximately 2 cm x 2 cm = 4 cm² (corresponding to 50 µl or mg/cm²)
- **Semi-occlusive patch:** the Webril cotton square (TruMed® or other) was used without the occlusive dressing:
    - ✓ **200 µl (or mg)** on Webril cotton of approximately 2 cm x 2 cm = 4 cm² (corresponding to 50 µl or mg/cm²)

If the amount of investigational product(s) used per patch was modified compared to the study protocol, it was indicated as a deviation in the final report (xxx µl/patch or xxx g/patch).

For that purpose the Sponsor provided to the Investigating laboratory a document called "Summary chart / conditions of application" annexed to the specific study protocol.

I.5.3. Location of patches

The Investigational Products were applied to the back on areas free of scars, tattoos, beauty spots, warts or any other cutaneous disease.

As much as possible, patches were applied to the upper back. If not possible, other areas on the back where frictions with clothes were limited such as the lower back were used.

Test areas were reserved for negative control (patch without product and/or with distilled water…).

I.5.4. Randomization

If agreed with the Sponsor, treatment sites were rotated in order to minimize any local effects. To this end, the investigating centre prepared a rotation diagram which was communicated to the Sponsor.
If several investigational products contained perfumes or alcohol or ingredients subject to cross-reactivity, they were not applied to adjacent sites.

In case of replacement of drop-out subjects, an additional diagram was prepared.
The randomization or absence of randomization was mentioned in the specific study protocol

I.5.5. Study performance

I.5.5.1. Administrative formalities before the start of the study

In addition to the information related to the investigational product (see dedicated paragraph), the additional information listed below was supplied before the study start.

I.5.5.1.1. Information provided by the Sponsor

- Proof of civil liability insurance subscribed by the Sponsor (according to the local regulation): mentioned in the specific study protocol: Responsabilité Civile Générale / AIG Europe Ltd, contract N° 7.109.393.

I.5.5.1.2. Information provided by the investigating centre

- Proof of insurance guaranteeing its responsibilities towards the subjects: HDI-Gerling Industrie Versicherung AG, Policy no.: 110-01325685-14023 as lead insurer and Axa Corporate Solutions as co-insurer: XFR0074974LI.
- Financial agreement
- Dates of the start and completion of the study
- Dates of the draft results and of the study report
- A written approval from the Ethics Committee involved in the study.

I.5.5.2. Study schedule

The study lasted 6 weeks.

It included 3 phases:

- An induction phase of 3 weeks
- A rest phase of 2 weeks
- A challenge phase of 1 week

The chronology of the study was as follows:

DAY 1	Selection of subjects: . Subjects information . Signature of informed consent form and information sheet . Verification of inclusion and non-inclusion criteria	
	Medical check-up: Examination of the back Final inclusion	
	Application of the IP: . On the induction site to the upper back . Under occlusive patch	**INDUCTION PHASE**
DAYS 3, 5, 8, 10, 12, 15, 17 and 19	. Removal of patch after 48-72 hours. . Reading of the cutaneous reactions 15 to 35 minutes after removal of the patches . IP re-application	
DAY 22	. Removal of patch after 72 hours. . Reading of the cutaneous reactions 15 to 35 minutes after removal of the patches	
DAYS 23-35	No product application	**REST PHASE**
DAY 36	Clinical examination of the test area Application of challenge patches to the back: . To the induction site . To an untreated site	**CHALLENGE PHASE**
DAY 38	Removal of patch after 48 hours . Reading of the cutaneous reactions 15 to 35 minutes after removal of the patches	
DAY 39	. For 48 hours patches, in case of reaction (erythema score ≥ 2) at previous reading "between 15 and 35 min", reading of the cutaneous reactions 24 ± 3 hours after removal of the patches	
DAY 40	For 48 hours patches, reading of the cutaneous reactions 48 ± 4 hours after removal of the patches	

I.5.5.2.1. Induction phase

On the first day the Investigator ensured that the information and consent forms had been duly signed by the subjects.

The Investigator checked that the subjects corresponded to the previously-defined selection criteria.

The decision to include or not the subject was based on the selection criteria, the medical history questioning of the subject and a clinical examination.

Before each patch application the skin could be wiped if necessary with a damp cotton pad.

The induction patches were applied 3 times a week (as an example in the standard protocol: on Mondays, Wednesdays and Fridays) during a 3-week period:

Monday = (D1-D8-D15), Wednesday = (D3-D10-D17), Friday = (D5-D12-D19)

Patches applied on Mondays and Wednesdays were worn for "48 $\pm$ 4 hours" and patches applied on Fridays were worn for "72 $\pm$ 4 hours" (unless instructed otherwise by the Sponsor).

Alternatively the 24-hour patches were applied on Monday, Wednesday and Friday at the investigating centre and removed by the subject on Tuesday, Thursday and Saturday at home.

The patches had to never be left on for more than "72 $\pm$ 4 hours".

The induction had to consist of 9 patches. If one patching session was missed by the volunteer, a **make-up patch (MU)** was applied, as far as possible, at the end of the induction.

For each product the applications were repeated to the same site, except in the case of a significant irritation/sensitization reaction (see below).

Relocation of patches

At the first sign of significant irritation (graded as erythema "2" – moderate to strong or graded as erythema "1" associated with any other intolerance sign judged significant), **the Sponsor had to be informed immediately** and the treatment moved to an adjacent site.
The test site was only changed once. In addition, in case of strong irritation, the type of patch could be modified (from occlusive to semi-occlusive).

The original patch test site was scored in parallel with the new test site until completion of the test. The scores for both sites were clearly documented.

In the case of a suspected allergic reaction, the product was not applied again and **the case was discussed immediately with the Sponsor.** The decision to re-apply or not the product in the challenge phase was taken jointly by the Investigator and the Sponsor.

In the exceptional and unforeseen event of the product proving too irritating for the selected patching regime, **the Sponsor was informed immediately** in order to consider modifying the protocol according to the product type (open application, reduction of the time the patch was worn, semi-occlusion instead of occlusion, reduced investigational product concentration, quantity applied, etc.).

Skin marking and location of test sites

During the induction phase and according to its SOPs, the investigating centre located precisely each subject's treated sites to be able to retrieve them after the rest phase.

The article entitled "Marking patch tests sites: description of a practical, clean, durable and inexpensive method" described a useful method to mark the test sites.

I.5.5.2.2. Rest phase

There was no patching for a period of 2 weeks following the end of the induction phase. The subjects were asked to inform the Investigator of any reactions which could occur during this phase.

I.5.5.2.3. Challenge phase

After the rest period, the subjects returned to the investigating centre for the application of the challenge patches.

Prior to this application a careful examination of the test areas was made and the subjects were questioned about any changes in their health and on any medication taken since their last visit.
The investigational product was not re-applied as long as an erythema score was $\geq$ 2. An additional 1-week rest period could have been necessary.

The investigational product was re-applied using the same patching regime as that used during induction, unless otherwise instructed by the Sponsor.
Each patch was applied to 2 sites: a virgin site and induced site, symmetrically located if possible.

Note: in case of application to an adjacent site during the induction period, the "induced site" for the challenge phase bas the site having received most applications.

At the end of the patch period (48 hours or 24 hours after application), the patches were removed and patch sites were graded as described hereinafter.

All adverse reactions should have been graded until resolution. This meant that grading could be carried out for up to seven days after removal of the patches. These supplementary reading days were mentioned in the final report.

I.5.5.2.4. Rechallenge phase (special cases)

All doubtful reactions had to be verified by an additional patch test (Rechallenge) performed between 3 to 6 weeks after the first appearance of the challenge reaction and after all reactions had ceased.

The type and duration of the rechallenge patches as well as the Investigational product tested were decided on a case-by-case basis jointly by the Sponsor and the Investigator.

A whole formula diluted or not as well as single ingredients or the formula with ingredients removed could be patched.

Grading was carried out 2 days, 3 days and 4 days after this new application and if necessary every day until resolution.

In case of rechallenge, an amendment to the study protocol was written by the Investigating centre.

I.5.5.2.5. Grading

Grading was performed using a day-light illuminator (D65 North daylight or equivalent).

Patched sites were graded as follows:

- **For patches applied 48 hours:**
    - For the Induction phase, grading had to be carried out "between 15 and 35 minutes" after removal of the patches.
    - For the Challenge phase, grading had to be carried out "between 15 and 35 minutes", 24 ± 3 hours (in case of reaction (erythema score > 2) "between 15 and 35 minutes") as well as "48 ± 4 hours" after removal of the patches (corresponding to 2, 3 (in case of reaction) and 4 days after application of the Investigational product) or more if necessary.
    - **All adverse reactions had to be graded until resolution.**
    - Subjects should have notified the investigating centre of any delayed skin reactions on the test site occurring after the 48-hour grading. The site had to be then re-examined by the Dermatologist.

- **For patches applied 24 hours:**
    - Subjects were requested to remove the patches at home after 24 hours.
    - For the Induction phase, grading had to be carried out "24 ± 3 hours" after removal of the patches.
    - For the Challenge phase, grading had to be carried out "24 ± 3 hours", as well as "72 ± 4 hours" after removal of the patches (corresponding to 2 and 4 days after application of the Investigational product) or more if necessary.
    - **All adverse reactions had to be graded until resolution.**
    - Subjects should have notified the investigating centre of any delayed skin reactions on the test site occurring after the 72-hour grading. The site had to be then re-examined by the Dermatologist.

Grading of test sites gave an accurate description of the skin reactions.

The main objective criteria used were: Erythema – infiltration (oedema, papules) – vesicles – bullae, which were graded according to the defined criteria.

The grading was performed according to the following steps and grading scales:

1. Scoring the Erythema according to the scale below:

(E) ERYTHEMA

0	No visible erythema
1	Mild erythema (faint pink)
2	Moderate erythema (well defined)
3	Severe erythema
4	Caustic erythema – erosive aspect and/or necrotic aspect

Note: according to the investigational centre procedures, additional mentions can be added to complete the evaluation.

2. If Erythema E > 1 then a palpation had to be proceeded

3. If there were findings on palpation then the ICDRG scoring scale below had to be proceeded:

(A) SCALE OF THE INTERNATIONAL CONTACT DERMATITIS RESEARCH GROUP: I.C.D.R.G.

(-)	0	No reaction*		
(+)	1	Weak positive reaction	:	Erythema, infiltration, possibly papules
(++)	2	Strong positive reaction	:	Erythema, infiltration, papules, vesicles
(+++)	3	Extreme positive reaction	:	Intense erythema, infiltration, vesicles may coalesce to form a blister

**No reaction according to the ICDRG*
For doubtful reactions (?+), score for erythema only

4. In all cases, (E=0 or E>0), the morphology of the test site was described according to the scale below:

(M) ADDITIONAL COMMENTS / OTHER REACTIONS

H/Oe	=	Homogeneous infiltration / oedema
P	=	Papules
V	=	Vesicles
B	=	Bullae
Pe	=	Petechiae
S	=	Spreading beyond the patch area (infiltration or erythema)
SV	=	Soap effect (shiny skin possibly wrinkles)
F	=	Fissuring
D	=	Desquamation
Dr	=	Dryness
C	=	Skin coloration – hyperpigmentation
HY	=	Hypopigmentation
Fr	=	Follicular reaction
NA	=	Product not applied
T	=	Tape reaction
I	=	Itching at the test site
*	=	Additional free comments
N9G	=	No 9th grade
Cr	=	Exudation and/or surface encrustation
X	=	Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction
- or Abs	=	Subject absent
MU	=	Make-up patch

Note: Additional comments are possible if they are not present in notation (M).

I.5.5.3. Dermatologist involvement and qualification of study personnel

The dermatologist had to **personally conduct at least** the following phases:

- Day 1: Inclusion of the subjects and medical examination
- Day 3: Readings of the cutaneous reactions after patches removal
- Day 36: Clinical examination of the test area(s) (as mentioned in the specific study protocol)
- All clinical examinations after patches removal during challenge phase
- Confirmation and follow-up of all **suspected allergic reactions** (score 2 and higher from ICDRG scale) during all the study
- All the rechallenge phase if any.

All study personnel involved in the study was appropriately trained and qualified. A specific attention should have been given to the training of study personnel involved in the grading of reactions.

I.5.6. Concomitant medication

Any information (commercial name, galenic form, administration regimen, start date and end date, indication) relating to concomitant medication was recorded in a "Concomitant Medication" paragraph in the Case Report Form. Subjects taking concomitant medications likely to interfere with the results of the study (see non-inclusion criteria of the protocol) could have been excluded from the data analysis.

I.5.7. Interpretation of the results

The interpretation of the results and the conclusion took into account all the data concerning:

- "Valid case" subjects as defined in §I.5.1.
- Non "valid case" subjects with reactions

I.5.7.1. Hypersensitivity response

Sensitizing potential of the Investigational product was evaluated on the basis of weight-of-evidence taking into account all reactions observed in all subjects during the course of the study (induction, challenge and rechallenge if any).

A site where erythema was graded 2 or more in the challenge, with or without **palpable lesions** had to be evaluated on subsequent days to note whether the reaction decreased or increased, in order to better differentiate between an allergic and an irritant reaction. **A rapidly decreasing reaction was indicative of irritation (descrescendo reaction).**

A reaction with infiltration/oedema that persisted and/or increased over time usually indicated an allergic reaction **(crescendo reaction).**

I.5.7.2. Criteria of evaluation of the irritancy potential

The irritancy aspect of the skin compatibility could be evaluated from the Erythema reactions observed (number, intensity and frequency) and compared to that established for a selected reference product, to the untreated control site or with the results of the investigating centre's internal database.

I.5.8. Statistics

All results were analysed descriptively. Means and standard deviations were calculated where applicable.

Since sensitization was not a matter of quantification, reactions were to be classified as allergic or not according to the results at Challenge compared to the results at Induction.

I.6. ADVERSE EVENT, SERIOUS ADVERSE EVENT, COMMUNICATION WITH SPONSOR

I.6.1. Adverse Event (AE)

An Adverse Event may be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the Investigational Product, whether or not related to the Investigational Product.

An Adverse Event, whether or not related to the Investigational Product, is recorded in the "Adverse Event form" together with the chronology of event (date of the onset, still in progress, finished), the duration of symptoms, the severity (light, moderate, severe, very severe), the relationship with the Investigational Product (no relation, doubtful, plausible, probable, certain), the sequelae and medical decision (whenever a medication was prescribed after an Adverse Event, it should be recorded in the "Adverse Event form" with the reason for treatment). Additional information may be requested when necessary. **Forms have to be carefully and completely filled in with as much details as possible.**

When an Adverse Event persists at the end of the study, **the Investigator will ensure that the subject is followed up until total resolution of the adverse event.**

If the severity of the symptoms justifies withdrawal of the subject from the study, at the subject's request or that of the Investigator, this is mentioned in the "Adverse Event form".

Depending on the nature and seriousness of the event, copies of the medical records of the subject may be requested as well as the results of laboratory analyses. In the case of hospitalization of the subject, a copy of the hospital records should be asked by the Investigator as soon as possible, if available. In certain cases, the Investigator may be requested to provide a letter summarising the events related to this case.

I.6.2. Serious Adverse Event (SAE)

A Serious Adverse Event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

Or

- Is a congenital anomaly/birth defect.

Recording, documentation and follow-up of such Serious Adverse Event will be realized in the same way as for an Adverse Event.

I.6.3. Conduct in the case of AE or SAE

If an AE or SAE occurred, the Investigator determined the action to take and the appropriate measures on a case-by-case basis to ensure safety of the subject(s) taking part in the study.
It was reminded that notably for the management of any SAE the Investigator had to respect the local regulations.

The Investigator could stop the study if the study revealed a risk to the health of the subjects. In such a case, the Sponsor should have been notified within 24 hours of the action(s) taken.

The Investigator could decide to exclude a subject (permanently or temporarily) in the course of the study, if the subject experiences AE or SAE incompatible with proper observance of the protocol, for example contracted an illness requiring treatment that could interfere with the study and affect interpretation of the results.

Under all circumstances, the Investigator had to follow-up the subject until the outcome of the event was known.

I.6.4. Communication with the Sponsor

Any Adverse Event was reported by the Investigator to the Sponsor within **48 hours** following its confirmation by the Investigator. The corresponding "Adverse Event form" was sent to the Sponsor in a timely manner.

A Serious Adverse Event had to be communicated immediately by the Investigator to the Sponsor. Any additional information requested by the Sponsor was provided within a period of **5 days.**

In addition, the investigating centre informed the Sponsor in the following situations:

- At the 1st sign of significant irritation (graded as Erythema "2" – moderate to strong or graded as Erythema "1" associated with any other intolerance sign judged significant), the **Sponsor had to be informed immediately** and the treatment moved to an adjacent site. A photograph could be taken by the Investigator.
- In the case of a suspected allergic reaction, the case **was discussed immediately with the Sponsor.**
- Any protocol modification had to be discussed with the Sponsor prior to be implemented except when necessary to eliminate immediate hazards to the subjects.

I.7. MANAGEMENT OF THE STUDY

The Coordinating centre ensured the liaison between the Sponsor and the Investigating centre.
Any information supplied by the Sponsor to the Coordinating centre was immediately transmitted to the Investigating centre by the Coordinating centre.
Any information from the Investigating centre related to the study implementation and performance of the study was transmitted to the Sponsor through the Coordinating centre.

I.8. DATA HANDLING AND RECORD KEEPING

I.8.1. Data handling

The CRF was established by the Investigating centre.
The data was recorded as and when available during the study. The Investigating centre set in place the necessary measures in order to protect the data (breach of confidentiality, loss of data, alteration of data, etc.).

The Investigating centre ensured the accuracy, completeness, legibility of the data in the CRF and reported to the Sponsor in all required study reports.

Any change or correction to a CRF or other working forms was dated, initialled (or signed) and explained and did not obscure the original entry according to the Investigating centre's SOP. In case of electronics records, an audit trail was maintained.

For traceability reason, all source data was identified with the study number.

Upon Sponsor's request, the Investigating centre provided direct access to source data and source documents for study-related monitoring, audits, consultation by the Ethics Committee and inspection by the appropriate regulatory authority (ies).

I.8.2. Record keeping

The investigating centre archived all documents related to the study for a 10-year period (otherwise specific requirement mentioned in the specific study protocol) in the dedicated room of its facilities and under conditions ensuring security and integrity of the data.

These documents are listed below (non exhaustive list):

Information concerning the investigational product

- Instructions for handling and storage and other documents related to the investigational product, product preparation and application
- Safety certificate for the investigational product signed by a safety assessor confirming its safety in the study
- Qualitative composition of the investigational product (archived by the Coordinating centre at the end of the study upon receipt from the Investigating centre)
- Rotation scheme if not included in the specific study protocol

Information concerning the subjects

- Signed informed consent forms and any other written instructions given to the subjects (as subject information sheet)
- CRF, medical questionnaire (if any) and any other forms related to the subjects in the study

Information related to the conduct of the study

- The signed standard protocol, the specific study protocol and protocol amendment(s) if any
- Insurance statement (according to local regulations)
- Signed agreement between Coordinating centre and Investigating centre (signed agreement between Sponsor and Coordinating centre archived by the Coordinating centre)
- Documented approval by the Ethics Committee concerning protocol and any amendments, CRF, informed consent forms and any other relevant documentation
- Final signed study report and report amendment(s) if any
- Any other source document generated during the course of the study.

The Coordinating centre archived all exchanges between the three parts related to the study as well as a copy of the final report except the raw data for a 10-year period at the following address: HOMEBOX – Technobruges – 1, rue de l'Hermite – 33520 BRUGES – France.

At any time, the Sponsor had the possibility to request the Investigating centre for the study file (copy or original).

On completion of the 10-year period, the Sponsor had the choice between three options:

- The study file to be returned to the Sponsor for archiving
- The study file to be stored for an additional time period and extra costs to be discussed
- The study file to be destroyed

The Investigating centre could destroy the study file only if the Sponsor had given a formal signed written agreement.

In case where the location of archives was modified the Investigating centre notified the Sponsor of this new location.

I.9. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control should have been applied to each stage of data handling to ensure that data was accurate and had been processed correctly.

The Investigating centre developed a quality audit program based on a rational approach in order to:

- Guarantee that the study performance and the study report were compliant with the standard protocol and the specific study protocol
- Verify that the study was carried out according to the Investigating centre's Standard Operating Procedures and in the spirit of ICH GCP.

The Investigating centre checked that all the required documentation was present, dated and signed (for instance the standard protocol, the specific study protocol…).

Quality control and quality audit actually performed on the study (or this type of study) was mentioned in the study report.

I.10. STUDY RESULTS AND REPORT

I.10.1. Study results

According to a deadline decided between the Sponsor and the Investigating centre, this last one sent to the Sponsor preliminary results for each formula.

I.10.2. Study report and summary sheet

According to a deadline decided between the Sponsor and the Investigating centre, this last one sent to the Sponsor for each formula:

- One issue of the original study report in English, on the Investigating centre's Headed paper, signed and dated was kept in the Investigating centre's Archives,
- The corresponding electronic file (in "PDF" format) by email or CD-Rom according to the current procedures.

This final study report included at least the following information:

- Address of the Investigating centre and address of the Sponsor
- Names, Responsibilities of Key scientific personnel involved in the study
- Quality assurance statement
- Investigator statement
- Short summary of the study objectives
- Study design and methods
- Number of subjects screened for eligibility, number of subjects disqualified and reasons for disqualification
- Number of subjects entering and completing the study (with individual test data results)
- Number of subjects who withdrew from the study and reasons for withdrawal
- All amendments and all deviations from the study protocol
- All unexpected adverse events or serious adverse events, their outcome and relationship if any with the investigational product
- Recapitulative results

- Summary and evaluation of the test data
- Conclusions
- Favourable opinion of the Ethic committee
- …

I.10.2.2. Summary sheet

According to the template supplied by the Sponsor, the Investigating centre sent to the Sponsor for each formula:

- One issue of the original summary sheet in English, signed and dated, on the Investigating centre's Headed paper, was kept in the Investigating centre's Archives
- The corresponding electronic file (in "PDF" format) by email or CD-Rom according to the current procedures.

I.11. BIBLIOGRAPHICAL REFERENCES

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Recommendations to research sponsors and to service providers
TCFS PSC, AFSSaPS, final version of December 2008

II – PRACTICAL CONDITIONS OF STUDY PERFORMANCE

II.1. PROTOCOL ADHERENCE

II.1.1. Study population

II.1.1.1. Number of test subjects

Number of test subjects included in the study	109	
Withdrawals	Test subjects concerned	Date and reasons
	Ref. 17b	30/07/2018 - for personal reasons independent of the study
	Ref. 29b	30/07/2018 - for personal reasons independent of the study
Exclusion	Test subjects concerned	Date and reasons
	None	Not applicable
Valid cases	107	

The number of recruited test subjects took into account the inclusion criteria, the constraints of the study and the period of the study performance.

At the beginning of the study, complementary test subjects (+9) were included to compensate the possible withdrawals or exclusions from the study independent of the investigational product.

II.1.1.2. Inclusion and non inclusion criteria

All the test subjects corresponded to the inclusion and non inclusion criteria.

The individual typological characteristics of the test subjects are reported in **Appendices 1**, and recapitulated below for the whole panel:

Age (years old)	Included test subjects	Valid cases
Minimum	19	19
Maximum	70	70
Mean	45	45
Median	45	45

60-70 age bracket	Included test subjects	Valid cases
Number of test subjects	10	10
% of test subjects	9%	9%

Criteria	Included test subjects		Valid cases	
	Nb	%	Nb	%
Phototype				
II	23	21%	22	21%
III	80	73%	80	75%
IV	6	6%	5	5%
Sex				
Female	70	64%	69	64%
Male	39	36%	38	36%

II.1.1.3. Specific information concerning the test subjects

The answers of the test subjects concerning the skin reactivity, the history of atopy, contraception (type) and the current medication are reported in **Appendices 2.**

Criteria	Included test subjects		Valid cases	
	Nb	%	Nb	%
Sensitive (declarative) / reactive skin on body	0	0%	0	0%
History of atopy	0	0%	0	0%

II.1.1.4. Study constraints imposed on the test subjects

All the constraints of the study, defined in the protocol, were respected by the test subjects.

The answers of the test subjects concerning the respect of the constraints defined in the protocol were reported in the CRF.

II.2. INVESTIGATIONAL PRODUCT

Experimental conditions of application of the investigational product

All the experimental conditions of application at the investigating center defined in the protocol were respected.

II.3. CHECKING OF THE SKIN COMPATIBILITY: RECORDING OF THE SKIN REACTIONS

All the skin examinations and questioning of the test subjects were performed in accordance with the conditions defined in the protocol.

III. RESULTS

III.1. Checking of the skin compatibility

For the investigational product, the individual data of the skin examination and questioning of the test subjects are reported in **Appendices 3.**

Induction period			
Type of reaction	**Description of the reaction on the induction site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

Challenge phase			
Type of reaction	**Description of the reactions on the induction site and the virgin site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

For the control product, the individual data of the skin examination and questioning of the test subjects are reported in **Appendices 4.**

Induction period			
Type of reaction	**Description of the reaction on the induction site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

Challenge phase			
Type of reaction	**Description of the reactions on the induction site and the virgin site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

III.2. OVERALL CONCLUSION

Under the experimental conditions adopted:

- During the induction phase, the repeated applications of the product **FACE CARE FORMULA** [redacted] under occlusive patch, on a panel of 107 test subjects, with all types of skin on body induced no reaction of irritation.

- During the challenge phase, the single application of the investigational product to the induction site and virgin site induced no allergic reaction.

Based on these results, the product has a very good skin compatibility and does not show a sensitizing effect.

APPENDICES

Appendix 2/1

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	[redacted]
Ref.	[redacted]			If yes *(specify commercial denomination, active substance and dosage, pathology treated)*	
1a		/	/	/	
2a		/	/	/	
3a		/	/	/	
4a		/	/	/	
5a		/	/	/	
6a		/	/	/	
7a		/	/	/	
8a		/	/	/	
9a		/	/	/	
10a		/	/	/	
11a		/	/	/	
12a		/	/	/	
13a		/	/	/	
14a		/	/	/	
15a		/	/	/	
16a		/	/	/	
17a		/	/	/	
18a		/	/	/	
19a		/	/	/	
20a		/	/	/	

Legends: / = no *NC: Not Concerned*

Appendix 2/2

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	[redacted]
Ref.	[redacted]			If yes *(specify commercial denomination, active substance and dosage, pathology treated)*	
21a		/	/	/	
22a		/	/	/	
23a		/	/	/	
24a		/	/	/	
25a		/	/	/	
26a		/	/	/	
27a		/	/	/	
28a		/	/	/	
29a		/	/	/	
30a		/	/	/	
31a		/	/	/	
32a		/	/	/	
33a		/	/	/	
34a		/	/	/	
35a		/	/	/	
36a		/	/	/	
37a		/	/	/	
38a		/	/	/	
39a		/	/	/	
40a		/	/	/	

Legends: / = no *NC: Not Concerned*

Appendix 2/3

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	[redacted]
Ref.	[redacted]			If yes *(specify commercial denomination, active substance and dosage, pathology treated)*	
41a		/	/	/	
42a		/	/	/	
43a		/	/	/	
44a		/	/	/	
45a		/	/	/	
46a		/	/	/	
47a		/	/	/	
48a		/	/	/	
49a		/	/	/	
50a		/	/	/	
51a		/	/	/	
52a		/	/	/	
53a		/	/	/	
54a		/	/	/	
55a		/	/	/	
1b		/	/	/	
2b		/	/	/	
3b		/	/	/	
4b		/	/	/	
5b		/	/	/	
6b		/	/	/	
7b		/	/	/	

Legends: / = no *NC: Not Concerned*

Appendix 2/4

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	[redacted]
Ref.	[redacted]			If yes *(specify commercial denomination, active substance and dosage, pathology treated)*	
8b		/	/	/	
9b		/	/	/	
10b		/	/	/	
11b		/	/	/	
12b		/	/	/	
13b		/	/	/	
14b		/	/	/	
15b		/	/	/	
16b		/	/	/	
17b		/	/	/	
18b		/	/	/	
19b		/	/	/	
20b		/	/	/	
21b		/	/	/	
22b		/	/	/	
23b		/	/	/	
24b		/	/	/	
25b		/	/	/	
26b		/	/	/	
27b		/	/	/	

Legends: / = no *Withdrawal* *NC: Not Concerned*

Appendix 2/5

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	[redacted]
Ref.	[redacted]			If yes *(specify commercial denomination, active substance and dosage, pathology treated)*	
28b		/	/	/	
29b		/	/	/	
30b		/	/	/	
31b		/	/	/	
32b		/	/	/	
33b		/	/	/	
34b		/	/	/	
35b		/	/	/	
36b		/	/	/	
37b		/	/	/	
38b		/	/	/	
39b		/	/	/	
40b		/	/	/	
41b		/	/	/	
42b		/	/	/	
43b		/	/	/	
44b		/	/	/	
45b		/	/	/	
46b		/	/	/	
47b		/	/	/	

Legends: / = no [redacted] *Withdrawal* *NC: Not Concerned*

Appendix 2/6

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	[redacted]
Ref.	[redacted]			If yes *(specify commercial denomination, active substance and dosage, pathology treated)*	
48b		/	/	/	
49b		/	/	/	
50b		/	/	/	
51b		/	/	/	
52b		/	/	/	
53b		/	/	/	
54b		/	/	/	

Legends: / = no *NC: Not Concerned*

Appendix 3-1/1

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

***E: Erythema**: **0** = no visible erythema, **0.5** = very slight erythema – barely perceptible, **1** = mild erythema – faint pink, **2** = moderate erythema – well defined, **3** = severe erythema, **4** = caustic effect – erosive aspect and/or necrotic aspect*
d= diffuse / p = punctuated / peri = peripheral

***M: Additional comments/Others reactions: H or Oe** = Homogeneous infiltration / oedema, **P** = Papules, **V** = Vesicles, **B** = Bullae, **Pe** = Petechiae, **S:** Spreading beyond the patch, **SV** = Soap effect (shiny skin with possibly wrinkles), **F** = Fissuring , **D** = Desquamation, **Dr** = Dryness, **C** = Skin coloration, hyperpigmentation, **HY** = Hypopigmentation, **Fr** = Follicular reaction, **NA** = Product not applied, **T**= Tape reaction, **I** = Itching at the test site, **Cr** = Exsudation and/or Surface encrustation, **Sc** = Scab, **Pr** = Pruritus, **He** = Heating, **Pu** = Pustules, * = Additional free comments, **N9G** = No 9th grade, **X** = Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction, **Abs or "–"** = Subject absent, **MU** = Make-up patch*

/: no reaction

***A: ICDRG scale**: **IR** = Irritation reaction, **-** = No allergic reaction, **?+ =** Doubtful reaction (only slight erythema), **(+) =** Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules, **(++) =** Strong positive reaction: erythema, papules, vesicles, infiltration, **(+++) =** Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)*

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
1a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
2a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
3a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
4a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
5a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
6a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
7a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
8a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
9a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
10a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
11a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
12a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
13a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 3-1/2

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
14a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
15a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
16a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
17a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
18a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
19a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
20a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
21a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
22a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
23a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
24a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
25a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
26a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
27a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
28a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
29a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
30a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 3-1/3

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
31a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
32a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
33a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
34a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
35a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
36a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
37a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
38a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
39a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
40a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
41a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
42a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
43a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
44a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
45a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
46a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
47a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 3-1/4

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
48a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
49a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
50a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
51a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
52a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
53a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
54a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
55a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
1b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
2b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
3b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
4b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
5b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
6b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
7b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
8b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 3-1/5

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
9b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
10b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
11b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
12b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
13b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
14b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
15b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
16b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
17b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
18b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
19b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
20b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
21b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
22b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
23b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
24b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Legend: *Withdrawal*

Appendix 3-1/6

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
25b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
26b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
27b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
28b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
29b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
30b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
31b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
32b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
33b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
34b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
35b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
36b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
37b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
38b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
39b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
40b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
41b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Legend: *Withdrawal*

Appendix 3-1/7

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
42b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
43b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
44b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
45b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
46b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
47b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
48b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
49b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
50b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
51b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
52b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
53b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
54b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 3-2/1

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

***E: Erythema**: **0** = no visible erythema, **0.5** = very slight erythema – barely perceptible, **1** = mild erythema – faint pink, **2** = moderate erythema – well defined, **3** = severe erythema, **4** = caustic effect – erosive aspect and/or necrotic aspect*
d= diffuse / p = punctuated / peri = peripheral

***M: Additional comments/Others reactions: H or Oe** = Homogeneous infiltration / oedema, **P** = Papules, **V** = Vesicles, **B** = Bullae, **Pe** = Petechiae, **S:** Spreading beyond the patch, **SV** = Soap effect (shiny skin with possibly wrinkles), **F** = Fissuring , **D** = Desquamation, **Dr** = Dryness, **C** = Skin coloration, hyperpigmentation, **HY** = Hypopigmentation, **Fr** = Follicular reaction, **NA** = Product not applied, **T**= Tape reaction, **I** = Itching at the test site, **Cr** = Exsudation and/or Surface encrustation, **Sc** = Scab, **Pr** = Pruritus, **He** = Heating, **Pu** = Pustules, * = Additional free comments, **N9G** = No 9th grade, **X** = Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction, **Abs or "–"** = Subject absent, **MU** = Make-up patch*

/: no reaction

***A: ICDRG scale**: **IR** = Irritation reaction, **-** = No allergic reaction, **?+ =** Doubtful reaction (only slight erythema), **(+) =** Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules, **(++) =** Strong positive reaction: erythema, papules, vesicles, infiltration, **(+++) =** Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)*

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
1a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
2a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
3a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
4a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
5a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
6a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
7a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
8a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
9a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
10a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
11a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
12a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
13a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 3-2/2

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
14a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
15a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
16a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
17a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
18a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
19a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
20a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
21a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
22a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
23a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
24a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
25a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
26a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
27a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
28a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
29a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
30a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 3-2/3

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
31a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
32a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
33a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
34a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
35a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
36a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
37a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
38a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
39a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
40a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
41a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
42a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
43a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
44a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
45a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
46a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
47a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 3-2/4

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
48a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
49a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
50a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
51a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
52a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
53a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
54a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
55a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
1b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
2b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
3b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
4b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
5b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
6b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
7b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 3-2/5

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
8b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
9b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
10b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
11b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
12b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
13b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
14b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
15b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
16b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
17b	E						
	M						
	A						
18b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
19b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
20b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
21b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
22b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
23b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
24b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Legend: [ ] *Withdrawal*

Appendix 3-2/6

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
25b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
26b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
27b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
28b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
29b	E						
	M						
	A						
30b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
31b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
32b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
33b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
34b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
35b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
36b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
37b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
38b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
39b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
40b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Legend: *Withdrawal*

Appendix 3-2/7

INVESTIGATIONAL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
41b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
42b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
43b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
44b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
45b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
46b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
47b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
48b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
49b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
50b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
51b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
52b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
53b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
54b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 4-1/1

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

***E: Erythema**: **0** = no visible erythema, **0.5** = very slight erythema – barely perceptible, **1** = mild erythema – faint pink, **2** = moderate erythema – well defined, **3** = severe erythema, **4** = caustic effect – erosive aspect and/or necrotic aspect*
d= diffuse / p = punctuated / peri = peripheral

***M: Additional comments/Others reactions: H or Oe** = Homogeneous infiltration / oedema, **P** = Papules, **V** = Vesicles, **B** = Bullae, **Pe** = Petechiae, **S:** Spreading beyond the patch, **SV** = Soap effect (shiny skin with possibly wrinkles), **F** = Fissuring , **D** = Desquamation, **Dr** = Dryness, **C** = Skin coloration, hyperpigmentation, **HY** = Hypopigmentation, **Fr** = Follicular reaction, **NA** = Product not applied, **T**= Tape reaction, **I** = Itching at the test site, **Cr** = Exsudation and/or Surface encrustation, **Sc** = Scab, **Pr** = Pruritus, **He** = Heating, **Pu** = Pustules, * = Additional free comments, **N9G** = No 9th grade, **X** = Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction, **Abs or "–"** = Subject absent, **MU** = Make-up patch*

/: no reaction

***A: ICDRG scale**: **IR** = Irritation reaction, **-** = No allergic reaction, **?+ =** Doubtful reaction (only slight erythema), **(+) =** Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules, **(++) =** Strong positive reaction: erythema, papules, vesicles, infiltration, **(+++) =** Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)*

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
1a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
2a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
3a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
4a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
5a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
6a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
7a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
8a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
9a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
10a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
11a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
12a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
13a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 4-1/2

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
14a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
15a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
16a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
17a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
18a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
19a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
20a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
21a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
22a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
23a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
24a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
25a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
26a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
27a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
28a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
29a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
30a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 4-1/3

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
31a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
32a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
33a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
34a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
35a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
36a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
37a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
38a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
39a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
40a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
41a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
42a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
43a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
44a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
45a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
46a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
47a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 4-1/4

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
48a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
49a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
50a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
51a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
52a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
53a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
54a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
55a	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
1b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
2b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
3b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
4b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
5b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
6b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
7b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
8b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 4-1/5

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
9b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
10b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
11b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
12b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
13b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
14b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
15b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
16b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
17b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
18b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
19b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
20b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
21b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
22b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
23b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
24b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Legend: *Withdrawal*

Appendix 4-1/6

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
25b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
26b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
27b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
28b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
29b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
30b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
31b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
32b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
33b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
34b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
35b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
36b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
37b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
38b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
39b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
40b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
41b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Legend: *Withdrawal*

Appendix 4-1/7

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
42b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
43b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
44b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
45b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
46b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
47b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
48b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
49b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
50b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
51b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
52b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
53b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
54b	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 4-2/1

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

***E: Erythema**: **0** = no visible erythema, **0.5** = very slight erythema – barely perceptible, **1** = mild erythema – faint pink, **2** = moderate erythema – well defined, **3** = severe erythema, **4** = caustic effect – erosive aspect and/or necrotic aspect*
d= diffuse / p = punctuated / peri = peripheral

M: Additional comments/Others reactions: H or Oe** = Homogeneous infiltration / oedema, **P** = Papules, **V** = Vesicles, **B** = Bullae, **Pe** = Petechiae, **S:** Spreading beyond the patch, **SV** = Soap effect (shiny skin with possibly wrinkles), **F** = Fissuring , **D** = Desquamation, **Dr** = Dryness, **C** = Skin coloration, hyperpigmentation, **HY** = Hypopigmentation, **Fr** = Follicular reaction, **NA** = Product not applied, **T**= Tape reaction, **I** = Itching at the test site, **Cr** = Exsudation and/or Surface encrustation, **Sc** = Scab, **Pr** = Pruritus, **He** = Heating, **Pu** = Pustules, ** = Additional free comments, **N9G** = No 9th grade, **X** = Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction, **Abs or "–"** = Subject absent, **MU** = Make-up patch*

/: no reaction

***A: ICDRG scale**: **IR** = Irritation reaction, **-** = No allergic reaction, **?+ =** Doubtful reaction (only slight erythema), **(+) =** Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules, **(++) =** Strong positive reaction: erythema, papules, vesicles, infiltration, **(+++) =** Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)*

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
1a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
2a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
3a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
4a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
5a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
6a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
7a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
8a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
9a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
10a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
11a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
12a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
13a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 4-2/2

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
14a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
15a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
16a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
17a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
18a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
19a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
20a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
21a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
22a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
23a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
24a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
25a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
26a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
27a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
28a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
29a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
30a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 4-2/3

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
31a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
32a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
33a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
34a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
35a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
36a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
37a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
38a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
39a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
40a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
41a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
42a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
43a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
44a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
45a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
46a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
47a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 4-2/4

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
48a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
49a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
50a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
51a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
52a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
53a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
54a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
55a	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
1b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
2b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
3b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
4b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
5b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
6b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
7b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 4-2/5

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
8b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
9b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
10b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
11b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
12b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
13b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
14b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
15b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
16b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
17b	E						
	M						
	A						
18b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
19b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
20b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
21b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
22b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
23b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
24b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Legend: *Withdrawal*

Appendix 4-2/6

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
25b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
26b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
27b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
28b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
29b	E						
	M						
	A						
30b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
31b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
32b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
33b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
34b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
35b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
36b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
37b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
38b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
39b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
40b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Legend: [ ] *Withdrawal*

Appendix 4-2/7

CONTROL PRODUCT
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
41b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
42b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
43b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
44b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
45b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
46b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
47b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
48b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
49b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
50b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
51b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
52b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
53b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
54b	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

[redacted]

[redacted]

[redacted] Study No. [redacted]

[redacted]

Human Repeat Insult Patch Test with Challenge

Sponsor: [redacted]

Document type: Clinical Study Report

Study Material: Formula No. 1024355

Batch Number [redacted]

Product Type Shampooing product contains 1.5% Distearyl Ether

Study Monitor: [redacted]

Investigator: [redacted]

Document status: Final **Date:** June 12, 2006

[redacted]

SIGNATURES

[redacted]

06/06/06
Date

06/07/06
Date

STATEMENT OF QUALITY ASSURANCE

This report has been reviewed by the [redacted] Corporate Quality Assurance Department and the report accurately reflects the raw data for this study.

Clinical research studies are performed by [redacted] accordance with all applicable federal regulations and proposed guidelines for Good Clinical Practices, which include:

21 CFR Part 312,	Investigational New Drug Application
21 CFR Part 50,	Protection of Human Subjects
21 CFR Part 56,	Institutional Review Boards

[redacted]

6/12/06
Date

Study Title: Human Repeat Insult Patch Test with Challenge

Sponsor: [redacted]

Protocol #:

Contract Research Organization: [redacted]

[redacted] **Study Report #:**

Study Site:

Dates of Study: April 10, 2006 – May 19, 2006

STUDY PERSONNEL

Principal Investigator [redacted]

Clinical Research Coordinator,
Manager, Dermatological Safety Testing

Assistant Manager, Dermatological Safety Testing

Assistant Study Coordinator

TABLE OF CONTENTS

SUMMARY

One product, Formula No. 1024355, was evaluated as a 1.0% w/w aqueous solution to determine its ability to sensitize the skin of normal volunteer subjects using an occlusive human repeat insult patch test. One hundred eight subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization or significant irritation to Formula No. 1024355.

1 STUDY OBJECTIVE

The main objective of this study was to confirm that the application of a cosmetic product to volunteer subjects under maximized conditions according to the "modified Marzulli and Maibach" method did not cause a delayed contact allergic response.

Secondarily, skin compatibility of certain products may have been evaluated during the induction phase.

2 STUDY DESIGN

2.1 OVERALL STUDY DESIGN

This was a single center, within-subject comparison study of the investigational product. All subjects had sites designated for the investigational product on the infrascapular area of the back for the purpose of determining sensitization potential.

During the induction phase of the study, the study products were applied to 1 side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites was assessed clinically using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation. A total of 9 applications were made during the induction phase.

Following induction, subjects had a 2-week rest phase, after which they entered the challenge phase that consisted of one 48-hour patch application to the original site and a naive site on the opposite side of the back. Observations at the naive site during challenge and the patterns of reactivity during the induction period provided a basis for an interpretation of contact sensitization.

If a cutaneous response observed in the challenge phase indicated possible sensitization, or at the discretion of the investigator, a rechallenge was performed. In such cases, a narrative description of reactions in the challenge and rechallenge phases were reported together with the opinion of the investigator as to whether such reactions were felt to be indicative of contact sensitization.

A total of 10 patch applications were made over a period of 6 weeks.

2.2 DISCUSSION OF DESIGN

This study design is based on the Modified Draize procedure, and is accepted standard methodology used for assessment of skin sensitization [1].

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions [2].

Repeated insult patch test (RIPT) evaluation is a predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure.

2.3 STUDY PROCEDURES

2.3.1 Screening / Day 1

At Screening, the subjects were informed of the study procedures and the informed consent of each volunteer was obtained. Background information, including the date of birth, gender, and race, and a medical history for each subject was reviewed and recorded at screening. Eligibility was determined by review of the inclusion/exclusion criteria. If the subject fulfilled all the inclusion and none of the exclusion criteria, he/she was allowed to participate in the study, and received a unique enrollment number. Qualified subjects were given oral and written instructions as follows:

- When bathing, avoid getting the patches and the application areas wet by taking a low tub bath or shower the front of your body only.
- No swimming is permitted during the study.
- You must notify staff if patches come off.
- Do not engage in activities (especially sports) that cause excessive sweating.
- Throughout the entire study, and for 2 weeks after study completion, avoid exposure to the sun or tanning beds.
- Avoid excessive scrubbing around patch area, which may cause irritation and may remove patch site markings.
- Do not apply any products in or around the patch area (including sunscreens). You must notify the staff if you do.
- Inform the staff of any vaccinations and/or use of medications during the study.
- Notify the staff if anything unusual occurs at any time during the study or within 2 weeks of completing the study. Please bear in mind that if [redacted] discontinues your participation in this study due to an adverse experience or severe reaction, you will be paid for your participation.
- Please inform us if you experience any discomfort beyond mild itching. Contact us as soon as possible at [redacted]
- During the entire study, including rest week, we ask that you not participate in any other patch or photopatch study with any research company.
- Do not participate in a similar study within 3 months of completing this study.

The patches were affixed to the test sites on either the left or right side of the infrascapular area of the subject's back. The choice of left or right side was made by the clinical staff based on a visual inspection of skin clarity. A blank patch served as a negative control.

2.3.2 Induction

The induction phase consisted of a series of 9 consecutive applications of the study material and subsequent evaluations of the application sites. Patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. The subjects returned to the facility at 48-hour intervals to have the patches removed. Using a tissue, the evaluator removed any remaining excess study material to avoid transference of materials between sites. The sites were evaluated 15 to 30 minutes after patch removal using the scoring system detailed in Section 2.7.1. Scores were entered into the data sheets by the evaluator. Identical patches were then applied to the same sites. Patches applied on a Friday remained in place for 72 hours until Monday.

Subjects who missed the 9th evaluation but had 9 patch applications were considered to have completed the induction phase.

2.3.3 Rest Period

During the 2-week rest period, subjects did not receive any application of study materials.

2.3.4 Challenge

At challenge, subjects who completed the induction phase and the rest period had identical patches applied to the original sites and to naive sites. Patches remained in place for 48 hours. The sites were graded at least 30 minutes as well as 48 hours following patch removal (ie, 48 and 96 hours after patch application) using the procedures described above for the induction phase.

To be considered a **completed case**, a subject must have had 9 applications of the study material and no fewer than 8 subsequent readings during induction and 1 application followed by subsequent readings during challenge. Only completed cases were used to assess sensitization.

2.3.5 Rechallenge

At the discretion of the investigator and after discussion with the sponsor, a subject may have been rechallenged to the study material in the event of a doubtful reaction during the challenge phase. Rechallenge patches would be applied as soon as challenge reactions had resolved. The study material would be applied to naive sites on the back for 48 hours and graded at 48, 72 and 96 hours after application

A similar or more severe response observed at rechallenge would have been considered indicative of a sensitization reaction. At the investigator's discretion, further follow-up or retesting may have been necessary to confirm an interpretation of the finding.

2.3.6 Study Flow Chart

Week 1
1 Obtain informed consent, review completed medical screening form, apply patches
3 Staff removes patches, grades, applies patches
5 Staff removes patches, grades, applies patches

Week 2
1 Staff removes patches, grades, applies patches
3 Staff removes patches, grades, applies patches
5 Staff removes patches, grades, applies patches

Week 3
1-7 Same as Week 2

Week 4
1 Staff removes patches, grades
2-7 Begin rest period

Week 5
1-7 Rest period

Week 6
1 Staff applies patches
3 Staff removes patches, grades
5 Staff grades

2.4 DESCRIPTION OF PATCH CONDITIONS

Products evaluated under occlusive patch conditions are applied under a Finn Chamber. This chamber, formed of an 8 mm aluminum cup affixed to Scanpor tape, provides an isolation chamber in which the study material is placed. An amount of study material sufficient to fill the chamber (usually 20 µL) is placed within the Finn Chamber such that it does not extend onto the adhesive tape surfaces. Liquid study material is soaked into a small filter disk placed within the Finn Chamber. For gels and ointments, an amount sufficient to fill the chamber is applied. The chamber is maintained in place by a hypoallergenic adhesive strip (Micropore) and serves to limit the study material to the designated skin contact site.

Products evaluated under semi-occlusive patch conditions are applied to a 1 cm x 1 cm Webril pad. An amount of study material sufficient to cover the pad (usually 20 µL) is applied and the patch pad is secured by hypoallergenic tape (Mircropore).

2.5 SELECTION OF SUBJECTS

A sufficient number of subjects were enrolled in order to provide 100 completed subjects evaluable for analysis; an individual subject was allowed to participate in the study 1 time only.

2.5.1 Inclusion Criteria

Subjects included in the study were those who:

1. were healthy males or females, 18 to 65 years of age (no more than 10% ages 60-65), with a permanent address;

2. were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;

3. were of any skin type or race providing the skin pigmentation allowed discernment of erythema;

4. had completed a medical screening procedure; and

5. had read, understood and signed an informed consent agreement after being informed of the study procedures.

2.5.2 Exclusion Criteria

Subjects excluded from the study were those who:

1. had any visible skin disease or marks at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;

3. had psoriasis and/or atopic dermatitis/eczema;

4. were females who were pregnant, planning to become pregnant during the study, or breastfeeding;

5. had a history of contact allergies;

6. were participating in another bio-medical study or planned to concurrently to this study;

7. had an organ removed, a transplant, or suffered from a cranial trauma with after-effects;

8. had an immune deficiency;

9. had a fever lasting for more than 24 hours during the 8 days prior to the study;

10. was currently under treatment for an allergic reaction, eg, asthma, periodic spasmodic rhinitis, conjunctivitis;

11. had long-term treatment or were currently under long-term treatment involving insulin, antihistamines, corticoids, beta-blocker (including eye drops) antibiotics, immunosuppressive drugs (cyclosporine) and/or were in a period of de-sensitization;

12. had treatment with vitamin A or its derivatives less than 3 months prior to the study;

13. had been vaccinated in the 3 weeks prior to the study or intended to be vaccinated during the study;

14. had a sensitivity to tape or patches;

15. showed a disorder due to excessive alcohol or drug use; and/or

16. had the test area exposed to natural sunshine or UV lamp during the month prior to the study.

2.5.3 Informed Consent

A properly executed informed consent document in compliance with FDA regulations (21 CFR Part 50) was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix III).

2.5.4 Interruption or Discontinuation of Treatment

In accordance with legal requirements and ICH-GCP guidelines, every subject or his/her legal representative had the right to refuse further participation in the study at any time and without providing reasons. A subject's participation was terminated immediately upon his/her request. The investigator or designee was to seek to obtain and record the reason.

The termination of an individual's participation was to be considered in the case of a serious adverse event (SAE). If the subject, during the course of the study, developed a condition(s) which would have prevented his/her entry into the study according to the safety-related medical exclusion criteria, he/she was to be withdrawn immediately.

The subject may have been withdrawn from the study at any time at the discretion of the investigator for medical reasons and/or due to non-adherence to the treatment scheme and other duties stipulated in the study protocol. The reasons were to be fully documented on the CRF.

An erythema score of 2 or more to a study product (see Section 2.7.1 for interpretation of score) observed at the first or second reading of the induction phase would have indicated the subject was most likely pre-sensitized and application of the product in question would have been discontinued. If this reaction was observed in subsequent readings, this would have necessitated a change in patch location to an adjacent site, and potentially patch conditions, for the remaining applications in the induction phase. In the case of an allergic reaction, the product would not be applied and the decision to reapply would be discussed with the sponsor.

Withdrawals

The following medical and other reasons justified a premature termination (by subject or investigator) of any of the study products:

- withdrawal of informed consent,
- serious adverse events,
- allergic reactions to the study materials,
- subject’s request,
- occurrence of one of the safety criteria for exclusion after treatment had been instituted,
- the patches became dislodged or were misplaced such that continuous contact with the skin had been interrupted,
- subject was lost to follow-up, and/or
- investigator’s judgment.

If a subject withdrew from the study, all efforts were made to complete a final evaluation, if possible. Subjects discontinued for having experienced an adverse event (AE) were followed until the AE was resolved, a reasonable explanation was provided for the event, or the subject was referred to his/her own primary medical doctor (PMD). The specific AE in question was recorded on the appropriate CRF.

2.6 STUDY MATERIAL

2.6.1 Study Material Specifications

IP Category	:	Shampooing
Formula Number	:	1024355
Batch Number	:	[redacted]
Description	:	
Amount Applied	:	20 uL
Patch Condition	:	occlusive
Evaporation	:	no
Dilution	:	yes (1% in water)
Special Instructions	:	Change to semi-occlusive patch if reactions occur.

2.6.2 Storage, Handling, and Documentation of Study Products

Receipt of the material used in this study was documented in a general log book which serves as a permanent record of the receipt, storage, and disposition of all study material received by [redacted] On the basis of information provided by the sponsor, the study material was considered reasonably safe for evaluation on human subjects. All study material is kept in a locked product storage room accessible to clinical staff members only. The study material was destroyed upon acceptance of the final report and a sample will be retained for a period of 6 months.

2.6.3 Treatment Compliance

All patches were applied and removed by clinical study staff. Whereas bathing was allowed (low tub bath/frontal showers), the patched area was not to be soaked and was to be kept as dry as possible, per the instructions given to each subject (see Section 2.3.1). A trained, experienced evaluator assessed study compliance. Records of patch applications and visit schedule compliance were recorded on the subjects' CRFs.

2.7 SAFETY EVALUATIONS

2.7.1 Local Tolerability Assessments

Assessment of the patch sites was performed 9 times during the induction phase, 2 times following challenge and, if applicable, 3 times following rechallenge. The scores outlined in Text Tables 2-1 and 2-2 were used to express the response observed at the time of examination. Other notations are outlined in Text Table 2-3.

Text Table 2-1 Erythema Results (E)

Response	Score
No Visible Erythema	0
Doubtful Erythema	+/-
Mild Erythema (faint pink)	1
Moderate Erythema (well defined)	2
Severe Erythema; definite edema	3
Caustic Erythema – erosive aspect and/or necrotic aspect	4

Text Table 2-2 Allergic Results (A)

Response	Score
No Reaction	0
Weak Positive Reaction: erythema, infiltration, possibly papules	1
Strong Positive Reaction: erythema, vesicles, papules, infiltration	2
Extreme Positive Reaction: intense erythema, infiltration, vesicles may coalesce to form a blister	3

Text Table 2-3 Additional Comments (M)

Response	Symbol
Oedema	E
Papules	P
Vesicles	V
Bullae	B
Spreading of Reaction Beyond Patch Area	S
Petechiae	Pe
Soap Effect	SV
Fissuring	F
Desquamation	D
Dryness	Dr
Skin Coloration – Hyperpigmentation	C
Hypopigmentation	H
Follicular Reaction	Fr
Not Applied	NA
Tape Reaction	T
Additional Free Comments	*
No Ninth Grading	N9G
Exudation and/or Surface Encrustation	Cr
Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction	X**
Subject Absent	-

** The symbol X was used to denote subject absence instead of the symbol -.

2.7.2 Adverse Events

An adverse event is defined as an occurrence of a new symptom(s) of a medical nature during use of the study material whether or not considered related to the study material, eg, headache, influenza, broken bones, fever, nausea. A serious adverse event is defined as death, a life threatening adverse experience, inpatient hospitalization, a persistent or significant disability/incapability, or a congenital anomaly/birth defect. Serious adverse events were to be reported to the sponsor within 24 hours of the investigative personnel's knowledge of the event. All AEs, whether observed by the clinical staff or by the subject, and whether or not thought to be study-related, were to be recorded on an Adverse Event form. Assessment of severity and causality will be based on definitions found on the AE form. Pregnancy, although not itself an adverse event, was also to be reported on an adverse event form.

Expected Adverse Events

Any observed response that was denoted using the irritation criteria summarized in Text Tables 2-1, 2-2, and 2-3 was not considered an AE. Likewise, any tape-related irritation was not noted as an AE.

2.8 QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, the medical screening forms and informed consent documents were reviewed in-process of the study, and the regulatory binder was reviewed post-study.

2.9 QUALITY ASSURANCE

The [redacted] conducted a systematic and independent examination of study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, standard operating procedures (SOPs), and good clinical practice (GCP), and the appropriate regulatory requirements.

3 DATA MANAGEMENT

3.1 DOCUMENTATION

[redacted]

3.2 DATABASE MANAGEMENT AND QUALITY CONTROL

Data were double-keyed and validated using ClinPlus (DZS Software Solutions), which directly generated SAS® data sets. After resolution of double-key discrepancies and a combination of manual and automated data review procedures, the final data sets were subject to a quality assurance (QA) audit. SAS® programs for data analysis and presentation were applied to secure validated data sets.

4 STATISTICAL METHODS

4.1 SAMPLE SIZE

With a sample size of 100, in the absence of any sensitization reactions, a 95% upper confidence bound on the population rate of sensitization would be 3.5%.

4.2 POPULATIONS

All subjects who were treated were evaluable for adverse events. The evaluation of sensitization was based on all subjects who completed the challenge phase of the study.

4.3 SAFETY ANALYSES

Dermal Sensitization Potential

The determination of dermal sensitization potential was based on specific scoring criteria derived from observations in the challenge phase of the study, and confirmed in the rechallenge phase, if necessary.

The recurrence of a cutaneous response at rechallenge equivalent to or more severe than that observed at challenge was considered indicative of a sensitization reaction. The observation of such a response in even a single subject suggested that the study product may have the potential to cause hypersensitivity.

For all subjects who entered rechallenge, a narrative description of reactions in the challenge and rechallenge phases was to be provided together with the opinion of the investigator as to whether such reactions were felt to be indicative of contact sensitization.

4.4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Per protocol, a sufficient number of subjects were to be enrolled such that 100 subjects would be evaluable for analysis. Actual enrollment was 117 subjects; a total of 108 subjects completed the study and were evaluable for sensitization analysis.

5 RESULTS

Summary data tables are provided in Appendix I of this report. Supportive listings are provided in Appendix II.

5.1 SUBJECTS EVALUATED

5.1.1 Subject Disposition

Subject disposition is shown in Table 1 and summarized in Text Table 5-1; these data are supported by Data Listing 1.

Text Table 5-1 Subject Disposition

Number of subjects enrolled	117
Number of subjects treated	115
Number of subjects discontinued	9
Lost to follow-up	5
Voluntarily withdrew consent	3
Protocol violation (subject scratched patch area)	1
Number of subjects completed	108

Source: Appendix I, Table 1

5.1.2 Protocol Deviations

Subject 112 scratched the patch area, which made the area unevaluable. The subject was discontinued from the study.

5.1.3 Baseline Demographic and Background Characteristics

Demographic information is summarized in Table 2; these data are supported by Data Listing 2. The study population was comprised of 96 (82%) females and 21 (18%) males; 81 (69%) Caucasians, 35 (30%) Hispanics, and 1 (1%) Black. Subject ages ranged from 19 to 65 years; the mean subject age was 46 years.

5.2 SAFETY RESULTS

5.2.1 Induction and Challenge Responses

One hundred eight subjects completed the induction phase and were included in determining the presence of significant irritation. One hundred eight subjects completed the challenge phase of the study and were included in the sensitization analysis. A summary of the repeated insult patch test responses during the induction and challenge phases of the study is provided in Table 3, Appendix I, a by-subject listing of the sensitization response data is provided in Data Listing 3 Appendix II.

5.2.2 Overall Experience of Adverse Events

There were no adverse events reported.

6 CONCLUSIONS

Under the conditions employed in this study, there was no evidence of sensitization or irritation to Formula No. 1024355.

7 REFERENCES

1. Jordan, WP. 24-, 48-, and 48/48-hour Patch Tests. *Contact Dermatitis* 1980. 6: 151-152.

2. Lanman, BM, EB Elvers, and CJ Howard. "The Role of Human Patch Testing in a Product Development Program." Joint Conference on Cosmetic Goods Association, Washington DC, April 21-23, 1968.

APPENDIX II

DATA LISTINGS

DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

Page 1 of 3

Subject No.	Study Dates: Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days on Study
1	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
2	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
3	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
4	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
5	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
6	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
7	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
8	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
9	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
10	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
11	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
12	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
13	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
14	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
15	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
16	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
17	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
18	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
19	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
20	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
21	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
22	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
23	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
24	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
25	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
26	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
27	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
28	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
29	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
30	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
31	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
32	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
33	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
34	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
35	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
36	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
37	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
38	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
39	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40

Key: Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal
V=Protocol violation, AE=Adverse event, O=Other)

Program: DISPLIST1.SAS/USES: DEMOGS, LRESPONS, FINAL/26MAY06:11:15:12

DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION
Page 2 of 3

Subject No.	Study Dates: Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days on Study
40	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
41	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
42	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
43	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
44	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
45	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
46	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
47	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
48	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
49	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
50	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
51	04/10/06	04/10/06		04/24/06	I5	S	15
52	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
53	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
54	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
55	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
56	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
57	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
58	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
59	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
60	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
61	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
62	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
63	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
64	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
65	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
66	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
67	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
68	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
69	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
70	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
71	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
72	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
73	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
74	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
75	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
76	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
77	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
78	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40

Key: Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal
V=Protocol violation, AE=Adverse event, O=Other)

Program: DISPLIST1.SAS/USES: DEMOGS, LRESPONS, FINAL/26MAY06:11:15:12

DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION
Page 3 of 3

Subject No.	Study Dates: Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days on Study
79	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
80	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
81	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
82	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
83	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
84	04/10/06	04/10/06		04/12/06	I0	L	3
85	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
86	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
87	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
88	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
89	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
90	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
91	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
92	04/10/06	04/10/06		04/12/06	I0	L	3
93	04/10/06	04/10/06		04/17/06	I2	S	8
94	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
95	04/10/06	04/10/06		04/21/06	I4	S	12
96	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
97	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
98	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
99	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
100	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
101	04/10/06	04/10/06		04/14/06	I1	L	5
102	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
103	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
104	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
105	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
106	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
107	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
108	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
109	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
110	04/10/06	04/10/06		04/21/06	I4	L	12
111	04/10/06	04/10/06		04/21/06	I4	L	12
112	04/10/06	04/10/06		04/21/06	I4	V	12
113	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
114	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
115	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
116	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40
117	04/10/06	04/10/06	05/15/06	05/19/06	C2	C	40

Key: Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal
V=Protocol violation, AE=Adverse event, O=Other)

Program: DISPLIST1.SAS/USES: DEMOGS, LRESPONS, FINAL/26MAY06:11:15:12

DATA LISTING 2: SUBJECT DEMOGRAPHICS

Subject No.	Age	Gender	Race
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
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21			
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32			
33			
34			
35			
36			
37			
38			
39			
40			

Program: DEMOLIST.SAS/USES: DEMOGS/26MAY06:11:15:13

DATA LISTING 2: SUBJECT DEMOGRAPHICS
Page 2 of 3

Subject No.	Age	Gender	Race
41	[redacted]		
42			
43			
44			
45			
46			
47			
48			
49			
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51			
52			
53			
54			
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72			
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74			
75			
76			
77			
78			
79			
80			

Program: DEMOLIST.SAS/USES: DEMOGS/26MAY06:11:15:13

DATA LISTING 2: SUBJECT DEMOGRAPHICS
Page 3 of 3

Subject No.	Age	Gender	Race
81	[redacted]		
82			
83			
84			
85			
86			
87			
88			
89			
90			
91			
92			
93			
94			
95			
96			
97			
98			
99			
100			
101			
102			
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104			
105			
106			
107			
108			
109			
110			
111			
112			
113			
114			
115			
116			
117			

Program: DEMOLIST.SAS/USES: DEMOGS/26MAY06:11:15:13

DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

[redacted]

											-----Challenge Phase----					
	----------Induction Reading----------										48-hour		96-hour		120-hour(*)	
Subject	1	2	3	4	5	6	7	8	9		L	R	L	R	L	R
No.	EAM	EAM	EAM	EAM	EAM	EAM	EAM	EAM	EAM	MU	EAM	EAM	EAM	EAM	EAM	EAM
1	00	00	00	00	00	00	00	00	00		00	00	00	00		
2	00	00	00	00	00	00	00	00	00		00	00	00	00		
3	00	00	00	00	00	00	00	10	10		00	00	00	00		
4	00	10	00	10	00	00	00	00	10		00	00	00	00		
5	00	00	00	00	00	00	00	00	00		00	00	00	00		
6	00	00	00	10	00	00	10	10	10		00	00	00	00		
7	00	00	00	00	00	00	00	00	00		00	00	00	00		
8	00	00	00	10	00	00	00	00	00		00	00	00	00		
9	00	00	00	00	00	00	00	10	10		00	00	00	00		
10	00	00	00	00	00	10	10	00	10		00	00	00	00		
11	00	00	00	00	00	00	00	00	00		00	00	00	00		
12	00	00	00	00	00	00	00	00	00		00	00	00	00		
13	00	00	00	10	00	00	00	00	00		00	00	00	00		
14	00	00	00	00	00	00	00	00	00		00	00	00	00		
15	00	00	00	00	10	10	10	10	10		00	00	00	00		
16	00	00	00	10	00	00	00	10	00		00	00	00	00		
17	00	00	00	00	00	00	00	00	00		00	00	00	00		
18	00	00	00	00	00	00	00	00	00		00	00	00	00		
19	00	00	00	00	00	00	00	00	00		00	00	00	00		
20	00	00	00	00	00	00	00	00	00		00	00	00	00		
21	00	00	00	00	00	00	00	00	00		00	00	00	00		
22	00	00	00	00	00	00	10	00	10		00	00	00	00		
23	00	00	00	00	00	00	00	00	00		00	00	00	00		

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores
Program: DETAIL5.SAS/Uses: LRESPONS, PRODLIST/26MAY06:11:15:16

DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

	Induction Reading										Challenge Phase					
											48-hour		96-hour		120-hour(*)	
Subject	1	2	3	4	5	6	7	8	9		L	R	L	R	L	R
No.	EAM	EAM	EAM	EAM	EAM	EAM	EAM	EAM	EAM	MU	EAM	EAM	EAM	EAM	EAM	EAM
24	00	00	00	00	00	00	00	00	00		00	00	00	00		
25	00	00	00	00	00	00	00	00	00		00	00	00	00		
26	00	00	00	00	00	00	00	10	00		00	00	00	00		
27	00	00	00	00	00	00	00	00	00		00	00	00	00		
28	00	00	00	00	00	00	00	10	10		00	00	00	00		
29	00	00	00	00	00	00	00	00	00		00	00	00	00		
30	00	00	00	00	00	00	00	00	00		00	00	00	00		
31	00	00	00	00	00	00	10	10	10		00	00	00	00		
32	00	00	00	00	00	00	00	00	00		00	00	00	00		
33	00	00	00	00	00	00	00	00	00		00	00	00	00		
34	00	00	00	00	00	00	10	10	00		00	00	00	00		
35	00	00	00	00	00	00	00	00	00		00	00	00	00		
36	00	00	00	00	00	00	00	00	00		00	00	00	00		
37	00	00	00	00	00	00	00	10	00		00	00	00	00		
38	00	00	00	00	00	00	00	00	00		00	00	00	00		
39	00	00	00	00	00	00	00	00	00		00	00	00	00		
40	00	00	00	00	00	00	00	00	00		00	00	00	00		
41	00	00	00	00	00	00	00	00	00		00	00	00	00		
42	00	10	00	10	10	10	00	10	10		10	10	10	10		
43	00	00	00	00	00	00	00	00	00		00	00	00	00		
44	00	00	00	00	00	00	00	00	00		00	00	00	00		
45	00	00	00	00	00	00	00	00	00		00	00	00	00		
46	00	00	00	00	00	00	00	00	00		00	00	00	00		

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores
Program: DETAIL5.SAS/Uses: LRESPONS, PRODLIST/26MAY06:11:15:16

DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

											-----Challenge Phase----					
	----------Induction Reading----------										48-hour		96-hour		120-hour(*)	
Subject	1	2	3	4	5	6	7	8	9		L	R	L	R	L	R
No.	EAM	EAM	EAM	EAM	EAM	EAM	EAM	EAM	EAM	MU	EAM	EAM	EAM	EAM	EAM	EAM
47	00	00	00	00	00	00	00	00	00		00	00	00	00		
48	00	00	00	00	00	00	00	00	00		00	00	00	00		
49	00	00	00	00	00	00	00	00	00		00	00	00	00		
50	00	00	00	00	00	00	00	00	00		00	00	00	00		
51	00	00	00	00	00	X	--	--	--		--	--	--	--		
52	00	00	00	10	10	10	10	10	10		00	00	00	00		
53	00	00	00	10	00	00	00	00	10		00	00	00	00		
54	00	00	00	00	10	00	00	10	10		00	00	00	00		
55	00	00	00	10	10	10	10	10	10		00	00	00	00		
56	00	00	00	00	00	00	00	00	00		00	00	00	00		
57	00	00	00	00	00	00	00	10	00		00	00	00	00		
58	00	00	00	00	00	00	00	00	00		00	00	00	00		
59	00	00	00	00	00	00	00	00	00		00	00	00	00		
60	00	00	00	00	00	00	10	10	10		00	00	00	00		
61	00	00	00	10	00	10	10	10	10		00	00	00	00		
62	00	00	10	10	10	10	10	00	00		00	00	00	00		
63	00	00	00	00	00	00	00	00	00		00	00	00	00		
64	00	00	00	00	00	00	00	00	00		00	00	00	00		
65	00	00	00	10	00	00	00	10	00		00	00	00	00		
66	00	00	00	00	00	10	10	10	10		00	00	00	00		
67	00	00	00	00	00	00	00	10	10		00	00	00	00		
68	00	00	00	00	00	00	00	00	00		00	00	00	00		
69	00	00	00	00	00	00	00	00	00		00	00	00	00		

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores
Program: DETAIL5.SAS/Uses: LRESPONS, PRODLIST/26MAY06:11:15:16

DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

[redacted]

	Induction Reading										Challenge Phase					
											48-hour		96-hour		120-hour(*)	
Subject No.	1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	MU	L EAM	R EAM	L EAM	R EAM	L EAM	R EAM
70	00	00	00	00	00	00	00	10	00		00	00	00	00		
71	00	00	00	00	00	00	00	00	00		00	00	00	00		
72	00	00	00	00	00	00	00	00	00		00	00	00	00		
73	00	00	00	00	00	00	00	10	00		00	00	00	00		
74	00	00	00	00	00	00	00	10	00		00	00	00	00		
75	00	00	00	00	00	00	00	00	00		00	00	00	00		
76	00	00	00	00	00	00	00	00	00		00	00	00	00		
77	00	00	00	00	00	00	00	00	00		00	00	00	00		
78	00	00	00	00	00	00	00	00	00		00	00	00	00		
79	00	00	00	00	00	00	00	00	00		00	00	00	00		
80	00	00	00	00	00	00	00	00	10		00	00	00	00		
81	00	00	00	00	00	00	00	00	00		00	00	00	00		
82	00	00	00	00	00	00	00	00	00		00	00	00	00		
83	00	00	00	00	00	00	10	10	10		00	00	00	00		
84	X	--	--	--	--	--	--	--	--		--	--	--	--		
85	00	00	00	00	00	00	00	10	10		00	00	00	00		
86	00	00	00	10	00	00	00	00	00		00	00	00	00		
87	00	00	00	00	00	00	00	00	00		00	00	00	00		
88	00	00	00	10	10	00	10	10	10		00	00	00	00		
89	00	00	00	00	00	00	00	00	00		00	00	00	00		
90	00	00	00	00	00	00	00	00	00		00	00	00	00		
91	00	00	00	00	00	00	00	00	00		00	00	00	00		
92	X	--	--	--	--	--	--	--	--		--	--	--	--		

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores
Program: DETAIL5.SAS/Uses: LRESPONS, PRODLIST/26MAY06:11:15:16

DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

	Induction Reading										Challenge Phase: 48-hour		96-hour		120-hour(*)	
Subject No.	1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	MU	L EAM	R EAM	L EAM	R EAM	L EAM	R EAM
93	00	00	X	--	--	--	--	--	--		--	--	--	--		
94	00	00	00	00	00	00	00	00	00		00	00	00	00		
95	00	00	00	00	X	--	--	--	--		--	--	--	--		
96	00	00	00	00	00	00	00	00	00		00	00	00	00		
97	00	00	00	00	00	00	00	00	00		00	00	00	00		
98	00	00	00	00	00	00	00	00	10		00	00	00	00		
99	00	00	00	00	00	00	00	00	00		00	00	00	00		
100	00	00	00	10	00	00	10	10	10		00	00	00	00		
101	00	X	--	--	--	--	--	--	--		--	--	--	--		
102	00	00	00	10	00	00	10	10	10		00	00	00	00		
103	00	00	00	00	00	00	00	00	00		00	00	00	00		
104	00	00	00	00	00	00	00	00	00		00	00	00	00		
105	00	00	00	00	00	00	00	00	00		00	00	00	00		
106	00	00	00	00	00	00	00	00	00		00	00	00	00		
107	00	00	00	10	00	00	10	00	00		00	00	00	00		
108	00	00	00	00	00	00	00	00	00		00	00	00	00		
109	00	00	00	00	00	00	00	00	10		00	00	00	00		
110	00	00	00	00	X	--	--	--	--		--	--	--	--		
111	00	00	00	00	X	--	--	--	--		--	--	--	--		
112	00	00	00	00	X	--	--	--	--		--	--	--	--		
113	00	00	00	00	00	00	00	00	00		00	00	00	00		
114	00	00	00	00	00	00	00	00	00		00	00	00	00		
115	00	00	00	00	00	00	00	00	00		00	00	00	00		
116	00	00	00	00	00	00	00	00	00		00	00	00	00		
117	00	00	00	00	00	00	00	00	00		00	00	00	00		

(*) when required
E = Erythema results A = Allergic results M = Additional comments MU = Make-up visit
See Table 3.1 for Key to Symbols and Scores Program: DETAIL5.SAS/Uses: LRESPONS, PRODLIST/26MAY06:11:15:16

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: April 12, 2021

SUBJECT: Cetyl Dimethylbutyl Ether

Anonymous. 2021. Summary information Cetyl Dimethylbutyl Ether.

April 2021

Summary Information Cetyl Dimethylbutyl Ether

1. Method of manufacture

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

2. Dermal irritation and sensitization data

HRIPT (24 hours, occlusive patches) was conducted (completed May 31, 2019) on a dermal contact leave-on product containing Cetyl Dimethylbutyl Ether at 19.3%. 99 subjects completed the test. Neither dermal irritation nor skin sensitization was induced.

3. Genotoxicity

Ames test (*Salmonella typhimurium* TA98 and TA100; 20 – 5000 μg Cetyl Dimethylbutyl Ether/ plate; with and without S9 mix) – Negative.

Concentration of Use by FDA Product Category – Dialkyl Ethers*

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

Ingredient	Product Category	Maximum Concentration of Use
Dicaprylyl Ether	Baby lotions, oils and creams Not powder	0.45%
Dicaprylyl Ether	Hair conditioners	0.14-4.8%
Dicaprylyl Ether	Hair sprays Pump spray	10%
Dicaprylyl Ether	Shampoos (noncoloring)	0.06%
Dicaprylyl Ether	Tonics, dressings and other hair grooming aids	24%
Dicaprylyl Ether	Foundations	18%
Dicaprylyl Ether	Other makeup preparation	3%
Dicaprylyl Ether	Deodorants Not spray	10.3%
Dicaprylyl Ether	Aftershave lotions	8%
Dicaprylyl Ether	Shaving cream	0.0019%
Dicaprylyl Ether	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.34-14.2%
Dicaprylyl Ether	Face and neck products Not spray	2-4%
Dicaprylyl Ether	Body and hand products Not spray	5-25%
Dicaprylyl Ether	Moisturizing products Not spray	0.005-5%
Dicaprylyl Ether	Night products Not spray or powder	6%
Dicaprylyl Ether	Other skin care preparations	10%
Dicaprylyl Ether	Suntan products Not spray	1-6%
Distearyl Ether	Eye lotions	0.05%
Distearyl Ether	Shampoos (noncoloring)	0.23%
Distearyl Ether	Suntan products Not spray	0.05%
Cetyl Dimethylbutyl Ether	Foundations	19.3%
Cetyl Dimethylbutyl Ether	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	13.3%
Cetyl Dimethylbutyl Ether	Moisturizing products Not spray	10%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2019
Table prepared: July 23, 2019

2021 VCRP Frequency of Use Data – Fatty Ethers

INGREDIENT_NAME	CATEGORY	CPIS_COUNT
Dicaprylyl Ether		
Total Uses: 239		
Dicaprylyl Ether	01A - Baby Shampoos	1
Dicaprylyl Ether	01B- Baby Lotions, Oils, Powders, and Creams	1
Dicaprylyl Ether	01C - Other Baby Products	1
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	8
Dicaprylyl Ether	05E - Rinses (non-coloring)	1
Dicaprylyl Ether	05F - Shampoos (non-coloring)	10
Dicaprylyl Ether	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
Dicaprylyl Ether	05I - Other Hair Preparations	6
Dicaprylyl Ether	07B - Face Powders	1
Dicaprylyl Ether	07C - Foundations	1
Dicaprylyl Ether	07E - Lipstick	5
Dicaprylyl Ether	07F - Makeup Bases	1
Dicaprylyl Ether	10A - Bath Soaps and Detergents	4
Dicaprylyl Ether	10B - Deodorants (underarm)	10
Dicaprylyl Ether	10E - Other Personal Cleanliness Products	1
Dicaprylyl Ether	11A - Aftershave Lotion	1
Dicaprylyl Ether	11E - Shaving Cream	1
Dicaprylyl Ether	11G - Other Shaving Preparation Products	2
Dicaprylyl Ether	12A - Cleansing	7
Dicaprylyl Ether	12B - Depilatories	1
Dicaprylyl Ether	12C - Face and Neck (exc shave)	39
Dicaprylyl Ether	12D - Body and Hand (exc shave)	25
Dicaprylyl Ether	12F - Moisturizing	65
Dicaprylyl Ether	12G - Night	11
Dicaprylyl Ether	12H - Paste Masks (mud packs)	1
Dicaprylyl Ether	12J - Other Skin Care Preps	7
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: 4		
Distearyl Ether	05F - Shampoos (non-coloring)	4