Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics

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

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/ Writer, CIR.

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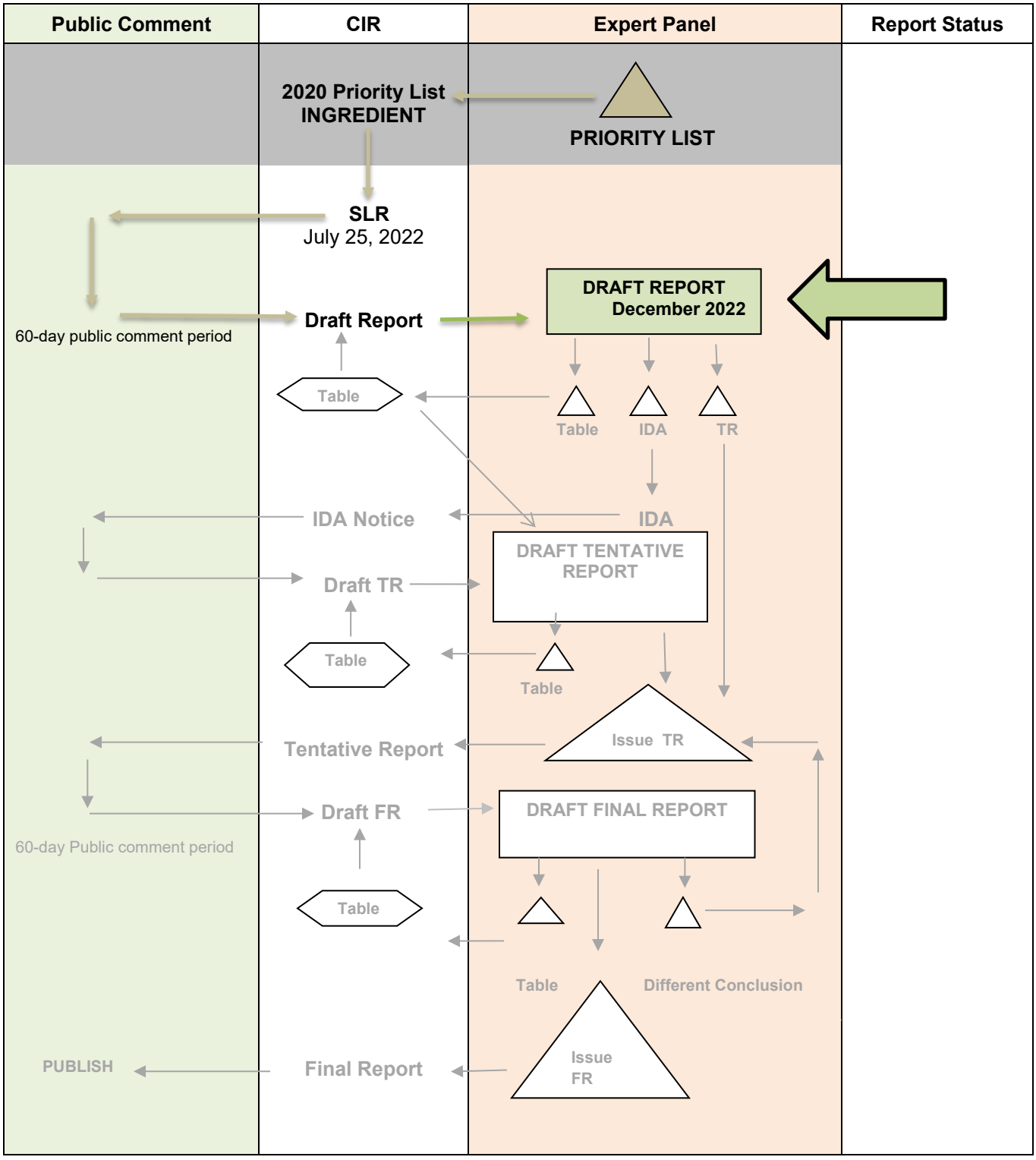
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Olea europaea* (Olive)-Derived Ingredients

MEETING December 2022



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Analyst/Writer, CIR
Monice M. Fiume, Senior Director, CIR
Date: November 10, 2022
Subject: Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Report on the Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics. (It is identified as *report_Olive_122022* in the pdf document). The Scientific Literature Review (SLR) of these 20 ingredients was issued by CIR on July 25, 2022. Most of the *Olea europaea* (olive)-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin-conditioning agents (emollient, humectant, or miscellaneous). Olea Europaea (Olive) Husk Powder and Olea Europaea (Olive) Seed Powder are reported to only function as abrasives.

According to 2022 VCRP survey data (*VCRP_Olive_122022*), Olea Europaea (Olive) Leaf Extract has the highest frequency of use; it is reported to be used in 182 formulations, with a majority of uses in leave-on skin care preparations. Olea Europaea (Olive) Fruit Extract is reported to be used in 118 formulations, also with the majority of uses in leave-on skin care preparations. All other in-use ingredients are reported to be used at much lower numbers. The results of the concentration of use survey conducted by the Council in 2020 (*data1_Olive_122022*) indicate that Olea Europaea (Olive) Leaf Extract has the highest concentration of use in a leave-on formulation; it is used at up to 2% in suntan preparations. The highest concentration of use reported for products resulting in rinse-off dermal exposure is 10% in Olea Europaea (Olive) Fruit Unsaponifiables in shaving cream. Eleven ingredients are reported to be not in use, according to the VCRP and industry survey.

At the September 2022 Panel meeting, a change to the current Use Table format was discussed. At that time, the Panel requested that both Use Table formats (i.e., the existing and the proposed format) be included in a Draft Report to provide a side-by-side comparison. That has been presented in this document to impart an example of the different formats in a report with numerous ingredients. It should be noted that while most of the descriptors in the body of the report highlighting the types of use of the ingredients (i.e., inhalation, mucous membrane, etc.) will remain if the new format is adopted, reference to the highest leave-on/rinse-off concentrations of use will not be included, in that it is not definitively known what the duration of exposure is for all formulations. (This is one of the driving issues behind the consideration of a new Use Table format.) **CIR is asking that you compare the tables and provide your preference as to which format should be used in all future safety assessments.**

In addition to concentration of use survey data, the Council provided the following data:

- method of manufacturing on Olea Europaea (Olive) Leaf Extract, Olea Europaea (Olive) Leaf Water, and Olea Europaea (Olive) Leaf Powder (*data2_Olive_122022*)
- method of manufacturing on Olea Europaea (Olive) Fruit Extract (*data3_Olive_122022*)
- human dermal irritation, sensitization, and photosensitization data on Olea Europaea (Olive) Leaf Extract, Olea Europaea (Olive) Fruit Extract, and Olea Europaea (Olive) Seed Powder (*data4_Olive_122022* and *data5_Olive_122022*)
- method of manufacturing, chemical properties, and composition data on Olea Europaea (Olive) Leaf Extract and Olea Europaea (Olive) Fruit Extract (*data6_Olive_122022*)
- method of manufacturing and composition data on Olea Europaea (Olive) Fruit Juice Extract and method of manufacturing, composition data, animal safety test data, and animal and human dermal irritation and sensitization data on Olea Europaea (Olive) Leaf Extract (*data7_Olive_122022*)

The Panel should note that information from one supplier (*data3_Olive_122022*) states that the product they sell under the INCI name Olea Europaea (Olive) Fruit Extract is actually olive oil. The ingredient names for olive fruit extract and olive oil cover similar materials and may in some cases be synonymous. As a reminder, the Panel has previously reviewed the safety of Olea Europaea (Olive) Fruit Oil and concluded that this ingredient is safe for use in cosmetics.

Comments provided by the Council on the SLR have been addressed (*PCPCcomments_Olive_122022* and *response-PCPCcomments_Olive_122022*). Of note for Panel consideration, the Council has asked if Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, and Hydrolyzed Olive Leaf Extract should be included in this safety assessment. Currently, no uses are reported in the VCRP for these ingredients. The safety assessment does include data on hydrolyzed olive fruit extract that the Panel may or may not

consider relevant to assessing the safety of the ingredients currently listed in the report. **Does the Panel want to add these 3 ingredients to the safety assessment?**

Other supporting documents for this report package include a flow chart (*flow_Olive_122022*), report history (*history_ Olive_122022*), a search strategy (*search_ Olive_122022*), and a data profile (*dataprofile_Olive_122022*).

If no further data are needed to reach a conclusion of safety, the Panel should formulate a Discussion and issue a Tentative Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an Insufficient Data Announcement.

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: August 4, 2022

SUBJECT: Scientific Literature Review: Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics (release date: July 25, 2022)

The Personal Care Products Council has no suppliers listed for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) Leaf and Olea Europaea (Olive) Wood Extract.

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of *Olea Europaea* (Olive)-Derived Ingredients as Used in Cosmetics.

Key Issues

Since the CIR report includes data on a hydrolyzed olive fruit extract, perhaps the following INCI names should be added to the report: Hydrolyzed Olive Fruit and Hydrolyzed Olive Fruit Extract. Hydrolyzed Olive Leaf Extract should also be considered for addition to this report.

When studies from reference 69 are presented (both in the text and tables), it should state that the hydrolyzed olive pulp extract was an aqueous extract (as stated in the title of the reference).

Additional Considerations

Introduction; Summary – Please revise the following sentence as it suggests that "skin bleaching agent" is an example of multiple drug functions reported for these ingredients. "Functions such as skin bleaching agent (reported for Olea Europaea (Olive) Fruit Extract and Olea Europaea (Olive) Leaf Extract) are not considered cosmetic functions in the United States (US) and, therefore, are not addressed in this assessment." It should be made clear that "skin bleaching" is the only drug function reported for two of the ingredients in this report.

Non-Cosmetic Use – Please provide some examples of the chronic conditions for which olive leaves have been historically used as an herbal drug in the Mediterranean.

Acute – Units of mg/kg bw should be called “dose” not “concentration”.

Short-Term and Subchronic – Please state the species used in the 42-day study of the aqueous olive leaf extract.

DART – Please state the species used in the developmental toxicity study of hydrolyzed olive pulp.

Summary – The durations of the repeat-dose studies should be stated in the summary. Please correct “maximum concentration tested of 1000 mg/kg bw/d” to “maximum dose tested of 1000 mg/kg bw/d”.

Table 5 – Because different solvents were used, can the concentrations of constituents in the Italian cultivars really be compared to the Tunisian cultivars? Perhaps the word “Comparison” should be removed from the title of this table.

Table 8, reference 70 – Please check this study. Did the authors consider the “significant differences in hematological parameters” to have biological significance? A conclusion for this paper available on the internet says: “Measured hematological and biochemical parameters and histopathology corroborated the results, since they did not show any abnormalities, regardless of gender and age of the animals studied.”

Reference 70 – Please correct “ehtanolic”

***Olea europaea* (Olive)-Derived Ingredients - December 2022 – Christina Burnett**	
Comment Submitter: Alexandra Kowcz, Personal Care Products Council **Date of Submission: August 4, 2022**	
Comment	**Response/Action**
Key Issue: Since the CIR report includes data on a hydrolyzed olive fruit extract, perhaps the following INCI names should be added to the report: Hydrolyzed Olive Fruit and Hydrolyzed Olive Fruit Extract. Hydrolyzed Olive Leaf Extract should also be considered for addition to this report.	The Panel will need to consider the addition of these 3 ingredients. Currently, there are no uses reported for these 3 ingredients in the VCRP database.
Key Issue: When studies from reference 69 [Christian et al. 2004] are presented (both in the text and tables), it should state that the hydrolyzed olive pulp extract was an aqueous extract (as stated in the title of the reference).	"Aqueous" added to description of test material.
Introduction; Summary – Please revise the following sentence as it suggests that "skin bleaching agent" is an example of multiple drug functions reported for these ingredients. "Functions such as skin bleaching agent (reported for Olea Europaea (Olive) Fruit Extract and Olea Europaea (Olive) Leaf Extract) are not considered cosmetic functions in the United States (US) and, therefore, are not addressed in this assessment." It should be made clear that "skin bleaching" is the only drug function reported for two of the ingredients in this report.	Plural use changed to singular.
Non-Cosmetic Use – Please provide some examples of the chronic conditions for which olive leaves have been historically used as an herbal drug in the Mediterranean.	Sentence reworked. Examples and citations added.
Acute – Units of mg/kg bw should be called "dose" not "concentration".	Corrected.
Short-Term and Subchronic – Please state the species used in the 42-day study of the aqueous olive leaf extract.	Added "rat" to sentence.
DART – Please state the species used in the developmental toxicity study of hydrolyzed olive pulp.	Added "rats" to sentence.
Summary – The durations of the repeat-dose studies should be stated in the summary. Please correct "maximum concentration tested of 1000 mg/kg bw/d" to "maximum dose tested of 1000 mg/kg bw/d".	Added "90-d" to the first sentence. All other durations were already stated. Corrected to "dose".
Table 5 – Because different solvents were used, can the concentrations of constituents in the Italian cultivars really be compared to the Tunisian cultivars? Perhaps the word "Comparison" should be removed from the title of this table.	Removed "comparison" from title of Table 5.
Table 8, reference 70 [Gaube Guex et al. 2018] – Please check this study. Did the authors consider the "significant differences in hematological parameters" to have biological significance? A conclusion for this paper available on the internet says: "Measured hematological and biochemical parameters and histopathology corroborated the results, since they did not show any abnormalities, regardless of gender and age of the animals studied."	Findings were as reported, however, in the discussion of the paper, the authors determined hematological and biochemical parameters with significant differences may be due to experimental variations and were not treatment-related. This has been added to the results write-up in this table (now Table 9, reference 76).
Reference 70 [Gaube Guex et al. 2018] – Please correct "ehtanolic"	Corrected.

Olea Europaea (Olive)-Derived Ingredients History

July 25, 2022– The Scientific Literature Review was issued for public comment.

August-October, 2022 – Unpublished data were received.

Olea Europaea (Olive)-Derived Ingredients* – December 2022 – Christina Burnett																														
					Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents/ Impurities	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
Olea Europaea (Olive) Bark Extract				X				X																						
Olea Europaea (Olive) Branch Extract																														
Olea Europaea (Olive) Bud Extract				X																										
Olea Europaea (Olive) Flower Extract				X																										
Olea Europaea (Olive) Flower Water			X																											
Olea Europaea (Olive) Fruit	X			X																									X	
Olea Europaea (Olive) Fruit Extract	X	X	X	X							X			X							X			X	X					
Olea Europaea (Olive) Fruit Juice																														
Olea Europaea (Olive) Fruit Juice Ext.			X	X																										
Olea Europaea (Olive) Fruit Unsapon.	X		X																											
Olea Europaea (Olive) Fruit Water			X																											
Olea Europaea (Olive) Husk Powder			X																											
Olea Europaea (Olive) Leaf				X																										
Olea Europaea (Olive) Leaf Extract	X		X	X				X			X				X	X			X	X	X		X	X	X					
Olea Europaea (Olive) Leaf Powder	X		X	X																										
Olea Europaea (Olive) Leaf Water	X		X																											
Olea Europaea (Olive) Sap Extract	X			X																										
Olea Europaea (Olive) Seed	X			X																										
Olea Europaea (Olive) Seed Powder	X		X																		X			X					
Olea Europaea (Olive) Wood Extract				X																										
hydrolyzed olive pulp (fruit) extract								X			X			X	X	X														

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

Olea Europaea (Olive)-Derived Ingredients

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Olea Europaea (Olive) Leaf Extract		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Bark Extract		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Branch Extract		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Bud Extract		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Flower Extract			√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Flower Water		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Fruit		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Fruit Extract	84012-27-1	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Fruit Juice		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Fruit Juice Extract		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Oil Ethyl Ester		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Fruit Unsaponifiables		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Fruit Water		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Husk Powder		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Leaf		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Leaf Powder		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Leaf Water		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Sap Extract		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Seed		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive)Seed Powder		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Olea Europaea (Olive) Wood Extract		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	

Last updated on October 11, 2022.

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	AGRICOLA	IFRA	RIFM
Olea europaea (Olive)	84012-27-1	√	√	√	√	√	√	√	√

Search Strategy

[*document search strategy used for PubMed –**for your search strategy that goes to the Panel, show the terms used in the search**. For example:*
((((Caprylhydroxamic Acid) OR 7377-03-9[EC/RN Number]) OR Octanamide, N-Hydroxy-) OR N-hydroxyoctanamide) OR Octanohydroxamic Acid – 7 hits/2 useful]

(((olea europaea) AND (olive)) AND (leaf extract)) NOT (oil) – 429 hits, 39 relevant
(((olea europaea) AND (olive)) AND (bark extract)) NOT (oil) – 13 hits, 9 relevant
(((olea europaea) AND (olive)) AND (branch extract)) NOT (oil) – 16 hits, 5 relevant
(((olea europaea) AND (olive)) AND (bud extract)) NOT (oil) – 2 hits, 2 relevant
(((olea europaea) AND (olive)) AND (flower extract)) NOT (oil) – 128 hits, 12 relevant
(((olea europaea) AND (olive)) AND (flower water)) NOT (oil) – 10 hits, 1 relevant
(((olea europaea) AND (olive)) AND (fruit)) NOT (oil) – 620 hits, 14 relevant
(((olea europaea) AND (olive)) AND (fruit extract)) NOT (oil) – 171 hits, 50 relevant
(((olea europaea) AND (olive)) AND (fruit juice)) NOT (oil) – 5 hits, 2 relevant
(((olea europaea) AND (olive)) AND (fruit juice extract)) NOT (oil) – 3 hits, 2 relevant
(((olea europaea) AND (olive)) AND (oil ethyl ester)) – 11 hits, 7 relevant
(((olea europaea) AND (olive)) AND (fruit unsaponifiables)) NOT (oil) – 0 hits
(((olea europaea) AND (olive)) AND (fruit water) NOT (oil) – 88 hits, 3 relevant
(((olea europaea) AND (olive)) AND (husk powder)) NOT (oil) – 0 hits
(((olea europaea) AND (olive)) AND (leaf)) NOT (oil) – 765 hits, 42 relevant
(((olea europaea) AND (olive)) AND (leaf powder)) NOT (oil) – 20 hits, 12 relevant
(((olea europaea) AND (olive)) AND (leaf water)) NOT (oil) – 172 hits, 40 relevant
(((olea europaea) AND (olive)) AND (sap extract)) NOT (oil) – 1 hit, relevant
(((olea europaea) AND (olive)) AND (seed)) NOT (oil) – 139 hits, 26 relevant
(((olea europaea) AND (olive)) AND (seed powder)) NOT (oil) – 1 hit, relevant
(((olea europaea) AND (olive)) AND (wood extract)) NOT (oil) – 16 hits, 10 relevant

LINKS

Search Engines

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

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

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices - http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – https://ifrafragrance.org/
- Research Institute for Fragrance Materials (RIFM) - https://www.rifm.org/#gsc.tab=0
  http://fragrancematerialsafetyresource.elsevier.com/

Last updated on October 11, 2022.

Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/ Writer, CIR.

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ABBREVIATIONS

ALP = alkaline phosphatase
CAE = catechin equivalents
CIR = Cosmetic Ingredient Review
Council = Personal Care Products Council
CPSC = Consumer Product Safety Commission
DART = developmental and reproductive toxicity
dw = dry weight
ECE = epicatechin equivalents
FDA = Food and Drug Administration
FEMA = Flavor and Extract Manufacturers Association
GAE = gallic acid equivalents
HRIPT = human repeated-insult patch test
GRAS = generally recognized as safe
HS-SPME-GC-FID = headspace solid-phase micro-extraction coupled with gas chromatography with flame ionized detector
IgE = immunoglobulin E
MEA = monoethanolamine
LDH = lactate dehydrogenase
LOAEL = lowest-observable-adverse-effect level
LPS = lipopolysaccharide
NOAEL = no-observable-adverse-effect level
OECD = Organization for Economic Co-Operation and Development
Panel = Expert Panel for Cosmetic Ingredient Safety
PEG = polyethylene glycol
PMNC = polymorphonuclear cells
QAE = quillaja equivalents
QE = quercetin equivalents
RE = rutin equivalents
SIOPT = single-insult occlusive patch test
TG = test guideline
US = United States
VCRP = Voluntary Cosmetic Registration Program
wINCI *Dictionary* = web-based *International Cosmetic Ingredient Dictionary and Handbook*

INTRODUCTION

This assessment reviews the safety of the following 20 *Olea europaea* (olive)-derived ingredients as used in cosmetic formulations:

Olea Europaea (Olive) Bark Extract
Olea Europaea (Olive) Branch Extract
Olea Europaea (Olive) Bud Extract
Olea Europaea (Olive) Flower Extract
Olea Europaea (Olive) Flower Water
Olea Europaea (Olive) Fruit
Olea Europaea (Olive) Fruit Extract
Olea Europaea (Olive) Fruit Juice
Olea Europaea (Olive) Fruit Juice Extract
Olea Europaea (Olive) Fruit Unsaponifiables
Olea Europaea (Olive) Fruit Water
Olea Europaea (Olive) Husk Powder
Olea Europaea (Olive) Leaf
Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Seed
Olea Europaea (Olive) Seed Powder
Olea Europaea (Olive) Wood Extract

Most of the *Olea europaea* (olive)-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin-conditioning agents (emollient, humectant, or miscellaneous), according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*; see Table 1).[1] Olea Europaea (Olive) Husk Powder and Olea Europaea (Olive) Seed Powder are reported to only function as abrasives, and Olea Europaea (Olive) Flower Water and Olea Europaea (Olive) Fruit Juice are reported to only function as antioxidants. The reported function as a skin bleaching agent (for Olea Europaea (Olive) Fruit Extract and Olea Europaea (Olive) Leaf Extract) is not considered a cosmetic function in the United States (US) and, therefore, is not addressed in this assessment as use as such is not under the purview of the Panel.

The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of *Olea europaea* (olive) fruit oil, *Olea europaea* (olive) oil unsaponifiables, hydrogenated olive oil, hydrogenated olive oil unsaponifiables, potassium olivate, sodium olivate, *Olea europaea* (olive) husk oil, and olive acid.[2] The Panel concluded these ingredients are safe in the present practices of use and concentration, as described in the safety assessment.

Some of the ingredients reviewed in this safety assessment may be consumed as food, and daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. The primary focus of the safety assessment of these ingredients as used in cosmetics is on the potential for effects from topical exposure.

Botanicals, such as *Olea europaea* (olive)-derived ingredients, may contain hundreds of constituents. Thus, in this assessment, the Panel will assess the safety of each of these ingredients as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical ingredients.

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 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.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Note: The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics will be followed (i.e., *Olea europaea*). Often in the published literature, the general name "olive" is used, and it is not known how the substance being tested compares to the ingredient as used in cosmetics. Therefore, if it is not known whether the material being discussed is a cosmetic ingredient, the generic terminology, in all lowercase (e.g., olive leaf extract or olive fruit), will be used. However, if it is known that the material is a cosmetic ingredient, the naming convention provided in the *Dictionary* (e.g. Olea Europaea (Olive) Leaf Extract or Olea Europaea (Olive) Fruit) will be used.

CHEMISTRY

Definition and Plant Identification

The definitions of the ingredients included in this review are provided in Table 1.[1] The generic CAS number for several olive ingredients in this report is 84012-27-1.

Olea europaea L. is an evergreen tree or shrub native to the Mediterranean region of the world, and is one of the earliest domesticated fruit trees in the world, used for its oil, edible fruit, and medicinal properties since antiquity.[3-5] There are at least 30 species within the genus *Olea*, but only *Olea europaea* is cultivated.[6]

Table 2 lists the generic definitions of the parts of plants that are most pertinent to the ingredients in this report.[1] The olive tree is short and thick, averaging about 10 m in height.[7] The tree has a large diameter trunk and is bent and twisted. Branches are reedy with opposite branchlets, and the leaves are shortly-stalked, narrow, oblong, and leathery, and are pale green on the top-side and silvery-whitish on the bottom-side in color. The bark is pale grey in color. The fruit is small,

ovoid, and blackish-violet when ripe. The fruit and seed, or drupe, is comprised of an external epicarp, a middle mesocarp, and an internal endocarp, which becomes totally lignified at the end of the epi-mesocarp expansion growth.[8] The seed coat encloses the endosperm and embryo.

Chemical Properties

Chemical properties for the *Olea europaea* (olive)-derived ingredients are summarized in Table 3. Specific gravity (at 25º C) for Olea Europaea (Olive) Fruit Extract (prepared in butylene glycol/water) and Olea Europaea (Olive) Leaf Extract (prepared in water) were reported to be 1.02 and 1.00, respectively.[9,10] Both of these preparations are reported to be soluble in any proportion of water.

Method of Manufacture

Unpublished data were submitted describing methods of manufacture for some ingredients. In several cases, the definition of the ingredients, as given in the *Dictionary*, provides insight as to the method of manufacture. It is unknown if the general methodologies of the processing of *Olea europaea* (olive)-derived ingredients described below apply to cosmetic ingredient manufacturing.

Olea Europaea (Olive) Flower Water

According to the *Dictionary*, Olea Europaea (Olive) Flower Water is obtained through steam distillation of the flowers of *Olea europaea*.[1] No further details are provided.

Olea Europaea (Olive) Fruit Extract

A standardized aqueous olive pulp (fruit) extract was reported to be prepared as a byproduct during the processing of the pulp of olives (*Olea europaea* L.) for oil extraction.[11] The extract was produced as a freeze-dried powder.

Another supplier reported that Olea Europaea (Olive) Fruit Extract is manufactured by extracting olive fruit with specified eluent/s (water, butylene glycol, safflower seed oil, glycerin, and/or propylene glycol) under appropriate temperature conditions, to yield a concentrate.[9] The concentrate is then blended with the desired diluent/s and preservation system to produce the final ingredient. The ingredient is evaluated for physicochemical properties according to the specification requirements for the batch to be released. In addition, the concentrate is also evaluated for contaminants and physicochemical properties as needed.

A supplier reported that it sells olive oil under the INCI name Olea Europaea (Olive) Fruit Extract.[12] The material can be extracted through several processes, including pressing and filtering, using hexane, or through super critical carbon dioxide extraction.

Olea Europaea (Olive) Fruit Unsaponifiables

According to the *Dictionary*, Olea Europaea (Olive) Fruit Unsaponifiables is the remaining fraction of olive fruit remaining after fractional distillation.[1] No further details are provided.

Olea Europaea (Olive) Fruit Water

According to the *Dictionary*, Olea Europaea (Olive) Fruit Water is obtained through steam distillation of the fruits of *Olea europaea*.[1] No further details are provided.

Olea Europaea (Olive) Husk Powder

According to the *Dictionary*, Olea Europaea (Olive) Husk Powder is obtained from drying and grinding the husks of *Olea europaea*.[1] No further details are provided.

Olea Europaea (Olive) Juice Extract

A supplier reported that Olea Europaea (Olive) Juice Extract is produced from concentrated olive juice that is extracted with 50 vol% 1,3-butylene glycolic solution.[13] The resulting material then undergoes sedimentation, filtration, and adjustment prior to packaging.

Olea Europaea (Olive) Leaf Extract

Olea Europaea (Olive) Leaf Extract is manufactured by extracting olive leaves with specified eluent/s (water, butylene glycol, safflower seed oil, glycerin and/or propylene glycol) under appropriate temperature conditions, to yield a concentrate.[10] The concentrate is then blended with the desired diluent/s and preservation system to produce the final ingredient. The ingredient is evaluated for physicochemical properties according to the specification requirements for the batch to be released. In addition, the concentrate is also evaluated for contaminants and physicochemical properties as needed.

A supplier reported that Olea Europaea (Olive) Leaf Extract is manufactured by extracting the leaves of *Olea europaea* with water/glycerin or sunflower oil. The process involves maceration and filtration.[14]

Another supplier reported that Olea Europaea (Olive) Leaf Extract is produced by extracting dried raw olive leaves with 50 vol% ethanol solution and concentrating.[13] The resulting material is then dissolved in 50 vol% 1,3-butylene glycolic solution and then undergoes sedimentation, filtration, and adjustment prior to packaging.

A microwave-assisted aqueous extract of olive leaves produced for research was made by first oven-drying leaves before grinding them and running them through a metal mesh sieve.[15] The resulting material was then microwaved with distilled water, vacuum-filtered, and lyophilized.

Olea Europaea (Olive) Leaf Powder

According to the *Dictionary*, Olea Europaea (Olive) Leaf Powder is obtained from drying and grinding the leaves of *Olea europaea*.[1] A supplier reported that Olea Europaea (Olive) Leaf Powder is manufactured by grinding dry olive leaves prior to sieving and sterilization (by gamma ray or heat).[16]

Olea Europaea (Olive) Leaf Water

According to the *Dictionary*, Olea Europaea (Olive) Leaf Water is obtained through steam distillation of the leaves of *Olea europaea*.[1] A supplier reported that Olea Europaea (Olive) Leaf Water is manufactured through hydrodistillation of the leaves of *Olea europaea* in water.[14]

Olea Europaea (Olive) Seed Powder

According to the *Dictionary*, Olea Europaea (Olive) Seed Powder is obtained from drying and grinding the seeds of *Olea europaea*.[1] No further details are provided.

Composition and Impurities

The composition of constituents of *Olea europaea* (olive)-derived ingredients can vary annually, and is dependent on the cultivar, production area, climate, season, and soil characteristics.[17,18] Composition may also vary with use of fresh versus dried raw materials.[19] Oleuropein is the main phenolic component of the unprocessed fruit and leaves of *Olea europaea* L.[17] Content of oleuropein in leaves is dependent on the leaf tissue conditions (i.e., fresh, frozen, dried, or lyophilized). One study of leaf extracts with different solvents and two different cultivars found the total phenolic content, total flavonoids, and oleuropein content to be similar between cultivars, but it was noted that the leaves had been harvested from the same location in Australia.[20]

Olea Europaea (Olive) Bark Extract

Mineral content of the powdered bark of a subspecies of *Olea europaea* was 18.31 ppm calcium, 9.63 ppm magnesium, 8.94 ppm potassium, 0.22 ppm iron, 0.08 pm copper, 0.03 ppm lead, and below the threshold of detection for zinc.[21] From phytochemical analysis, the primary metabolites of the powdered bark is comprised of 36.01% total proteins, 0.82% total lipids, and 43.68% total carbohydrates. The yield of secondary metabolites, described in Table 4, varied with the type of solvent used; for example, total flavonoids was 64.44 mg/g for a chloroform extract and 8.11 mg/g for a water extract.

In crude stem bark extracts of a subspecies of *Olea europaea*, the total phenolic content of methanol, ethanol, and chloroform extracts were 399, 351, and 312 µg/mg (catechol equivalents), respectively.[22] A methanol extract of the bark of a subspecies of *Olea europaea* was reported to have the following classes of bioactive compounds: alkaloids, tannins, and flavonoids.[23] Further description was not provided.

Olea Europaea (Olive) Bud Extract and Olea Europaea (Olive) Flower Extract

Phenolic compounds identified in both the methanol extracts of dried buds and open flowers of one Tunisian olive cultivar included secoiridoids, flavonoids, simple phenols, cinnamic acid derivatives, and lignans.[24] Secoiridoids were measured at a higher percentage of total phenols in open flowers (41.7%) than in buds (30.5%). Conversely, flavonoids were measured at a higher percentage of total phenols in buds (38.1%) than in open flowers (26.7%). Cinnamic acid derivative and simple phenols were comparable. Lignans were measured at 0.4% and 1.0% of total phenols in buds and open flowers, respectively.

Olea Europaea (Olive) Flower Extract

In an 80% ethanol extract of olive flowers, phenolic acids (vanillic acid, *p*-coumaric acid, vanillin, caffeic acid), flavonoids (luteolin, apigenin, rutin, diosmetin), simple phenols (hydroxytyrosol, tyrosol), secoiridoids (oleuropein, ligstroside), and the cinnamic acid derivative, verbascoside, were identified using liquid chromatography with tandem mass spectrometry.[25] The flavonoids (9.4 mg/g dry matter) and secoiridoids (7.7 mg/g dry matter) comprised most of the phenols; total phenols were determined to be 22.7 mg/g dry matter.

Olea Europaea (Olive) Fruit

Constituents of olive fruit are reported to include monounsaturated fatty acids, aliphatic and triterpene alcohols, sterols, hydrocarbons, and several antioxidants.[26] Pentacyclic triterpenes in olive fruit include maslinic acid (1.2 - 1.8 mg/g dry weight (dw)) and oleanolic acid (0.4 - 0.6 mg/g dw), which are exclusively located in the epicarp and decrease as the fruit

ripen.[27] Total phenolics in 10 types of commonly consumed olives ranged from 0.21 mg gallic acid equivalents (GAE)/g to 2.20 mg GAE/g.[28]

Through headspace solid-phase micro-extraction coupled with gas chromatography with flame ionized detector (HS-SPME-GC-FID) of fruit homogenates, the ethanol content in olive fruit was found to vary between different cultivars (0.56 to 58 mg/kg for 3 different cultivars).[29] Regardless of cultivar, ethanol content of fruit increased during the ripening process.

Olea Europaea (Olive) Fruit Extract

A comparison of the constituent composition between cultivars and production area for olive fruit extracts is found in Table 5.[30] Total polyphenol content for Italian cultivars ranged from 182.35 - 290.21 mg GAE/g, while for Algerian cultivars, the total polyphenol content ranged from 147.13 - 272.83 mg GAE/g.

Several biphenols have been identified in methanol:water extracts of drupes, including oleuropein, hydroxytyrosol, tyrosol, vanillin, apigenin, luteolin, and quercetin.[31] Oleuropein, tyrosol, and hydroxytyrosol content in these extracts ranged as follows, respectively: < 0.037 - 145 mg/kg, < 0.045 - 40.3 mg/kg, and < 0.048 - 426 mg/kg. An ethanolic extract of olive fruit was approximately 11.25% hydroxytyrosol.[32]

Ethanol:water extracts (80:20) of olive fruit were analyzed for hydroxycinnamic acids and flavonoids.[33] Measured values of hydroxycinnamic acids included trace amounts of ferulic acid and *p*-coumaric acid, trace to1.0 mg/kg dw caffeic acid, and 3.6 - 60.1 mg/kg dw chlorogenic acid. Flavonoids measured values were 36.7 - 583.9 mg/kg dw rutin, 0.5 - 2.7 mg/kg quercetin, 20.9 - 121.0 mg/kg luteolin, 1.6 - 8.7 mg/kg luteolin-7-*O*-rutinoside, and trace to 1.3 mg/kg naringenin.

A commercial olive fruit extract (prepared for analysis in 50% ethanol) was determined to have a total phenol content of 4.64 mg GAE/g and a total flavonoid content of 24.17 mg quercetin equivalent (QE)/g.[34] The major phenolic components included hydroxytyrosol, elenolic acid, verbascoside, luteolin-7-*O*-glucoside, secoiridoids, and oleuropein.

A standardized aqueous olive pulp (fruit) extract powder was composed of 98% - 99% dry solids, including 1% - 2% citric acid and 6% polyphenols.[11] Other constituents included protein, fat, and carbohydrates. Of the polyphenols, the major constituent was hydroxytyrosol (50% - 70%), with oleuropein (5% - 10%), tyrosol (0.3%), and oleuropein aglycone + gallic acid (~20% combined) also present.

A supplier reported the microbial plate count for Olea Europaea (Olive) Fruit Extract prepared in butylene glycol and water to be less than 100 organisms/g.[9] No further details provided.

Olea Europaea (Olive) Juice Extract

A supplier reported that Olea Europaea (Olive) Juice Extract is comprised of saccharides and tannin.[13] Heavy metals content is not more than 20 ppm and arsenic content is not more than 2 ppm. No further details provided.

Olea Europaea (Olive) Leaf

Pentacyclic triterpenes found in olive leaf include oleanolic acid (29.2 - 34.5 mg/g), maslinic acid (4.8 - 7.3 mg/g), ursolic acid (2.0 - 2.5 mg/g), erythrodiol (0.8 - 1.5 mg/g), and uvaol (0.7 - 1.5 mg/g). These quantities change in abundance and profile as leaves mature.[27]

Olea Europaea (Olive) Leaf Extract

Olive leaf extract contains several biphenols, including oleuropein, tyrosol, hydroxytyrosol, apigenin, luteolin, quercetin, pinoresinol, catechin, ferulic acid, gallic acid, and vanillic acid.[31,35] Yields of constituents are dependent on solvent type and extraction methods. For example, oleuropein content of olive leaf extract in methanol:water (80:20, v/v) ranged from < 0.00013 – 0.29 mg/g,[31] while the oleuropein content from a microwave assisted aqueous extract was 11.59 mg/g (dry base),[15] and an ultrasound-assisted extraction of olive leaves produced 13.39 mg/g oleuropein.[36]

Constituent levels in olive leaves by extract type, cultivar, and production area are described in Table 6.[3,37] Ethanolic extracts of Italian olive cultivars had higher levels of oleuropein than methanolic extracts of Tunisian olive cultivars (7.49 - 30.46 g/kg dw versus 0.246 - 0.520 g/kg dw, respectively). Total phenolic content for the ethanolic extracts of Italian cultivars ranged from 11.39 - 48.62 g GAE/kg dw, while the methanolic extracts of Tunisian cultivars ranged from 18.96 - 47.47 g GAE/kg and total flavonoid content ranged from 3.08 - 7.29 mg catechin equivalents (CAE)/g.

The major phenolic compounds in methanolic leaf extracts of Tunisian olive cultivars were identified as hydroxytyrosol, tyrosol, 4-hydroxybenzoic acid, rutin, luteolin-7-*O*-glucoside, apigenin-7-*O*-glucoside, oleuropein, apigenin, and catechin hydrate.[3] Aqueous extracts of leaves from Tunisian olive cultivars had total phenolic content of 480.3 - 546.1 mg GAE/g, flavonoid content of 506.4 - 605.3 mg CAE/g, and flavonol content of 73.0 - 109.4 mg rutin equivalents (RE)/g.[38]

Aqueous extracts of olive leaves from Turkey yielded a total phenolic content of 92.13 mg GAE/g, a total flavonoid content of 21.64 mg RE/g and a total saponin content of 180.04 quillaja equivalents (QAE)/g.[39] In a methanol extract (70:30 methanol: water) of olive leaves, total phenols were 23.52 mg GAE/g dw, ortho-diphenols were 58.74 mg GAE/g dw, total flavonoids were 16.96 mg CAE/g dw, and tannins were 7.09 mg epicatechin equivalents (ECE)/g dw.[40]

A commercial olive leaf extract (prepared for analysis in 50% ethanol) was determined to have a total phenol content of 7.87 mg GAE/g and a total flavonoid content of 32.03 mg QE/g.[34] The major phenolic components included hydroxytyrosol, oleuropein aglycone-1, elenolic acid, verbascoside, luteolin-7-*O*-glucoside, flavonoid glucosides, and oleuropein. In another ethanolic extract of olive leaves, hydroxytyrosol was measured at 7.26%.[32]

An aqueous extract of olive leaves was determined to have the following soluble carbohydrates: myo-inositol, mannitol, galactose, glucose, fructose, sucrose, raffinose, and stachyose.[41] Of these carbohydrates, glucose and mannitol were present at the highest percentages (49.2% and 41.0%, respectively).

A supplier reported that Olea Europaea (Olive) Leaf Extract is comprised of organic acid and tannin.[13] Heavy metals content is not more than 20 ppm and arsenic content is not more than 2 ppm. Oleuropein content is not less than 0.03% w/v. No further details provided.

Another supplier reported that the following heavy metals were not detected at respective reporting limits for Olea Europaea (Olive) Leaf Extract (testing conducted on concentrate in alcohol base): antimony, arsenic, cadmium, chromium, iron, lead, mercury, and nickel.[10] Additionally, no residual pesticides were detected. The microbial plate count for Olea Europaea (Olive) Leaf Extract prepared in water was reported to be less than 100 organisms/g.

Olea Europaea (Olive) Leaf Powder

A supplier reported that Olea Europaea (Olive) Leaf Powder is 100% olive leaves.[16] No further details provided.

Olea Europaea (Olive) Sap Extract

Constituents of olive sap metabolites includes terpenoids, phytohormones, alkaloids, sterols/steroids, retinols/retinoids, tocopherols, and carotenoids.[18]

Olea Europaea (Olive) Seed

Methanol and methanol/water extracts of olive stones and seeds were found to have hydroxycinnamic acid derivatives, phenolic alcohols, flavonoids and flavonoid glucosides, secoiridoids, fatty acids, and terpenes.[42] The main bioactive component of olive seeds has been identified as hydroxytyrosol.[43]

Olea Europaea (Olive) Wood Extract

The main constituents of olive wood chips extracted with ethyl acetate have been identified as tyrosol, hydroxytyrosol, cycloolivil, ligustroside, oleuropein, and 7-deoxyloganic acid.[44] Secoiridoids determined from the same extract are as follows: oleuropein-3”-methyl ether (0.7 mg/g), 7”(*S*)-hydroxyoleuropein (2.8 mg/g), jaspolyanoside (2.2 mg/g), ligustroside 3’-*O*-β-D-glucoside (1.3 mg/g), jaspolyoside (3.3 mg/g), isojaspolyoside A (0.6 mg/g), and oleuropein 3’-*O*-β-D-glucoside (0.7 mg/g).[45]

USE

Cosmetic

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

According to 2022 VCRP survey data, Olea Europaea (Olive) Leaf Extract has the highest frequency of use; it is reported to be used in 182 formulations, with a majority of uses in leave-on skin care preparations (Table 7).[46] Olea Europaea (Olive) Fruit Extract is reported to be used in 118 formulations, also with the majority of uses in leave-on skin care preparations. All other in-use ingredients are reported to be used at much lower numbers. The results of the concentration of use survey conducted by the Council in 2020 indicate that Olea Europaea (Olive) Leaf Extract has the highest concentration of use in a leave-on formulation; it is used at up to 2% in suntan preparations.[47] The highest concentration of use reported for products resulting in rinse-off dermal exposure is 10% in Olea Europaea (Olive) Fruit Unsaponifiables in shaving cream. [For comparison, Table 8 provides the frequency and concentration of use data by product category.] The 11 ingredients not in use, according to the VCRP and industry survey, are listed in Table 9.[46,47]

Some *Olea europaea* (olive)-derived ingredients may be incidentally ingested or be used near the eye or mucous membranes. For example, Olea Europaea (Olive) Fruit Extract is reported to be used in lipstick (0.24%), eye lotion and other eye makeup preparations (concentration not reported), and bar soaps and detergents (up to 0.11%).[47] Additionally, some of the ingredients are used in cosmetic sprays and powders and could possibly be inhaled; for example, Olea Europaea (Olive) Leaf Extract is used at 0.018% in hair spray and Olea Europaea (Olive) Fruit Extract is used in face powders (no concentration reported).[46,47] In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

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

The *Olea europaea* (olive)-derived ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[48]

Non-Cosmetic

Different parts of the olive tree have been used for centuries for nutritional properties and protective health effects.[42] The leaves of the olive tree have been historically used as an herbal drug in folk medicine, with use as therapy for chronic conditions like gout, diabetes, and hypertension.[17,49,50] Leaves, fruit, and their constituents have been studied for health benefits such as antioxidant,[17,26,35,51] antimicrobial,[35,52-54] (including anti-malarial),[55] anti-inflammatory,[17,26,34,56,57] antiviral (including anti-HIV activity),[58] cardioprotective,[17,59] hepatoprotective,[60] neuroprotective[17,61,62], and anti-cancer effects[17,63] Olive leaves, extracts, and constituents have also been studied as potential treatments for diabetes (types 1 and 2),[64-66] hypertension,[67,68] and for protective effects against oxidative stress on kidneys and liver.[69] Additional therapeutic uses for olive leaf and olive fruit have been studied for the treatment of wounds,[70] intestinal morphological injuries,[26] and multiple sclerosis and other neurodegenerative diseases.[35] Olive drupes (fruit, pit and seed) have been studied for treating gastric disturbances,[43] reducing blood sugar, cholesterol, and uric acid;[42] and for protective effects on the tissues and functions of the liver, kidneys, and heart.[42,71] Olive pits (including the seed) have been used in folk medicine to treat gastric disturbances.[43] Olive bark and wood have been studied for antioxidant,[22,72] antidiabetic and anticancer activity,[21] as well as antimicrobial activity[22,23] (including anti-malarial).[73]

Olive leaves and fruit extracts have been studied for use in natural food preservation and packaging.[15,32,74,75] The Expert Panel for the Flavor and Extract Manufacturers Association (FEMA) generally recognized as safe (GRAS) program has provided recommended use levels for olive fruit extract as a flavor ingredient based on the average usual use level of 120 ppm and the average maximum use level of 720 ppm.[76]

TOXICOKINETIC STUDIES

No relevant toxicokinetic studies on *Olea europaea* (olive)-derived ingredients were found in the published literature, and unpublished data were not submitted. In general, toxicokinetics data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Acute toxicity studies on *Olea europaea* (olive)-derived ingredients are summarized in Table 10. In mouse studies of olive stem bark extract, an aqueous hydrolyzed olive pulp (fruit) extract, and olive leaf extracts, the LD_{50} was greater than 2000 mg/kg, which was the maximum dose tested for each ingredient.[13,55,73,77] In rat studies, an aqueous hydrolyzed olive pulp (fruit) extract had an LD_{50} greater than 5000 mg/kg, and olive leaf extract had an LD_{50} greater than 2000 mg/kg.[77,78]

Short-Term and Subchronic Toxicity Studies

Repeated-dose oral toxicity studies on *Olea europaea* (olive)-derived ingredients are summarized in Table 11. No treatment-related mortalities were observed in rats that received olive fruit extract (up to 1381 mg/kg bw/d) or hydrolyzed olive pulp (fruit) extract (aqueous; up to 2000 mg/kg/d) via gavage for 90 d.[77,79] The lowest-observable-adverse-effect level (LOAEL) was 1381 mg/kg bw/d and the no-observable-adverse-effect level (NOAEL) was 691 mg/kg bw/d in the olive fruit extract study, and the NOAEL for the hydrolyzed olive pulp (fruit) extract was 2000 mg/kg/d. In studies of a proprietary olive leaf extract (1000, 1500, or 2000 mg/kg/d) in rats, dose-dependent hyaline droplet nephropathy was observed in males in the 1000 and 2000 mg/kg dose groups, but not in lower dose males or in any females in a 14-d study.[80] No mortality, clinical signs of toxicity, or abnormalities in liver and kidneys were observed in a 28-d study with olive leaf extract (ethanol)

at up to 400 mg/kg, but the concentration of blood urea nitrogen was significantly increased in males in the 100 and 400 mg/kg dose groups when compared to controls.[78] In a 42-d rat study with up to 0.9% olive leaf extract (aq.), livers had fatty changes and hepatocellular necrosis was observed in all test groups, but the effects were more prominent in the 0.7% and 0.9% dose groups.[4] Kidneys in the treated groups had streaky hemorrhages and congestion in the cortical region, with more severe hemorrhage in the two higher dose groups. The NOAEL in a 90-d rat study was the maximum test concentration of 1000 mg/kg bw/d for a proprietary olive leaf extract.[80]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

DART studies on *Olea europaea* (olive)-derived ingredients are summarized in Table 12. In male rats treated at up to 450 mg/kg olive fruit extract (hydroalcoholic) for 48 d, a significant decrease in testicle weights (all treatment groups) and seminal vesicle weight (150 mg/kg dose group only) was observed, as were significant decreases in testosterone hormone levels, sperm counts, and sperm motility (all treatment groups for each end point).[81] Hydrolyzed olive pulp (fruit) extract (aqueous; up to 2000 mg/kg/d) produced no treatment-related mortalities in F_0 mature rats or F_1 rat pups, and produced no adverse effects in fertility or reproduction.[77] The NOAEL for developmental toxicity in rats was greater than 2000 mg/kg/d when dams received the same test material during gestation days 6 through 20.[11,77]

GENOTOXICITY STUDIES

In vitro and in vivo genotoxicity studies on *Olea europaea* (olive)-derived ingredients are summarized in Table 13. Mutagenic activity was observed in a bacterial reverse mutation assay of a hydrolyzed olive pulp (fruit) extract (aqueous; tested up to 5000 µg/plate with metabolic activation); however, inconsistencies between trials, antibacterial properties of the test material, and positive findings in only two concentrations complicated the interpretation of the findings. [77] Mutagenic activity was also observed in a chromosome aberration assay (aqueous; tested up to 1000 µg/ml) of the hydrolyzed olive pulp (fruit) extract when tested with metabolic activation; however, this test material was not mutagenic in an in vivo micronucleus assay (aqueous; tested up to 5000 mg/kg/d via gavage) in rats. A proprietary olive leaf extract was not considered genotoxic in a bacterial reverse mutation assay (tested up to 5000 µg/plate or in a mammalian chromosome aberration test (tested up to 1500 µg/ml) in V79 Chinese hamster lung cells.[80] A bacterial Vitotox™ test and an alkaline comet assay in human hepatic cells performed on different olive leaf extracts from Tunisia were negative in 3 of the 4 extracts tested (up to 5000 µg/ml); however, borderline genotoxicity was observed in the 4th extract, [82] A proprietary olive leaf extract was not genotoxic in an in vivo micronucleus assay (tested up to 200 mg/ml) in mice.[80]

CARCINOGENICITY STUDIES

Relevant carcinogenicity data for the *Olea europaea* (olive)-derived ingredients were not found in the published literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Cytotoxicity

Olea Europaea (Olive) Fruit Extract

The effects of the extract of olive fruit skins on cell proliferation and apoptosis was studied in HT-29 human colon cancer cells.[83] Olive fruit was extracted with chloroform and methanol. The pentacyclic triterpene profile of the extract was 73.25% maslinic acid, 25.75% oleanolic acid, 1% erythrodiol, and trace amounts of maslinic acid derivatives. Dose-dependent effects showed antiproliferative activity without displaying necrosis. Apoptosis was observed through microscopic changes in membrane permeability and detection of DNA fragmentation in cells that were incubated for 24 h with olive fruit extract. Caspase-3 was activated in a dose-dependent manner after a 24-h incubation, with up to 6-fold increased activity over the control cells. The production of superoxide anions in the cell mitochondria of the treated cells indicated that programmed cell death was induced by the intrinsic pathway. The authors concluded that olive fruit extract inhibited cell proliferation without cytotoxicity and the restoration of apoptosis in this study with human colon cancer cells.

Olea Europaea (Olive) Leaf Extract

In a cytotoxicity study, olive leaf extract was added to polymorphonuclear cells (PMNC) at a concentration of 320 µg/ml for 16 h after stimulation with 1 µg/ml of lipopolysaccharide (LPS).[35] The test material was extracted in ethanol. No significant effect on cell viability was observed when compared with cell culture with or without LPS stimulation. The test material was not cytotoxic.

DERMAL IRRITATION AND SENSITIZATION

Dermal irritation and sensitization data for the *Olea europaea* (olive)-derived ingredients are summarized in Table 14. Olea Europaea (Olive) Leaf Extract, tested at 100% in an in vitro primary skin irritation study in accordance with Organization for Economic Co-Operation and Development (OECD) test guideline (TG) 439, was predicted to be a non-

irritant.[13] In rabbit studies, Olea Europaea (Olive) Leaf Extract was not a dermal irritant in primary or cumulative skin irritation tests when tested at up to 100%.[13] No irritation was observed with a face cream containing 0.0005% Olea Europaea (Olive) Fruit Extract in a human single-insult occlusive patch test (SIOPT) nor in a 4-d clinical use test.[84,85] No irritation was observed in human dermal irritation studies of up to 100% Olea Europaea (Olive) Leaf Extract.[13,86-88] A body scrub containing 0.025% Olea Europaea (Olive) Seed Powder (tested at 0.5% aq.) elicited a ± response in 1 out of 21 subjects in an SIOPT; no other reactions were observed.[89] No significant clinical changes or subjective discomfort were reported in 1-wk clinical use test of a bar soap containing 1% Olea Europaea (Olive) Seed Powder.[90] In a guinea pig sensitization study, Olea Europaea (Olive) Leaf Extract was negative for sensitization when tested at up to 100% for both induction and challenge phases.[13] In human repeated-insult patch tests (HRIPT), a product containing 0.0025% Olea Europaea (Olive) Fruit Extract and 0.035% Olea Europaea (Olive) Seed Powder (tested as a 0.5% w/v aqueous solution) produced no dermal sensitization in 100 subjects.[91] Dermal sensitization was also not observed in a maximization study of a lip balm containing 5% Olea Europaea (Olive) Leaf Extract (25 subjects), a product containing 20% Olea Europaea (Olive) Leaf Extract (54 subjects), or a product containing 0.3% Olea Europaea (Olive) Leaf Extract (109 subjects).[13,92,93] In an HRIPT with semi-occlusive patches, a product containing 25% Olea Europaea (Olive) Seed Powder was not a dermal sensitizer in 54 subjects.[94] A product containing 0.01% Olea Europaea (Olive) Fruit Extract and a product containing 10% Olea Europaea (Olive) Leaf Extract were not photosensitizers in studies of 27 subjects and 25 subjects, respectively.[95,96]

OCULAR IRRITATION STUDIES

Ocular irritation data for *Olea europaea* (olive)-derived ingredients were not found in the published literature, and unpublished data were not submitted.

CLINICAL STUDIES

Case Reports

Anaphylaxis was reported in at 21-yr-old woman with a history of allergic rhinitis and asthma following consumption of olives on 3 separate occasions.[97] Symptoms included oropharynx, itchy palms, cough, and dyspnea. No history of food allergy had been reported prior. Skin prick tests were positive to different dust mites and negative for pollens, including olive tree pollen. Prick-by-prick testing with raw olive fruit gave a positive result (25 mm x 20 mm wheal and general skin itching). Five control subjects were negative. Additional testing with a prick-by-prick test of olive oil results in a 6 mm^2 wheal and general itching. Total immunoglobulin E (IgE) was 2524 kU/l and specific IgE was negative for pollens and foods. Immunoblotting suggested an IgE-mediated food allergy to lipoproteins in olive fruit.

Other Clinical Reports

Olea Europaea (Olive) Fruit Extract

A skin lotion containing olive fruit extract (concentration not reported) and tetramethoxyluteolin was given to 25 mastocytosis patients and an additional 8 patients with acute dermatitis or psoriasis.[98] The patients in the first group were requested to try the lotion on any body part twice per day for at least 2 wk, and were then surveyed regarding any skin symptoms associated with the use of the lotion. The second group were directed to apply the lotion on relevant affected areas twice per day for 1 mo. Eighteen patients in the first group responded to the survey, with none of the patients reporting irritation. No adverse effects to the lotion were reported in the second group of 8 patients.

Olea Europaea (Olive) Leaf Extract

In a study of the oxidative effects of olive leaf extract supplementation, groups of 15 young, healthy adult male and female subjects (total n = 45) were randomized into 3 groups.[99] Two groups received commercial olive leaf extract as a liquid (5 ml) or as a capsule. Concentration of olive leaf extract in the commercial supplements was not reported. The third group served as a control and received a liquid placebo. In addition to being randomized, the study was a single-center and single-blinded. The subjects ingested the test materials 3 times/d for 28 d. Urine samples were taken at baseline and follow-up time periods and measured for creatine, isoprostanes, and 8-hydroxy-2'-deoxyguannosine. All subjects completed the study, but only 36 were compliant with all protocols throughout the test period. No adverse effects were recorded. No significant effects of olive leaf extract on oxidative markers were observed when compared to controls.

In an efficacy study, 36 females with photoaging skin (including wrinkles, skin roughness, dryness, irregular pigmentation, telangiectasia, sallowness, and brown spots) were instructed to apply 0.6 g of a cream lotion containing olive leaf extract to their whole face twice daily for 2 mo.[100] Clinical evaluations were made at baseline, 1 and 2 mo after the start of application, and 1 mo after discontinuation of the cream. No other products were to be applied during the treatment period. No serious adverse events were reported during the study at follow-up visits. However, 16.7% of the subjects reported to have mild and transient acneiform eruption after the cream treatment started.

SUMMARY

Most of the *Olea europaea* (olive)-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin-conditioning agents, according to the *Dictionary*. Olea Europaea (Olive) Husk Powder and Olea Europaea (Olive) Seed Powder are reported to only function as abrasives, and Olea Europaea (Olive) Flower Water and Olea Europaea (Olive) Fruit Juice only as antioxidants. Reported function as a skin bleaching agent (for Olea Europaea (Olive) Fruit Extract and Olea Europaea (Olive) Leaf Extract) is not considered cosmetic functions in the US and, therefore, are not addressed in this assessment.

Olea europaea L. is an evergreen tree or shrub native to the Mediterranean region of the world, and is one of the earliest domesticated fruit trees in the world, used for its oil, edible fruit, and medicinal properties since antiquity. Composition of constituents of *Olea europaea* (olive)-derived ingredients can vary annually, and is dependent on the cultivar, production area, climate, season and soil characteristics. Oleuropein is the main phenolic component of the unprocessed fruit and leaves of *Olea europaea* L.

According to 2022 VCRP survey data, Olea Europaea (Olive) Leaf Extract is reported to be used in 182 formulations, with a majority of uses in leave-on skin care preparations. Olea Europaea (Olive) Fruit Extract is reported to be used in 118 formulations, also with the majority of uses in leave-on skin care preparations. All other in-use ingredients are reported to be used at much lower numbers. The results of the concentration of use survey conducted by the Council in 2020 indicate Olea Europaea (Olive) Leaf Extract also has the highest concentration of use in a leave-on formulation; it is used at up to 2% in suntan preparations. The highest concentration of use reported for products resulting in rinse-off dermal exposure is 10% in Olea Europaea (Olive) Fruit Unsaponifiables in shaving cream. Eleven ingredients in this safety assessment have no reported uses.

Different parts of the olive tree have been used for centuries for nutritional properties and protective health effects. Leaves and fruits, extracts, and constituents have been studied for antioxidant, antimicrobial, and anti-inflammatory benefits, as well as for treatments for diabetes, hypertension, and protective effects.

In mouse studies of olive stem bark extract, an aqueous hydrolyzed olive pulp (fruit) extract, and olive leaf extract, the LD_{50} was greater than 2000 mg/kg, the maximum dose tested for each ingredient. In rat studies, an aqueous hydrolyzed olive pulp (fruit) extract had an LD_{50} greater than 5000 mg/kg, and olive leaf extract had an LD_{50} greater than 2000 mg/kg.

No treatment-related mortalities were observed in rats that received olive fruit extract (up to 1381 mg/kg bw/d) or hydrolyzed olive pulp (fruit) extract (aqueous; up to 2000 mg/kg/d) via oral gavage for 90 d. The LOAEL was 1381 mg/kg bw/d and the NOAEL was 691 mg/kg bw/d in the olive fruit extract study; and the NOAEL for the hydrolyzed olive pulp (fruit) extract was 2000 mg/kg/d. In studies of a proprietary olive leaf extract in rats, dose-dependent hyaline droplet nephropathy was observed in males in the 1000 and 2000 mg/kg dose groups, but not in lower dose males or in any females in a 14-d study. No mortality, clinical signs of toxicity, or abnormalities in liver and kidneys were observed in a 28-d study with olive leaf extract (ethanol) at up to 400 mg/kg, but blood concentration of blood urea nitrogen was significantly increased in males in the 100 and 400 mg/kg dose groups when compared to controls. In a 42-d rat study with up to 0.9% olive leaf extract (aq.), livers and kidneys had fatty changes (liver), hepatocellular necrosis, and streaky hemorrhages (kidneys) in all test groups, but the effects were more prominent in the 0.7% and 0.9% dose groups. The NOAEL in a 90-d study was the maximum dose tested of 1000 mg/kg bw/d for a proprietary olive leaf extract.

In male rats treated at up to 450 mg/kg olive fruit extract (hydroalcoholic) for 48 d, a significant decrease in testicle weights (all treatment groups) and seminal vesicle weight (150 mg/kg dose group only) was observed, as were significant decreases in testosterone hormone levels, sperm counts, and sperm motility (all treatment groups for each end point). Hydrolyzed olive pulp (fruit) extract (aqueous; up to 2000 mg/kg/d) produced no treatment-related mortalities in F_0 mature rats or F_1 rat pups, and produced no adverse effects in fertility or reproduction. The NOAEL for developmental toxicity in rats was greater than 2000 mg/kg/d when dams received the test material during gestation days 6 through 20.

Mutagenic activity was observed in a bacterial reverse mutation assay (tested up to 5000 µg/plate) and a chromosome aberration assay (tested up to 1000 µg/ml) of an aqueous hydrolyzed olive pulp (fruit) extract when tested with metabolic activation; however, this test material was not mutagenic in an in vivo micronucleus assay (tested up to 5000 mg/kg/d) in rats. Different olive leaf extracts were not considered genotoxic in a bacterial reverse mutation assay (tested up to 5000 µg/plate), a bacterial Vitrotox™ test (tested up to 5.0 mg/ml), an alkaline comet assay (tested up to 5.0 mg/ml) in human hepatic cells, and a mammalian chromosome aberration test (tested up to 1500 µg/ml) in V79 Chinese hamster lung cells. A proprietary olive leaf extract was not genotoxic in an in vivo micronucleus assay (tested up to 200 mg/ml) in mice.

Olive fruit extract inhibited cell proliferation without cytotoxicity and the restoration of apoptosis in human colon cancer cells. Olive leaf extract (ethanol extract) was not cytotoxic to PMNC.

Olea Europaea (Olive) Leaf Extract, tested at 100% in an in vitro primary skin irritation study, was predicted to be a non-irritant. In rabbit studies, Olea Europaea (Olive) Leaf Extract was not a dermal irritant in primary or cumulative skin irritation tests when tested at up to 100%. No irritation was observed in a face cream containing 0.0005% Olea Europaea (Olive) Fruit Extract in a human SIOPT nor in a 4-d clinical use test. No irritation was observed in human dermal irritation studies of up to 100% Olea Europaea (Olive) Leaf Extract. A body scrub containing 0.025% Olea Europaea (Olive) Seed

Powder (tested at 0.5% aq.) elicited a + response in 1 out of 21 subjects in an SIOPT; no other reactions were observed. No significant clinical changes or subjective discomfort were reported in 1-wk clinical use test of a bar soap containing 1% Olea Europaea (Olive) Seed Powder. In a guinea pig sensitization study, Olea Europaea (Olive) Leaf Extract was negative for sensitization when tested at up to 100% for both induction and challenge phases. In human repeated-insult patch tests (HRIPT), a product containing 0.0025% Olea Europaea (Olive) Fruit Extract and 0.035% Olea Europaea (Olive) Seed Powder (0.5% w/v aqueous solution) produced not dermal sensitization in 100 subjects. Dermal sensitization was also not observed in a maximization study of a lip balm containing 5% Olea Europaea (Olive) Leaf Extract (25 subjects), a product containing 20% Olea Europaea (Olive) Leaf Extract (54 subjects), or a product containing 0.3% Olea Europaea (Olive) Leaf Extract (109 subjects). A product containing 25% Olea Europaea (Olive) Seed Powder was not a dermal sensitizer in 54 subjects. A product containing 0.01% Olea Europaea (Olive) Fruit Extract and a product containing 10% Olea Europaea (Olive) Leaf Extract were not photosensitizers in studies of 27 subjects and 25 subjects, respectively.

Anaphylaxis has been reported in a patient with an IgE-mediated food allergy to lipoproteins in olive fruit. Clinical studies of a skin lotion containing olive fruit extract, an oral supplement containing olive leaf extract, and a skin lotion containing olive leaf extract noted no adverse effects.

No relevant carcinogenicity or ocular irritation studies were found in the published literature, and unpublished data were not submitted. No relevant toxicokinetic studies were found in the published literature; however, in general, toxicokinetics data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

DISCUSSION

To be determined.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions and reported functions of the ingredients in this safety assessment.[1]

Ingredient & CAS No.	Definition	Function(s)
Olea Europaea (Olive) Bark Extract 84012-27-1 (generic)	Olea Europaea (Olive) Bark Extract is the extract of the bark of *Olea europaea.*	Skin-conditioning agent – misc.
Olea Europaea (Olive) Branch Extract 84012-27-1 (generic)	Olea Europaea (Olive) Branch Extract is the extract of the branches of *Olea europaea.*	Skin-conditioning agent – misc.
Olea Europaea (Olive) Bud Extract 84012.27-1 (generic)	Olea Europaea (Olive) Bud Extract is the extract of the buds of the *Olea europaea.*	Antioxidant; skin-conditioning agent - emollient
Olea Europaea (Olive) Flower Extract 84012-27-1 (generic)	Olea Europaea (Olive) Flower Extract is the extract of the flowers of *Olea europaea.*	Skin-conditioning agent – misc.
Olea Europaea (Olive) Flower Water 84012-27-1 (generic)	Olea Europaea (Olive) Flower Water is an aqueous solution of the steam distillate obtained from the flowers of *Olea europaea*.	Antioxidant
Olea Europaea (Olive) Fruit	Olea Europaea (Olive) Fruit is the fruit obtained from *Olea europaea*.	Abrasive; skin-conditioning agent – misc.
Olea Europaea (Olive) Fruit Extract 84012-27-1	Olea Europaea (Olive) Fruit Extract is the extract of the fruit of *Olea europaea.*	Skin bleaching agent; skin-conditioning agent – misc.
Olea Europaea (Olive) Fruit Juice	Olea Europaea (Olive) Fruit Juice is the juice expressed from the fruit of *Olea europaea*.	Antioxidant
Olea Europaea (Olive) Fruit Juice Extract	Olea Europaea (Olive) Fruit Juice Extract is the extract of Olea Europaea (Olive) Fruit Juice.	Skin-conditioning agent – humectant
Olea Europaea (Olive) Fruit Unsaponifiables	Olea Europaea (Olive) Fruit Unsaponifiables is the fraction of olive fruit remaining after fractional distillation.	Antioxidant; binder; emulsion stabilizer; hair conditioning agent; skin conditioning agent – emollient
Olea Europaea (Olive) Fruit Water	Olea Europaea (Olive) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Olea europaea*.	Skin-conditioning agent – misc.
Olea Europaea (Olive) Husk Powder	Olea Europaea (Olive) Husk Powder is the powder obtained from the dried, ground husks of *Olea europaea*.	Abrasive
Olea Europaea (Olive) Leaf	Olea Europaea (Olive) Leaf is the leaf of *Olea europaea*.	Skin-conditioning agent – misc.
Olea Europaea (Olive) Leaf Extract 84012-27-1 (generic); 8060-29-5 (generic)	Olea Europaea (Olive) Leaf Extract is the extract of leaves of *Olea europaea*.	Skin bleaching agent; skin-conditioning agent – misc.
Olea Europaea (Olive) Leaf Powder 84012-27-1 (generic)	Olea Europaea (Olive) Leaf Powder is the powder obtained from the dried, ground leaves of *Olea europaea*.	Abrasive; skin-conditioning agent – misc.
Olea Europaea (Olive) Leaf Water 84012-27-1 (generic)	Olea Europaea (Olive) Leaf Water is an aqueous solution of the steam distillates obtained from the leaves of *Olea europaea* (olive).	Skin-conditioning agent – misc.
Olea Europaea (Olive) Sap Extract	Olea Europaea (Olive) Sap Extract is the sap obtained from the stems of *Olea europaea*.	Skin-conditioning agent – misc.
Olea Europaea (Olive) Seed	Olea Europaea (Olive) Seed is the seed of *Olea europaea*.	Abrasive; skin-conditioning agent – misc.
Olea Europaea (Olive) Seed Powder 84012-27-1 (generic)	Olea Europaea (Olive) Seed Powder is the powder obtained from the dried, ground seeds of *Olea europaea*.	Abrasive
Olea Europaea (Olive) Wood Extract	Olea Europaea (Olive) Wood Extract is the extract of the wood of *Olea europaea*.	Skin-conditioning agent – misc.

Table 2. Generic plant part definitions as they apply to olive-derived ingredients.[1]

Plant Part	Definition
Bark	Tough protective covering of the woody stems and roots of trees and other woody perennial plants, consisting of cells produced by a cork cambium
Bud	A not yet developed shoot in the axil of a leaf, often covered with scales; a young flower that has not yet opened
Flower	The reproductive shoot in flowering plants, usually with sepals, petals, stamens and pistil(s)
Fruit	Mature, ripened ovary of flowering plant, containing seeds
Husk	A dry outer covering of a fruit or seed
Juice	The liquid contained in the vegetative parts or fruits
Leaf	Flattened photosynthetic organs, attached to stems
Sap	The fluid transported through the vascular system of a plant
Seed	A propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm, or seed coat
Wood	Parts of woody stems or branches formed by lignification of cells

Table 3. Chemical properties.

Property	Value	Reference
Olea Europaea (Olive) Fruit Extract (prepared in butylene glycol and water)		
Physical Form	Colorless to light yellow liquid	[9]
Odor	Characteristic	[9]
Specific Gravity (@ 25 ºC)	1.02 (range 1.00 - 1.04)	[9]
Water Solubility	Soluble in any proportion in water	[9]
Olea Europaea (Olive) Leaf Extract (prepared in water)		
Physical Form	Colorless to light yellow liquid	[10]
Odor	Characteristic	[10]
Specific Gravity (@ 25 ºC)	1.00 (range 0.99 - 1.01)	[10]
Water Solubility	Soluble in any proportion of water	[10]

Table 4. Secondary metabolites for powdered olive bark (mg/g).[21]

Solvents	Total polyphenols	Total flavonoids	Total polysaccharides	Total glycosaponins
n-hexane	28.49	38.09	33.06	1.06
chloroform	35.61	64.33	156.235	74.06
methanol	28.33	14.71	195.66	78.01
ethanol	26.15	11.13	268.75	76.93
water	27.04	8.11	30.25	72.02

Table 5. Comparison of constituent levels in ethyl acetate extract of different olive fruit cultivars from Italy and Algeria (mg/kg dw, except where noted). [30]

Cultivar	total polyphenol content*	total tannin content**	*p*-hydroxy-benzoic acid	vanillic acid	caffeic acid	syringic acid	*p*-coumaric acid	ferulic acid	sinapic acid	tyrosol	hydroxy-tyrosol	verbascoside	oleuropein	luteolin	chrysoeriol
Italian cultivars															
Coratina	290.21	52.92	NR	134.66	80.65	32.84	6.57	37.78	30.64	134.75	1927.57	319.78	126.92	221.74	11.68
Frantoio	223.81	63.95	309.36	203.46	142.17	81.65	35.74	25.22	25.95	200.84	2338.45	693.77	2562.63	585.64	135.57
Leccino	224.92	86.86	66.43	NR	129.32	63.24	21.95	31.75	24.22	194.13	1876.23	643.09	1074.28	2828.86	303.14
Maiatica	182.35	66.27	308.87	493.94	96.46	120.68	19.33	156.54	44.67	17.96	3683.44	718.68	1361.47	513.24	549.25
Ogliarola	226.89	57.51	116.42	37.53	83.42	39.12	28.74	31.36	31.85	115.74	2974.14	335.34	804.56	1362.51	158.74
Algerian cultivars															
Chemlal	272.83	81.28	NR	34.84	8.72	6.64	17.65	103.09	23.46	100.21	2024.63	21.37	109.86	201.70	21.73
Sigoise	147.13	20.08	3.22	200.93	29.64	13.64	66.37	63.38	26.34	34.34	245.23	52.72	216.70	109.54	36.37

NR=not reported
*mg of gallic acid equivalents/g extract
**mg of tannic acid equivalents/g extract

Table 6. Constituent levels in leaf extracts of different olive cultivars from Italy and Tunisia (g/kg dw).

Cultivar	quinic acid	hydroxytyrosol	luteolin 7-*O*-glucoside	2-methoxy oleuropein	oleuropein	luteolin	verbascoside	tyrosol	4-hydroxybenzoic acid	rutin	apigenin
Ethanolic extracts of Italian olive cultivars[37]											
Apollo	21.31	8.17*	39.78	10.51	24.28	2.66	0.16	NR	NR	NR	NR
Ascolanatenera	12.71	10.96*	32.75	7.80	22.06	0.15	0.18	NR	NR	NR	NR
Carolea	13.93	17.34*	35.05	12.71	28.30	0.10	0.13	NR	NR	NR	NR
Cellina di Nardo	11.25	57.75*	23.31	22.14	9.69	2.62	0.20	NR	NR	NR	NR
Cipressino	13.31	3.58*	29.13	9.42	25.52	0.21	0.22	NR	NR	NR	NR
Itrana	25.19	1.13*	31.56	8.42	30.46	1.54	0.11	NR	NR	NR	NR
Maurino	14.81	2.05*	27.88	4.08	18.53	3.02	0.10	NR	NR	NR	NR
Minerva	6.05	2.42*	15.95	3.32	17.38	1.06	0.18	NR	NR	NR	NR
Moraiolo	9.20	11.88*	20.12	5.56	14.61	1.41	0.14	NR	NR	NR	NR
Nociara	10.22	7.14*	35.13	3.92	9.89	0.18	0.10	NR	NR	NR	NR
Ogliarola	6.24	7.90*	8.69	8.82	7.49	0.21	0.14	NR	NR	NR	NR
Pendolino	12.55	1.69*	17.84	2.55	12.58	0.88	0.15	NR	NR	NR	NR
Ravece	13.02	3.72*	15.85	3.07	18.12	0.09	0.13	NR	NR	NR	NR
Sant Agostino	16.50	3.48*	21.57	5.28	23.55	0.16	0.11	NR	NR	NR	NR
Taggiasca	12.54	4.58*	18.14	4.14	21.74	0.95	0.12	NR	NR	NR	NR
Methanolic extracts of Tunisian olive cultivars[3]											
Chetoui	NR	0.0913	0.176	NR	0.428	NR	NR	0.141	0.0838	0.156	0.0343
Meski	NR	0.0896	0.116	NR	0.520	NR	NR	0.114	0.0663	0.210	0.0292
Jarbouii	NR	0.0893	0.217	NR	0.259	NR	NR	0.0862	0.0811	0.249	0.0433
Ouslati	NR	0.0757	0.113	NR	0.246	NR	NR	0.0835	0.0548	0.146	0.0217

NR = not reported
*Reported as hydroxytyrosol glucoside

Table 7. Frequency (2022)[46] and concentration of use (2020)[47] according to duration and exposure type for *Olea europaea* (olive)-derived ingredients.

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Olea Europaea (Olive) Fruit		**Olea Europaea (Olive) Fruit Extract[d]**		**Olea Europaea (Olive) Fruit Unsaponifiables**	
Totals*	**15**	**0.6**	**118**	**0.0002-0.5**	**14**	**10**
Duration of Use						
Leave-On	*10*	*0.6*	*86*	*0.00025-0.45*	*14*	*NR*
Rinse-Off	*5*	*NR*	*30*	*0.0002-0.5*	*NR*	*10*
Diluted for (Bath) Use	*NR*	*NR*	*2*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	3	NR	NR	NR
Incidental Ingestion	NR	NR	11	0.24	NR	NR
Incidental Inhalation-Spray	5[a,b]	NR	1; 24[a]; 25[b]	0.0008	4[a]; 9[b]	NR
Incidental Inhalation-Powder	5[b]	NR	3; 25[b]	0.23-0.45[c]	9[b]	NR
Dermal Contact	14	0.6	88	0.00025-0.5	14	10
Deodorant (underarm)	NR	NR	NR	0.0008-0.005	NR	NR
Hair - Non-Coloring	1	NR	14	0.0002-0.069	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	5	NR	NR	NR
Mucous Membrane	3	NR	23	0.00025-0.24	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Olea Europaea (Olive) Leaf Extract		**Olea Europaea (Olive) Leaf Powder**		**Olea Europaea (Olive) Leaf Water**	
Totals*	**182**	**0.0002-2**	**1**	**0.1**	**1**	**NR**
Duration of Use						
Leave-On	*136*	*0.0002-2*	*1*	*0.1*	*1*	*NR*
Rinse Off	*46*	*0.0002-0.3*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	11	NR	NR	NR	NR	NR
Incidental Ingestion	1	0.002	NR	NR	NR	NR
Incidental Inhalation-Spray	43[a]; 53[b]	0.0002-0.018	1[a]	NR	1[b]	NR
Incidental Inhalation-Powder	1; 53[b]	0.0014-0.4[c]	NR	0.1[c]	1[b]	NR
Dermal Contact	168	0.0002-2	1	0.1	1	NR
Deodorant (underarm)	NR	0.0002-0.095	NR	NR	NR	NR
Hair - Non-Coloring	12	0.0005-0.018	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	29	0.0003-0.002	NR	NR	NR	NR
Baby Products	1	0.002-0.013	NR	NR	NR	NR
	Olea Europaea (Olive) Sap Extract		**Olea Europaea (Olive) Seed[e]**		**Olea Europaea (Olive) Seed Powder**	
Totals*	**NR**	**0.005**	**2**	**NR**	**10**	**NR**
Duration of Use						
Leave-On	*NR*	*0.005*	*2*	*NR*	*5*	*NR*
Rinse-Off	*NR*	*0.005*	*NR*	*NR*	*5*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	3[b]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	3[b]	NR
Dermal Contact	NR	NR	2	NR	10	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.005	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR

NR = Not reported.

* 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 may be sprays, but it is not specified whether the reported uses are sprays.

[b.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

[d] Includes 14 uses described as Olive Extract in the VCRP.

[e] Described as Olive Stone in the VCRP.

Table 8. Frequency (2022)[46] and concentration (2020)[47] of use by product category

Product Category	# of uses	Max conc of use	Likely Exposure Site
Olea Europaea (Olive) Fruit			
Tonics, Dressings, and Other Hair Grooming Aids	1	NR	hair
Bath Soaps and Detergents	3	NR	skin; mucous membrane
Cleansing	2	NR	skin
Face and Neck (exc shave)	3	NR	skin
Body and Hand (exc shave)	2	NR	skin
Moisturizing	4	0.6% (not spray)	skin
Totals	**15**	**0.6%**	**skin; mucous membrane, hair**
Olea Europaea (Olive) Fruit Extract (1ncludes 14 uses described as Olive Extract in the VCRP)			
Other Bath Preparations	2	NR	skin; mucous membrane
Eye Lotion	1	NR	eye area
Other Eye Makeup Preparations	2	NR	eye area
Other Fragrance Preparation	1	NR	skin
Hair Conditioner	6	0.0002%	hair
Shampoos (non-coloring)	4	0.0098%	hair
Tonics, Dressings, and Other Hair Grooming Aids	1	0.069% (not spray)	hair
Other Hair Preparations	3	NR	hair
Face Powders	3	NR	skin
Foundations	1	NR	skin
Lipstick	11	0.24%	skin; mucous membrane
Makeup Bases	1	NR	skin
Other Makeup Preparations	1	NR	skin
Nail Creams and Lotions	5	NR	nail
Bath Soaps and Detergents	5	0.00025-0.11%	skin; mucous membrane
Deodorants	NR	0.005% (not spray); 0.0008% (aerosol)	skin
Feminine Deodorants	1	NR	mucous membrane
Other Personal Cleanliness Products	4	NR	mucous membrane
Shaving Cream	NR	0.5%	skin
Cleansing	10	0.01%	skin
Face and Neck (exc shave)	12	0.4-0.45% (not spray)	skin
Body and Hand (exc shave)	12	0.23% (not spray)	skin
Moisturizing	21	0.00025% (not spray)	skin
Night	2	0.00025% (not spray)	skin
Paste Masks (mud packs)	1	NR	skin
Other Skin Care Preps	8	NR	skin
Totals	**118**	**0.0002-0.5%**	**skin; mucous membrane; eye area; hair; nails**
Olea Europaea (Olive) Fruit Unsaponifiables			
Shaving Cream	NR	10%	skin
Face and Neck (exc shave)	8	NR	skin
Body and Hand (exc shave)	1	NR	skin
Moisturizing	4	NR	skin
Other Skin Care Preps	1	NR	skin
Totals	**14**	**10%**	**skin**
Olea Europaea (Olive) Leaf Extract			
Baby Shampoos	1	0.0065%	hair; infant skin
Baby lotions, oils and creams	NR	0.013%	infant skin
Other baby products	NR	0.002%	infant skin
Eye Lotion	6	NR	eye area
Other Eye Makeup Preparations	5	NR	eye area
Hair Conditioner	3	0.003-0.018%	hair
Hair Spray (aerosol fixative)	NR	0.018% (pump spray)	hair
Rinses (non-coloring)	NR	0.0005%	hair
Shampoos (non-coloring)	4	0.001-0.018%	hair
Other Hair Preparations	4	NR	hair
Face Powders	1	NR	skin
Foundations	NR	0.1%	skin
Lipstick	1	0.002%	skin; mucous membrane
Other Makeup Preparations	1	NR	skin
Other Manicuring Preparations	1	NR	nail
Bath Soaps and Detergents	23	0.0003%	skin; mucous membrane
Deodorants	NR	0.095% (not spray); 0.0002% (aerosol)	skin
Other Personal Cleanliness Products	5	NR	skin; mucous membrane
Beard Softeners	1	NR	skin
Cleansing	5	0.0002-0.3%	skin
Depilatories	1	NR	skin
Face and Neck (exc shave)	31	0.0014-0.4% (not spray)	skin
Body and Hand (exc shave)	22	NR	skin
Moisturizing	41	0.0065% (not spray)	skin
Night	2	0.4% (not spray)	skin
Paste Masks (mud packs)	4	NR	skin
Other Skin Care Preps	20	0.002%	skin
Suntan products	NR	2% (not spray)	skin
Totals	**182**	**0.0002-2**	**skin; infant skin; mucous membrane; eye area; hair; nail**

Table 8. Frequency (2022)[46] and concentration (2020)[47] of use by product category

Product Category	# of uses	Max conc of use	Likely Exposure Site
Olea Europaea (Olive) Leaf Powder			
Body and Hand (exc shave)	NR	0.1% (not spray)	skin
Moisturizing	1	NR	skin
Totals	**1**	**0.1%**	**skin**
Olea Europaea (Olive) Leaf Water			
Face and Neck (exc shave)	1	NR	skin
Totals	**1**	**NR**	**skin**
Olea Europaea (Olive) Sap Extract			
Hair conditioners	NR	0.005%	hair
Shampoos (non-coloring)	NR	0.005%	hair
Other hair preparations (non-coloring)	NR	0.005%	hair
Totals	**NR**	**0.005%**	**hair**
Olea Europaea (Olive) Seed (reported as Olive Stone in the VCRP)			
Other Skin Care Preps	2	NR	skin
Totals	**2**	**NR**	**skin**
Olea Europaea (Olive) Seed Powder			
Other Personal Cleanliness Products	1	NR	mucous membrane
Cleansing	3	NR	skin
Face and Neck (exc shave)	1	NR	skin
Body and Hand (exc shave)	2	NR	skin
Paste Masks (mud packs)	1	NR	skin
Other Skin Care Preps	2	NR	skin
Totals	**10**	**NR**	**skin; mucous membrane**

Table 9. Ingredients not reported to be in use, according to VCRP and Council data.[46,47]

Olea Europaea (Olive) Bark Extract
Olea Europaea (Olive) Branch Extract
Olea Europaea (Olive) Bud Extract
Olea Europaea (Olive) Flower Extract
Olea Europaea (Olive) Flower Water
Olea Europaea (Olive) Fruit Juice
Olea Europaea (Olive) Fruit Juice Extract
Olea Europaea (Olive) Fruit Water
Olea Europaea (Olive) Husk Powder
Olea Europaea (Olive) Leaf
Olea Europaea (Olive) Wood Extract

Table 10. Acute toxicity studies.

Test Article	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
			ORAL			
olive stem bark extract; tested as a crude 80% methanol extract and as solvent fractions (80% methanol followed by fractionating with butanol, water, or chloroform)	Female Swiss albino mice	5	distilled water	Single 2000 mg/kg oral dose (total volume 10 ml/kg bw) in accordance with OECD TG 425; observations made for 14 d	> 2000 mg/kg for the 80% methanol extract and the solvent fractions; no gross physical or behavioral changes or mortality observed	[73]
hydrolyzed olive pulp (fruit) extract (aqueous)	Male and female CD-1 mice	5 per sex	deionized water	Single limit dose of 2000 mg/kg via gavage followed by a 14-d recovery period	> 2000 mg/kg; no mortalities or morbidities observed and no abnormal clinical signs or gross morphologic changes were noted	[77]
hydrolyzed olive pulp (fruit) extract (aqueous)	Male and female Crl: CD(SD)IGS BR VAF/Plus rats	5 per sex	0.5% methylcellulose	0, 1000, 1500, 2000, or 5000 mg/kg via gavage	> 5000 mg/kg; no mortalities or morbidities observed and no abnormal clinical signs or gross changes were observed at necropsy	[77]
olive leaf extract; tested as a crude 80% methanol extract and as solvent fractions (80% methanol followed by fractionating with butanol, water, or chloroform)	Female Swiss albino mice	5	distilled water	Single 2000 mg/kg oral dose (total volume 10 ml/kg bw) in accordance with OECD TG 425; observations made for 14 d	> 2000 mg/kg for the 80% methanol extract and the solvent fractions; no gross physical or behavioral changes or mortality observed	[55]
Olea Europaea (Olive) Leaf Extract (ethanol extract)	mice (strain not reported)	10/sex	not reported	Acute toxicity test, no further details provided	> 2000 mg/kg; no further details provided	[13]
olive leaf extract (ethanolic)	Wistar rats	3 per sex	as supplied	Single 2000 mg/kg dose via gavage; control group received 10 ml/kg ethanol solution (51%); observations made for 14 d; blood collected at observation end for hematological and biochemical study; liver and kidneys examined microscopically	> 2000 mg/kg; no mortality, clinical signs of toxicity, or significant changes to body weight gain observed in treated rats; significant differences in hematological parameters, including red blood cells, hemoglobin, mean corpuscular volume, mean cell corpuscular hemoglobin concentration, and platelets (details not provided); blood concentration of creatinine significantly decreased ($p < 0.05$) in treated females as compared to the control group, while cholesterol was significantly decrease in treated males; authors determined hematological and biochemical parameters with significant differences may be due to experimental variations and were not treatment-related; no abnormalities were observed in the liver and kidneys	[78]

Table 11. Repeated dose toxicity studies.

Test Article	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
ORAL						
olive fruit extract containing 35% hydroxytyrosol	Groups of 10 male and 10 female Wistar rats	90 d	Reverse osmosis water	0, 345, 691, or 1381 mg/kg bw/d via gavage; an additional 2 recovery groups included a vehicle control and a high dose group that were followed for 28 d after the completion of the 90-d treatment to assess recovery; study performed in accordance with OECD TG 408; animals observed twice daily for mortality and clinical signs; body weight and feed consumption measured weekly; ophthalmological examination performed prior to treatment and at treatment and recovery end; blood samples collected during weeks 4, 8, 13 and 15 (recovery) from the control and high dose groups; urinalysis samples collected from all rats at the end of the main study and recovery study; vaginal smears and sperm collection were made; gross pathological exams and absolute organ weights determinations in all animals; histopathological exams performed in control and high-dose groups	LOAEL = 1381 mg/kg bw/d and the NOAEL = 691 mg/kg bw/d; no mortality or morbidity were observed during the study period; no treatment-related clinical signs observed in the low dose groups, while the mid- and high-dose groups had mild to moderate intermittent salivation – observation was considered non-adverse; reduction in terminal body weight and statistically significant reduction in body weight gain observed at week 13 in high-dose males; statistically significant increase in relative weights of the liver, heart, and kidneys observed in high-dose males and females	[79]
hydrolyzed olive pulp (fruit) extract (aqueous)	Groups of 20 male and 20 female Crl: CD(SD)IGS BR VAF/Plus rats	90 d	0.5% methylcellulose	0, 1000, 1500, or 2000 mg/kg/d via gavage; physical and ophthalmic examinations conducted before and near the end of study; clinical signs were recorded daily, body weights and feed consumption were recorded weekly, and hematology and serum chemistry determinations were made at necropsy	NOAEL = 2000 mg/kg/d; small decreases in body weight gains observed in 2000 mg/kg/d males and in all groups of females; feed consumption comparable to controls; no adverse clinical, hematologic, biochemical, organ weight or gross necropsy effects; focal, minimal, or mild hyperplasia of the mucosal squamous epithelium of the limiting ridge of the forestomach occurred in some 2000 mg/kg rats, but this was attributed to local irritation from gavage procedures	[77]
olive leaf extract; proprietary product with a standardized olive polyphenol content of 40%	Male and female CRL: (WI)BR Wistar SPF rats; no further details provided	14 d	1% Tween 80 prepared in distilled water	0, 300, 600, 1000, or 2000 mg/kg bw/d oral dose study in accordance with OECD TG 407; no further details provided	Male rats in the 1000 and 2000 mg/kg bw/d groups had hyaline droplet nephropathy in a dose-dependent manner; this effect was not observed in 300 or 600 mg/kg dose group males or in females at any dose level; no other treatment-related significant findings noted; no further details provided	[80]
olive leaf extract (ethanol)	Groups of 5 male and 5 female Wistar rats	28 d	as supplied	100, 200, or 400 mg/kg oral dose; negative control group received 10 ml/kg ethanol solution (51%); body weight gain measured at the end of dosing, blood collected and hematological parameters measured; rats killed and liver and kidneys examined microscopically	No mortality or clinical signs of toxicity observed; body weight gains normal in all dose groups; hematological parameters in treated rats comparable to the controls; blood urea nitrogen significantly increased ($p < 0.05$) in males in the 100 and 400 mg/kg dose groups when compared to the controls, but no other biochemical parameters exhibited any differences; no abnormalities found in the liver and kidneys	[78]

Table 11. Repeated dose toxicity studies.

Test Article	Animals/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
olive leaf extract (aq.)	Groups of 6 male Wistar albino rats	42 d	Dietary feed	0, 0.2%, 0.4%, 0.7%, or 0.9%; rats observed daily for clinical signs; hematological and biochemical parameters, including concentration of alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, cholesterol, glucose, and triglycerides measured at the end of dosing; rats were killed and histological examination performed on livers, kidneys, and spleens	No clinical signs of toxicity observed; when compared to control group, a significant increase ($p < 0.001$) in serum ALP observed in all treated groups; a significant increase of total bilirubin observed in the 0.4%, 0.7%, and 0.9% dose groups; a significant decrease in serum triglycerides, glucose, and cholesterol observed in all test groups when compared to the control group; a significant decrease ($p < 0.05$) in values of red blood cell counts, hemoglobin, and packed cell volume observed in the 0.9% dose group; a significant decrease ($p < 0.05$) in hemoglobin and packed cell volume observed in the 0.2% dose group, and mean corpuscular volume was significantly higher in the 0.4%, 0.7%, and the 0.9% dose groups, when compared to the control group; a marked reduction in white blood cells in all treated groups compared to the control group; no pathological changes in the spleen observed in the control or the treated groups; livers in the 0.7% and 0.9% dose groups had fatty changes and hepatocellular necrosis; these changes were observed in a lesser degree in the 0.2% and 0.4% dose groups; kidneys in treated groups had streaky hemorrhages and congestion in the cortical region, with more severe hemorrhage in the two higher dose groups	[4]
olive leaf extract; proprietary product with a standardized olive polyphenol content of 40%	Male and female CRL: (WI)BR Wistar SPF rats; 10 per sex in main group and 5 per sex in satellite groups	90 d	1% Tween 80	0, 360, 600, or 1000 mg/kg bw/d at a dose volume of 10 ml/kg via gavage; toxicity study performed in accordance with OECD TG 408; animals observed twice daily for mortality; clinical signs observed once daily; body weight measured prior to treatment, twice weekly during weeks 1-4, once weekly during weeks 5-13, and immediately after rats were killed; ophthalmological examination performed prior to treatment in all animals and in control and high-dose animals at the end of treatment; blood samples collected at study end; gross pathological exams and absolute organ weights determinations in all animals; histopathological exams performed in control and high-dose groups; 28-d satellite study performed to determine whether the findings of the above 14-d study were repeatable	NOAEL = 1000 mg/kg bw/d in both sexes; 1 female in the 1000 mg/kg bw/d group died on day 2 and 1 male in the 1000 mg/kg bw/d group died on day 60 due to treatment procedure; no toxicologically relevant treatment-related clinical signs or effects on body weight or feed consumption observed compared to controls; no ophthalmological alterations observed; no toxicologically-relevant changes in hematology, blood coagulation, or clinical chemistry parameters observed; no test article-induced gross pathological lesions or organ weight difference observed in any organs or tissues in any dose groups compared to controls; histopathological exams did not reveal any treatment-related findings that were considered toxicologically significant; satellite study for nephropathy was negative	[80]

Table 12. DART studies.

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
ORAL						
olive fruit extract (hydro-alcoholic)	groups of 8 male Sprague-Dawley rats	saline	0, 50, 150, or 450 mg/kg	Test material administered via gavage for 48 d; body weight measured and blood samples taken prior to initial dosing and 24 h after final dosing; rats killed at treatment end and weights of left prostate, left testis, epididymis, and seminal vesicle taken; sperm count and sperm motility measured	A significant decrease ($p = 0.03$) observed in weights of the left testicle in all treatment groups and in weights of the seminal vesicle in the 150 mg/kg dose group; significant decreases in testosterone hormone levels ($p \leq 0.04$), sperm counts ($p \leq 0.001$), and sperm motility ($p \leq 0.04$) in all treatment groups; no significant effects observed in body, prostate, or epididymis weights or in estradiol hormone levels	[81]
hydrolyzed olive pulp (fruit) extract (aqueous)	groups of male and female Crl: CD(SD)IGS BR VAF/Plus rats	0.5% methylcellulose	0, 500, 1000, 1500, or 2000 mg/kg	Dosage-range reproduction study; rats received test material for 14 d before cohabitation and up until the day before necropsy (49 total doses for males; for females, after day 22 post-partum); clinical signs, body weights of males and females, feed consumption, estrous cycling, female maternal behavior, litter sizes, pup viability, pup body weights, and necropsy observations were records; pups from the F_1 generation weaned 21-d post-partum; 2 pups/sex/litter (80 rats/sex total) selected for a week of daily gavage treatments and recordings of clinical signs, body weights, and viability before being necropsied on post-partum day 28; remaining pups subjected to gross necropsy on post-partum day 21	No treatment-related mortality observed in F_0 males and females; only adverse clinical sign for F_0 rats was dose-dependent excess salivation; absolute and relative feed intake and feed consumption values comparable between groups; in treated F_0 males, non-dose-dependent increased body weight gains; all mating and fertility parameters, terminal body weights, and paired epididymal and testicular weights comparable among the groups; in treated F_0 females, body weight gains were increased during the pre-cohabitation period, were comparable during gestation, and were decreased in the 1500 and 2000 mg/kg/d dose groups compared to controls; no adverse effects in treated groups for number of estrous stages, in mating, fertility, gestation, delivery or litter parameters, or in parturition, lactation, or necropsy parameters; slight reductions in pup weight/litter on lactation days 14 and 21 were not statistically significant; no treatment-related deaths, clinical signs, or gross necropsy findings were observed in the F_1 generation pups; pups (2/sex/litter) treated for 7 d after weaning with all treatment levels had comparable body weights on post-partum day 28	[77]
hydrolyzed olive pulp (fruit) extract (aqueous)	groups of 25 mated female Crl: CD(SD)IGS BR VAF/Plus rats	0.5% methylcellulose	0, 500, 1000, 1500, or 2000 mg/kg	Developmental toxicity study; dams received test material on gestation days 6 – 20, and observed daily for viability and clinical signs, resorptions, and premature delivery; body weights recorded on gestation day 0 through necropsy; feed consumption values recorded on gestation days 0, 6, 9, 12, 15, 18, and 21	NOAEL > 2000 mg/kg/d; no mortalities observed during treatment period; one 2000 mg/kg/d dam killed due to premature labor, but no abnormalities observed with dam or litter; no adverse clinical or necropsy findings; no differences in maternal body weight, body weight gains, gravid uterine weights, corrected maternal body weights or body weight gains, or absolute or relative feed consumption in any dose group; litter parameters unaffected by test material; significantly increased mean number of corpora lutea in the high dose group within historical control ranges; all gross external, soft tissue, and skeletal fetal alternations comparable in type, incidence, and distribution to controls	[11,77]

Table 13. Genotoxicity studies.

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
hydrolyzed olive pulp (fruit) extract (aqueous)	5 - 5000 µg/plate	0.5% carboxymethylcellulose solution or dimethyl sulfoxide	*Salmonella typhimurium* TA97a, TA98, TA100, TA1335 or *Escherichia coli* WP2 uvrA	Bacterial reverse mutation assay, with and without metabolic activation	Mutagenic activity detected in strains TA98 and TA100 at 100 and 2500 µg/plate with metabolic activation; however, inconsistencies between regular and repeat trials, antibacterial properties of the test material, and observation of positive findings in only 2 concentrations (with precipitates and toxicity also present) complicated interpretation of findings	[77]
hydrolyzed olive pulp (fruit) extract (aqueous)	10-1000 µg/ml	dimethyl sulfoxide	Chinese hamster ovary cells	Chromosome aberration assay, with and without metabolic activation	A significant increase in the percentage of aberrant cells observed at 1000 µg/ml, with activation	[77]
olive leaf extract; proprietary product with a standardized olive polyphenol content of 40%	51.2, 128, 320, 800, 2000, and 5000 µg/plate	Ultrapure water	*S. typhimurium* TA98, TA100, TA1335, TA1537 or *E. coli* WP2 uvrA	Bacterial reverse mutation assay in accordance with OECD TG 471, with and without S9 metabolic activation	Not genotoxic; no substantial increases in revertant colony numbers observed in any of the strains, with or without metabolic activation, at any concentration level; sporadic increases in revertant colony numbers compared to vehicle control observed, however no dose-related increase beyond generally acknowledged border of biological relevance observed and mutation rates were well below threshold of being considered positive	[80]
4 different olive leaf extracts from different regions of Tunisia	Up to 5000 µg/ml	Aqueous, no further details	2 *S. typhimurium* TA 104 constructs	Bacterial Vitotox™ test, with and without S9 metabolic activation	Negative in 3 extracts, with or without metabolic activation; 4th extract had borderline genotoxicity with metabolic activation; antigenotoxic properties were not observed	[82]
4 different olive leaf extracts from different regions of Tunisia	Up to 5000 µg/ml	Aqueous, no further details	Human C3A hepatic cells	Alkaline comet assay; cells were incubated with test materials for 24 h without metabolic activation and lysed in alkaline solution before analysis for DNA damage	Not genotoxic in 3 extracts; an increase in DNA damage was observed in the 4th extract that had borderline genotoxicity in the bacterial study described above	[82]
olive leaf extract; proprietary product with a standardized olive polyphenol content of 40%	3 h exposure Without S9: 250, 500, 750, 1000, or 1250 µg/ml With S9: 250, 500, 750, or 1000 µg/ml 20 h exposure Without S9: 62.5, 125, 250, or 500 µg/ml With S9: 500, 750, 1000, 1250, or 1500 µg/ml	Dulbecco's Modified Eagle medium	V79 male Chinese hamster lung cells	Mammalian chromosome aberration test in accordance with OECD TG 473, with and without S9 metabolic activation; positive and negative controls used	Not clastogenic; test material did not induce increase number of cells with aberrations or rates of polyploidy or endoreduplicated metaphases at any concentration during either period of exposure, with or without metabolic activation; no statistically significant differences between treatment and solvent control groups, and no dose-response relationships were observed; controls yielded expected results	[80]

Table 13. Genotoxicity studies.

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VIVO			
hydrolyzed olive pulp (fruit) extract (aqueous)	0, 1000, 1500, 2000, or 5000 mg/kg/d	0.5% methylcellulose	groups of 5-7 male and 5-7 female Crl: CD(SD) IGS BR VAF/Plus rats	Micronucleus assay; rats given single or 28 consecutive daily doses (1000-2000 mg/kg/d) or 29 consecutive daily doses (5000 mg/kg/d); via gavage	Not mutagenic; numbers of micronucleated polychromatic erythrocytes not significantly increased in any group treated with test article when compared to negative controls	[77]
Olive leaf extract; proprietary product with a standardized olive polyphenol content of 40%	50, 100, or 200 mg/ml in a dose volume of 10 ml/kg bw	Humaqua sterile water	Groups of male SPF Crl: NMRI BR mice; negative control and high dose group had 10 mice each, remaining groups had 5 mice each	Micronucleus assay in accordance with OECD TG 474; mice received single dose via gavage; positive control (cyclophosphamide), low-, and mid-dose group mice were killed at 24 h post treatment, 5 mice each in the positive control and high-dose were killed at 24 h or 48 h	Not genotoxic; no mortality, clinical signs of toxicity, or adverse reactions were observed in the controls or the 500 or 1000 mg/kg bw dose groups; a slight decrease in activity and piloerection was observed in 4 out of 10 mice treated with 2000 mg/kg; no significant differences observed in frequency of micronucleated polychromatic erythrocytes between the 3 dose groups compared to negative control; in the 2000 mg/kg dose group, the number of polychromatic erythrocytes was slightly decreased compared to negative control at 48 h sampling time; positive control yielded expected results	[80]

Table 14. Dermal irritation and sensitization studies.

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
IN VITRO						
Olea Europaea (Olive) Leaf Extract	none	100%	not reported	OECD TG 439 primary skin irritation method; no further details provided	Not irritating	[13]
ANIMAL						
Olea Europaea (Olive) Leaf Extract	not reported	10% and 100%	3 rabbits; no further details provided	Primary skin irritation test; no further details provided	No irritation; no further details provided	[13]
Olea Europaea (Olive) Leaf Extract	not reported	12.5%, 25%, 50%, 100%	3 rabbits; no further details provided	Cumulative skin irritation test; no further details provided	No irritation; no further details provided	[13]
HUMAN						
Face cream containing 0.0005% Olea Europaea (Olive) Fruit Extract	none	As supplied	19 subjects	SIOPT	No irritation; primary irritation index = 0.0	[85]
Face cream containing 0.0005% Olea Europaea (Olive) Fruit Extract	none	As supplied	14 subjects	4-d clinical use test; test material applied twice daily to face	No significant clinical changes; no reports subjective discomfort	[84]
Liquid lip color containing 1% Olea Europaea (Olive) Leaf Extract	none	As supplied	20 subjects	SIOPT	No irritation; primary irritation index = 0.0	[88]
Lip product containing 1% Olea Europaea (Olive) Leaf Extract	none	As supplied	22 subjects	5-d clinical use test; test material applied twice daily to upper and lower lips	No significant clinical changes; no reported subjective discomfort	[86]
Olea Europaea (Olive) Leaf Extract	none	100%	46 subjects	Irritation study; occlusive patch; no further details provided	No irritation; no further details provided	[13]
Moisturizer lotion containing 0.047% Olea Europaea (Olive) Leaf Extract	none	As supplied	52 subjects; at least 50% considered to have sensitive skin	4-wk clinical use test; monadic design; subjects instructed to use test material twice daily; dermatological exams conducted at baseline, wk 2 and wk 4	Test material did not elicit any significant objective or subjective irritation; test material did not elicit significant dryness	[87]
Body scrub containing 0.025% Olea Europaea (Olive) Seed Powder	none	aqueous 0.5%	21 subjects	SIOPT; 24-h	One subject had a $\pm$ response, no other reactions observed; primary irritation index = 0.02	[89]
Bar soap containing 1% Olea Europaea (Olive) Seed Powder	none	As supplied	12 subjects	1-wk clinical use test; test material applied twice daily to whole body	No significant clinical changes; no reported subjective discomfort	[90]
SENSITIZATION						
ANIMAL						
Olea Europaea (Olive) Leaf Extract	not reported	25% for 1st induction; 100% for 2nd induction; 10% and 100% for challenge	5 guinea pigs/group; no further details provided	Skin sensitization study; no further details provided	Negative for sensitization; no further details provided	[13]
HUMAN						
Product containing 0.0025% Olea Europaea (Olive) Fruit Extract and 0.035% Olea Europaea (Olive) Seed Powder	Not reported	0.5% w/v aqueous solution; 0.2 ml applied	100 subjects	HRIPT under occlusive patches; induction patch applied on the back for 9 total applications; 10-15 d non-treatment period followed by challenge patch applied to naïve site and scored at 48 h and 72 h post-application; Webril patch was 2 cm^2	No dermal sensitization	[91]

Table 14. Dermal irritation and sensitization studies.

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Lip balm containing 5% Olea Europaea (Olive) Leaf Extract	As supplied	0.05 ml	25 subjects	Maximization study under occlusive patches; induction and challenge sites pretreated with 0.25% sodium lauryl sulfate (0.05 ml); induction patch applied on upper outer arm for five 48-h total applications, application site allowed to air dry for 30 min prior to patching; 7-10 d non-treatment period followed by challenge patch applied to naïve site and scored at ~48 and 72 h post-application; patch was 13 mm Webril disc	No dermal sensitization; no adverse events reported	[92]
Olea Europaea (Olive) Leaf Extract	Not reported	20%	54 subjects	HRIPT using modified Shelanski method; no further details provided	No contact sensitization; no further details provided	[13]
Product containing 0.3% Olea Europaea (Olive) Leaf Extract	As supplied	0.02 ml	109 subjects	HRIPT under occlusive patches; induction patch applied on back for total of 9 applications; 13 d non-treatment period followed by challenge patch applied to naïve site and scored at 48 h post-application; patches were 50 mm^2 Finn chambers	No primary or cumulative dermal irritation, mean irritation index = 0.01; no dermal sensitization	[93]
Product containing 25% Olea Europaea (Olive) Seed Powder	water	0.02 ml	54 subjects	HRIPT under semi-occlusive patches; induction patch applied on back for total of 9 applications; 2-wk non-treatment period followed by challenge patch applied to naïve site and scored at 48 and 96 h post-application; Webril patch was 1 cm^2	No dermal sensitization	[94]
PHOTOSENSITIZATION						
HUMAN						
Product containing 0.01% Olea Europaea (Olive) Fruit Extract	Neat	40 mg	27 subjects	Photosensitization study under occlusive patch; repeat insult patch test with ultraviolet radiation (solar simulated); test material administered to same test site on mid or lower back area for 6 induction exposures over a 3 wk period; induction patches in place for 24 h, after which the sites were wiped off with dry gauze and exposed to 2 minimal erythema doses from a xenon arc solar simulator; after a 10 d non-treatment period, challenge patch applied to naïve site for 24 h in duplicate, one set removed after 24 h and irradiated with ½ minimal erythema dose plus 4 J/cm^2 UV; unirradiated patches served as control sites; test sites examined for reactions at 48 and 72 h post-irradiation; patch was 2 x 2 cm^2 Webril pad	Not a photosensitizer; no adverse events reported	[95]
Product containing 10% Olea Europaea (Olive) Leaf Extract	Neat	40 mg	25 subjects	Photosensitization study under occlusive patch; repeat insult patch test with ultraviolet radiation (solar simulated); test material administered to same test site on mid or lower back area for 6 induction exposures over a 3 wk period, application site allowed to air dry for 30 min prior to patching; induction patches in place for 24 h, after which the sites were wiped off with dry gauze and exposed to 3 minimal erythema doses from a xenon arc solar simulator; after a 11 d non-treatment period, challenge patch applied to naïve site for 24 h in duplicate, one set removed after 24 h and irradiated with ½ minimal erythema dose plus 4 J/cm^2 UV; unirradiated patches served as control sites; test sites examined for reactions at 48 and 72 h post-irradiation; patch was 2 x 2 cm^2 Webril pad	Not a photosensitizer; no adverse events reported	[96]

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Concentration of Use By FDA Product Category – Olive-Derived Ingredients*

Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Bark Extract
Olea Europaea (Olive) Branch Extract
Olea Europaea (Olive) Bud Extract
Olea Europaea (Olive) Flower Extract
Olea Europaea (Olive) Flower Water
Olea Europaea (Olive) Fruit
Olea Europaea (Olive) Fruit Extract
Olea Europaea (Olive) Fruit Juice
Olea Europaea (Olive) Fruit Juice Extract
Olea Europaea (Olive) Fruit Oil Ethyl Ester
Olea Europaea (Olive) Fruit Unsaponifiables
Olea Europaea (Olive) Fruit Water
Olea Europaea (Olive) Husk Powder
Olea Europaea (Olive) Leaf
Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Seed
Olea Europaea (Olive) Seed Powder
Olea Europaea (Olive) Wood Extract

Ingredient	**Product Category**	**Maximum Concentration of Use**
Olea Europaea (Olive) Leaf Extract	Baby shampoos	0.0065%
Olea Europaea (Olive) Leaf Extract	Baby lotions, oils and creams	0.013%
Olea Europaea (Olive) Leaf Extract	Other baby products	0.002%
Olea Europaea (Olive) Leaf Extract	Hair conditioners	0.003-0.018%
Olea Europaea (Olive) Leaf Extract	Hair sprays Pump spray	 0.018%
Olea Europaea (Olive) Leaf Extract	Rinses (noncoloring)	0.0005%
Olea Europaea (Olive) Leaf Extract	Shampoos (noncoloring)	0.001-0.018%
Olea Europaea (Olive) Leaf Extract	Foundations	0.1%
Olea Europaea (Olive) Leaf Extract	Lipstick	0.002%
Olea Europaea (Olive) Leaf Extract	Bath soaps and detergents	0.0003%
Olea Europaea (Olive) Leaf Extract	Deodorants Not spray Aerosol	 0.095% 0.0002%
Olea Europaea (Olive) Leaf Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0002-0.3%
Olea Europaea (Olive) Leaf Extract	Face and neck products Not spray	 0.0014-0.4%
Olea Europaea (Olive) Leaf Extract	Moisturizing products Not spray	 0.0065%
Olea Europaea (Olive) Leaf Extract	Night products Not spray	0.4%
Olea Europaea (Olive) Leaf Extract	Other skin care preparations	0.002%
Olea Europaea (Olive) Leaf Extract	Suntan products Not spray	 2%
Olea Europaea (Olive) Fruit	Moisturizing products Not spray	 0.6%
Olea Europaea (Olive) Fruit Extract	Hair conditioners	0.0002%
Olea Europaea (Olive) Fruit Extract	Shampoos (noncoloring)	0.0098%
Olea Europaea (Olive) Fruit Extract	Tonics, dressings and other hair grooming aids	

	Not spray	0.069%
Olea Europaea (Olive) Fruit Extract	Lipstick	0.24%
Olea Europaea (Olive) Fruit Extract	Bath soaps and detergents	0.00025-0.11%
Olea Europaea (Olive) Fruit Extract	Deodorants Not spray Aerosol	 0.005% 0.0008%
Olea Europaea (Olive) Fruit Extract	Shaving cream	0.5%
Olea Europaea (Olive) Fruit Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01%
Olea Europaea (Olive) Fruit Extract	Face and neck products Not spray	 0.4-0.45%
Olea Europaea (Olive) Fruit Extract	Body and hand products Not spray	 0.23%
Olea Europaea (Olive) Fruit Extract	Moisturizing products Not spray	 0.00025%
Olea Europaea (Olive) Fruit Extract	Night products Not spray	 0.00025%
Olea Europaea (Olive) Fruit Extract	Other skin care preparations	0.01%
Olea Europaea (Olive) Fruit Oil Ethyl Ester	Aftershave lotions	0.5%
Olea Europaea (Olive) Fruit Unsaponifiables	Shaving cream	10%
Olea Europaea (Olive) Leaf Powder	Body and hand products Not spray	 0.1%
Olea Europaea (Olive) Sap Extract	Hair conditioners	0.005%
Olea Europaea (Olive) Sap Extract	Shampoos (noncoloring)	0.005%
Olea Europaea (Olive) Sap Extract	Other hair preparations (noncoloring)	0.005%

*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 2019-2020
Table prepared: February 27, 2020

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: August 9, 2022

SUBJECT: Method of Manufacture: Ingredients Made From *Olea europaea* Leaves

Anonymous. 2022. Method of Manufacture – Olea Europaea (Olive) Leaf Extract and Olea Europaea (Olive) Leaf Water.

Anonymous. 2022. Method of Manufacture – Olea Europeae (Olive) Leaf Powder.

August 2022

Method of Manufacture – Olea Europaea (Olive) Leaf Extract and Olea Europaea (Olive) Leaf Water

Leaves of *Olea europaea* are used to to manufacture :

- extracts with solvent water/glycerin or sunflower oil
  process: maceration and filtration (LEAF EXTRACT)

- water by hydrodistillation (LEAF WATER)

August 2022

Method of Manufacture – Olea Europeae (Olive) Leaf Powder

Olea Europaea (Olive) Leaf Powder is manufactured by :

- Grinding dry olive leaves
- Sieving
- Sterilising (by gamma ray or heat)

The ingredient is 100% olive leaves

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: August 15, 2022

SUBJECT: Olea Europaea (Olive) Fruit Extract

The Innovation Company. 2022. Olea Europaea (Olive) Fruit Extract Method of Manufacture.

August 2022

The Innovation Company

Olea Europaea (Olive) Fruit Extract

Our company sells olive oil under the INCI name Olea Europaea (Olive) Fruit Extract

It is extracted by several processes, as traditional water pressed and filtered. Or simply Hexane processed as most vegetable oils. It can also be produced using super critical CO_2 extraction.

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: August 16, 2022

SUBJECT: Olea Europaea (Olive) Leaf Extract, Olea Europaea (Olive) Fruit Extract, and Olea Europaea (Olive) Seed Powder

Anonymous. 2002. Clinical safety in use test – moisturizer containing 0.047% Olea Europaea (Olive) Leaf Extract.

Anonymous. 2008. 5-Day use test (lips) – product containing 1% Olea Europaea (Olive) Leaf Extract.

Anonymous. 2008. Human patch test – liquid lip color containing 1% Olea Europaea (Olive) Leaf Extract.

Anonymous. 2008. Evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay (product contains 5% Olea Europaea (Olive) Leaf Extract).

Anonymous. 2010. An assessment of the photosensitization potential of two topical coded test products using a human photocontact allergenicity assay (product contains 10% Olea Europaea (Olive) Leaf Extract).

Anonymous. 2011. An assessment of the photosensitization potential of three topical coded test products using a human photocontact allergenicity assay (blend contains 0.01% Olea Europaea (Olive) Fruit Extract).

Anonymous. 2013. 4-day face use test (face cream contains 0.0005% Olea Europaea (Olive) Fruit Extract).

Anonymous. 2013. Human patch test (face cream contains 0.0005% Olea Europaea (Olive) Fruit Extract).

Anonymous. 2013. Human patch test (scrub contains 0.025% Olea Europaea (Olive) Seed Powder).

Anonymous. 2013. 1-Week home use test of a bar soap containing 1% Olea Europaea (Olive) Seed Powder.

Anonymous. 2014. Repeated insult patch test (product contains 0.0025% Olea Europaea (Olive) Fruit Extract and 0.035% Olea Europaea (Olive) Seed Powder).

[redacted]

memorandum

TO: [redacted] Profile [redacted]
Study [redacted]

FROM: [redacted]

DATE: April 8, 2002

SUBJECT: **Retail Moisturizer – Clinical Safety In Use Test #** [redacted]

Summary

Retail Moisturizer [redacted] was evaluated for Safety in Use on a panel of 52 women for 4 weeks under the supervision of a board certified Dermatologist. A minimum of 50% of the subjects have self-assessed sensitive skin. All the subjects are routine daily users of moisturizers.

The Dermatologist concluded that under the normal use conditions of the study (twice daily), the moisturizer did not evoke any significant or product related clinical and subjective irritation. The moisturizer performed well and is considered acceptable.

Test Design: The test design was a monadic study for 4 weeks with dermatological exams at baseline, 2 and 4 weeks. The test population was comprised of 52 women who routinely use facial moisturizers and at least 50% consider their skin to be sensitive.

Product usage was twice daily. Subjects were instructed to keep a daily use diary and to document any comments they wished to make.

Test Materials:

Moisturizer Lotion [redacted] # [redacted] contains 0.047% Olea Europaea (Olive) Leaf Extract

Results:

Erythema/redness – The moisturizer did not evoke any product-related redness. The majority of subjects showed no change from their initial or baseline condition (46/52). Six subjects exhibited a minimal change in facial redness while on test. Three developed some mild redness; one subject cleared and two developed transient redness, which cleared by study end. All observations were very minimal in nature and considered normal occurrences within skin condition. None of the subjects discontinued product use.

Edema – There were no observations of any facial edema throughout the study.

Dryness – There were a few observations of facial dryness. All observations were mild in intensity and are considered within the limits of naturally occurring skin changes. Forty-five (45/52) subjects showed no change from their initial exam. Three subjects showed a clearing or improvement in dryness, one exhibited an increase in dryness, and three showed a minor fluctuation which cleared by the end of the study. None of the subjects discontinued product use.

Subjective comments – As part of the study design subjects were instructed to keep a daily diary on product usage. The diaries also provided an opportunity for subjects to make open-ended comments regarding the moisturizer. Overall, there were as many positive (favorable) as negative (unfavorable) comments. The majority of the favorable comments were on the product aesthetics. Subjects commented on the fragrance, how soft and smooth their skin felt; and the lack of irritation. The negative comments centered on the taste, sticky film, the drying effects and a tingly, stinging sensation.

Subject 24 had notified the lab on day 2, that she had a burning sensitive sensation. Product use for 1 day was modified and the resumed. She commented in her diary that with continued use she had no repeat of her initial response. There was one note of some dryness around the nose on one day. The subject also commented that she was unsure if the response was in any way connected to medication she had been taking.

There were 5 comments on tingling and stinging upon application. Most of the comments were very transient and mild in nature. Subject #53 commented of tingling when applying makeup over the moisturizer, which did not occur with the foundation by itself. The response did not cause her to disrupt or discontinue use.

There were also 4 comments that the product was not moisturizing enough and the face felt dry and tight. This is strictly a subjective observation since the dermatologist exam revealed essentially no real increases in facial dryness.

The negative comments are offset by the several positive comments regarding how good the skin feels and looks.

Report: A complete copy of the study report and supporting documentation is on file in the [redacted] archive files.

cc: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Test Material: Facial Moisturizer [redacted]

Facial Moisturizer Use Test

FINAL REPORT

50 Female Human Subjects

[redacted]

January 11, 2002

[redacted] Distri[redacted]

FACIAL MOISTURIZER USE TEST SYNOPSIS

[redacted]

TYPE OF TEST:	Facial Moisturizer Use Test
PURPOSE:	The purpose of this test was to evaluate the objective and subjective irritation potential of the test Facial Moisturizer in female human subjects, under normal use conditions. Approximately 50% of the subjects have self-assessed sensitive skin.
TEST MATERIALS:	Sixty-five bottles of Facial Moisturizer [redacted], were provided by [redacted]. The test materials were received at [redacted] on October 31, 2001 with the following instructions: Test as per Protocol #2119FMDA.
SPONSOR:	[redacted] Per: [redacted]
TEST DATES:	November 6, 2001 through December 4, 2001.
INVESTIGATORS:	[redacted], PhD Principal Investigator [redacted], MD, FAAD Medical (Dermatological) Investigator
TEST FACILITY:	[redacted]
RESULTS:	A total of 52 subjects completed the test.
CONCLUSION:	The test material, Facial Moisturizer [redacted], did not elicit significant objective or subjective irritation, nor did it elicit significant dryness on the faces of female human subjects, approximately 50% of whom have self-assessed sensitive skin, under normal use conditions.

[redacted]

[redacted] MD, FAAD
Medical (Dermatological) Investigator

1/11/02
Date

[redacted], PhD
Principal Investigator

[redacted]

Distrib[redacted]

FINAL REPORT

[redacted]

Facial Moisturizer Use Test

PURPOSE: The purpose of this test was to evaluate the objective and subjective irritation potential of the test Facial Moisturizer in female human subjects, under normal use conditions. Approximately 50% of the subjects have self-assessed sensitive skin.

INVESTIGATORS: [redacted]

[redacted] PhD
Principal Investigator

[redacted] MD, FAAD
Medical (Dermatological) Investigator

Project Manager: [redacted]

TEST MATERIALS: Sixty-five bottles of Facial Moisturizer [redacted], were provided by [redacted] The test materials were received at [redacted] on October 31, 2001 with the following instructions: Test as per Protocol #2119FMDA.

The test materials were weighed by [redacted] prior to the beginning of the study and upon completion of the study. The weights were recorded on the Weight Sheet. (See Appendix I.)

EXPERIMENTAL DESIGN: This study was conducted at [redacted] in conformity with [redacted] Protocol #2119FMDA including the Sponsor's Use Directions. (See Appendix II.)

Study Dates: This study was initiated on November 6, 2001 and concluded on December 4, 2001.

Panel Selection: Each subject completed an [redacted] History Form ([redacted], including relevant medical history. An updated History form is secured every two years. Each subject was assigned (or had been assigned) a permanent [redacted] Identification Number.

No subject was used on this test if she exhibited or had a history of chronic dermatological or other medical or physical condition(s) which would preclude topical application of the test material and/or could influence the outcome of the test. Approximately 50% of the subjects have self-assessed sensitive skin. No subject had a history of severe allergy problems to cosmetics, soaps, sunscreens, moisturizers or other facial products.

Sensitive skin individuals were selected on the basis of answers provided on a Skin Profile Questionnaire.

No subjects had treatment with antihistamines or corticosteroids within one week prior to initiation of the test. No known pregnant or nursing women were used on this test. Legally valid written informed consent, in conformity with 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

[redacted]

EXPERIMENTAL DESIGN: (continued)

Panel Selection: (continued) A total of 55 female subjects, ranging in age from 19 through 67 were empanelled. On Test Day 0, each subject was patched on her arm with the test Facial Moisturizer prior to use on her face, in order to rule out empanelling any subject who had an individual idiosyncratic reaction to the test Facial Moisturizer. No subject had a reaction to the patch test; thus the total number of subjects who began using the moisturizer was 55.

All subjects were habitual daily users of a facial moisturizer. No subject had participated in a facial area use test for at least one week prior to initiation of the study.

METHOD: Subjects were instructed not to make any changes in their normal cosmetological routine and that no new cosmetics were to be used. However, the only moisturizer to be used during this study was the test Facial Moisturizer, which was to be used 2 times a day. Each subject was given a bottle of the test Facial Moisturizer. Each subject was instructed to apply the test Facial Moisturizer 2 times a day.

Each subject was given a copy of Use Directions. (See Appendix II.) Panelist Instructions were also given to all subjects. (See Appendix III.) Each subject was instructed to document her application times and comments on her "Daily Diary". (See Appendix IV.)

Dermatological Examinations: At Baseline, Test Day 0, all subjects were examined and scored by the [redacted] Consulting Dermatologist, prior to inclusion on this panel. Erythema, Edema and Dryness / Scaling were graded using the Grading Scale. (See below.) Subjective Irritation which includes Stinging, Burning, Itching, Tautness and Dryness was graded by the subjects using the Grading Scales. (See below.) An Acne Global Evaluation Score was assigned using the Grading Scale. (See below.)

ERYTHEMA, EDEMA, DRYNESS / SCALING:

0	=	None
1	=	Mild
2	=	Moderate
3	=	Severe

SUBJECTIVE IRRITATION:

0	=	None	St	=	Stinging
1	=	Mild	B	=	Burning
2	=	Moderate	It	=	Itching
3	=	Severe	T	=	Tautness
			Dr	=	Dryness

ACNE GLOBAL EVALUATION:

0	=	None
1	=	Only a few lesions
2	=	Easily recognizable lesions but most of the face is clear
3	=	Moderate involvement, not random
4	=	Extensive, heavy concentration but less than half of the face is involved

[redacted]

[redacted]

[redacted]

METHOD: (continued)

Dermatological Examinations: (continued) Examinations were again made by the [redacted] Consulting Dermatologist at Mid-study (Test Day 14) and at the conclusion of the test, Test Day 28. All dermatological scores were recorded on the Data Form: Dermatological Examination. (See Appendix V.)

At each return visit, the entries on the Daily Diary for the previous weeks were checked by a trained [redacted] technician.

At the conclusion of the test, Test Day 28, the subjects were queried as to any dermal reaction, including irritation. Each subject completed a Questionnaire. (See copies of Questionnaires.)

RESULTS: See copies of Data Forms and Tables I – V. A complete set of individual Data Forms (Data Form: Dermatological Evaluation) is included herewith. These Data Forms are an integral part of this Final Report. The data therefrom are listed in Tables I – V.

One subject, #24 ([redacted]), notified [redacted] on Test Day 02 that she was experiencing a burning sensation on her face after applying the test Facial Moisturizer. She was asked to use the test Facial Moisturizer on the right side of her face only and report to us the next day. On Test Day 03, she notified [redacted] she had no burning reaction on the right side of her face, nor did she have any reaction when she applied the test Facial Moisturizer to her entire face. She agreed to continue to use the test Facial Moisturizer and notify us if she had any further reactions. She reported none for the duration of the test.

Three subjects, #14 ([redacted]), #32 ([redacted]) and #54 ([redacted]), discontinued the test due to personal reasons, thus; a total of 52 subjects completed the test.

Comments from Daily Diaries: See copies of Daily Diaries.

Subject #4 ([redacted]) wrote in her comments, "When I put the moisturizer on my skin feels moist, after 10 or 15 minutes, my skin feels dry and tight." She also wrote, "My skin looks and feels drier then it does with the moisturizer I usually use." Subject #06 ([redacted]) wrote in her comments on Test Day 01, "smells nice, skin feels tight and a little tingly."

Subject #24 ([redacted]) wrote in her comments on Test Day 01, "went on OK but feels a little sensitive on face." On Test Day 17, she wrote "small drying around nose – don't know if moisturizer. Plus, I don't have cold." She also wrote in her comments, "I don't know if my skin was getting used to moisturizer or if taken off Zocor. I did notice that the moisturizer didn't cause any sensitivity as in the beginning."

Subject #37 ([redacted]) wrote in her comments, "Tingles slightly when applying." Subject #41 ([redacted]) wrote in her comments on Test Day 01, "It burned at first." On Test Day 03, she wrote "It made my face itchy." Subject #42 ([redacted]) wrote in her comments, "Feels sticky on skin. Tingling." Subject #53 ([redacted]) wrote in her comments, "Mild tingling and stinging for 20 – 30 minutes after application." She later wrote, "The mild tingling and stinging re-occurs when I apply my foundation."

[redacted]

[redacted]

Test Material: Facial Moisturizer

RESULTS: (continued)

Erythema: Twenty-eight subjects exhibited persistent 1-level (Mild, Very Slight) Erythema. Fifteen of these 28 subjects have Rosacea. Six subjects exhibited transient 1-level (Mild, Very Slight) Erythema. All other subjects remained at a zero (0) level throughout the test.

Edema: All subjects remained at a zero (0) level throughout the test.

Dryness / Scaling: Seven subjects exhibited transient 1-level (Mild, Very Slight) Dryness / Scaling. All other subjects remained at a zero (0) level throughout the test.

Subjective Irritation: Subject #42 (experienced 1-level (Mild, Very Slight) Subjective Irritation on Test Day 28 only. She said it was a "slight tingling." All other subjects remained at a zero (0) level throughout the test.

Global Evaluation: Six subjects went down one grade. All other subjects remained the same.

CONCLUSION: The test material, Facial Moisturizer , did not elicit significant objective or subjective irritation, nor did it elicit significant dryness on the faces of female human subjects, approximately 50% of whom have self-assessed sensitive skin, under normal use conditions.

RETENTION: All of the original data forms will be retained by for a time period of at least three years or such time period as may otherwise be required by law.

As per the Sponsor's request, the unused test materials shall be disposed of as cosmetic waste.

Dated: January 11, 2002

This Final Report for
is submitted to:

, MA
Project Manager

PhD
Principal Investigator

, MD, FAAD
Medical (Dermatological) Investigator

Site Visits	Dates
	November 20, 2001 December 4, 2001

Distributed for Comme[redacted]

Test Material: Facial Moisturizer [redacted]

TABLE I: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: ERYTHEMA

SUBJ #	HRL #	INIT	AGE	SENS SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 28
01	21766	PR	67	NO	01	0	0	0
02	22034	JS	35	NO	02	1*	1*	1*
03	07381	DW	53	YES	03	1*	1*	1*
04	19288	RC	52	YES	04	1*	1*	1*
05	18714	CO	40	YES	05	1*	1*	1*
06	22840	MR	24	YES	06	0	1	1* +
07	18926	DF	44	NO	07	0	0	0
08	07324	EB	47	NO	08	1*	1*	1*
09	07977	DB	21	NO	09	0	0	0
10	28937	CB	31	NO	10	0	0	0
11	15197	KC	44	YES	11	1*	1*	1*
12	16370	KS	60	YES	12	1*	1*	1*
13	01388	CB	51	YES	13	0	1	0 F
14	22353	LA	30	NO	14	0	0	DISC
15	20083	GD	60	NO	15	1*	1*	1*
16	21818	SF	37	NO	16	0	0	0
17	16515	DC	42	YES	17	0	0	0
18	19099	AR	47	YES	18	0	0	0
19	16364	SK	52	YES	19	1*	1*	1*
20	05120	GP	67	NO	20	1*	1*	1*
21	15198	AD	41	YES	21	1*	1*	1*
22	02993	SB	52	YES	22	0	0	0
23	12991	CS	35	YES	23	1*	1*	1*
24	22074	AF	50	YES	24	1*	1*	1*
25	20611	DS	50	YES	25	1*	1*	1*
26	16463	AT	40	NO	26	0	1	1 +
27	19985	MG	46	YES	27	0	0	0

SCORING SCALE:

0	=	None	DISC	=	Discontinued
1	=	Mild, Very Slight	*	=	See Data Form
2	=	Moderate			
3	=	Severe			

[redacted]

[redacted]

TABLE I: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: ERYTHEMA (CONTINUED)

SUBJ #	HRL #	INIT	AGE	SEN SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 28	
28	11545	ML	60	YES	28	1*	0*	0*	-
29	13247	PC	50	YES	29	0	0	0	
30	15606	EC	22	YES	30	0	0	1	+
31	16344	JF	27	NO	31	1*	1*	1*	
32	18143	MB	41	YES	32	0	0	DISC	
33	02589	HW	54	YES	33	1*	1*	1*	
34	17952	DC	53	NO	34	1*	1*	1*	
35	00884	TP	62	NO	35	1*	1*	1*	
36	02552	CP	58	YES	36	1*	1*	1*	
37	09971	CB	52	YES	37	0	0	0	
38	14765	JT	45	NO	38	0	0	0	
39	18427	MD	55	YES	39	0	0	0	
40	21777	DP	38	YES	40	1*	1*	1*	
41	28939	NC	19	NO	41	0	0	0	
42	01300	VB	50	YES	42	1*	1*	1*	
43	21996	PS	34	NO	43	1*	1*	1*	
44	21600	SS	37	NO	44	0	0	0	
45	21268	LV	42	NO	45	1*	1*	1*	
46	16440	PN	39	YES	46	0	0	0	
47	03047	JB	56	YES	47	1*	1*	1*	
48	19844	GS	40	NO	48	0	0	0	
49	20974	LW	24	NO	49	1*	1*	1*	
50	17385	MV	42	NO	50	1*	1*	1*	
51	21191	KH	50	NO	51	0	1	0	F
52	21339	PE	52	NO	52	1*	1*	1*	
53	00005	DM	40	YES	53	0	0	0	
54	17109	JB	56	NO	54	1*	1*	DISC	
55	19161	JC	39	NO	55	1*	1*	1*	

SCORING SCALE:

0	=	None	DISC	=	Discontinued
1	=	Mild, Very Slight	*	=	See Data Form
2	=	Moderate			
3	=	Severe			

[redacted]

[redacted]

TABLE II: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: EDEMA

SUBJ #	HRL #	INIT	AGE	SENS SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 28
01	21766	PR	67	NO	01	0	0	0
02	22034	JS	35	NO	02	0	0	0
03	07381	DW	53	YES	03	0	0	0
04	19288	RC	52	YES	04	0	0	0
05	18714	CO	40	YES	05	0	0	0
06	22840	MR	24	YES	06	0	0	0
07	18926	DF	44	NO	07	0	0	0
08	07324	EB	47	NO	08	0	0	0
09	07977	DB	21	NO	09	0	0	0
10	28937	CB	31	NO	10	0	0	0
11	15197	KC	44	YES	11	0	0	0
12	16370	KS	60	YES	12	0	0	0
13	01388	CB	51	YES	13	0	0	0
14	22353	LA	30	NO	14	0	0	DISC
15	20083	GD	60	NO	15	0	0	0
16	21818	SF	37	NO	16	0	0	0
17	16515	DC	42	YES	17	0	0	0
18	19099	AR	47	YES	18	0	0	0
19	16364	SK	52	YES	19	0	0	0
20	05120	GP	67	NO	20	0	0	0
21	15198	AD	41	YES	21	0	0	0
22	02993	SB	52	YES	22	0	0	0
23	12991	CS	35	YES	23	0	0	0
24	22074	AF	50	YES	24	0	0	0
25	20611	DS	50	YES	25	0	0	0
26	16463	AT	40	NO	26	0	0	0
27	19985	MG	46	YES	27	0	0	0

SCORING SCALE:

0 = None
1 = Mild, Very Slight
2 = Moderate
3 = Severe

DISC = Discontinued

[redacted]

[redacted]

Distributed for Comm [redacted]

Test Material: Facial Moisturizer [redacted]

TABLE II: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: EDEMA (CONTINUED)

SUBJ #	HRL #	INIT	AGE	SENS SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 28
28	11545	ML	60	YES	28	0	0	0
29	13247	PC	50	YES	29	0	0	0
30	15606	EC	22	YES	30	0	0	0
31	16344	JF	27	NO	31	0	0	0
32	18143	MB	41	YES	32	0	0	DISC
33	02589	HW	54	YES	33	0	0	0
34	17952	DC	53	NO	34	0	0	0
35	00884	TP	62	NO	35	0	0	0
36	02552	CP	58	YES	36	0	0	0
37	09971	CB	52	YES	37	0	0	0
38	14765	JT	45	NO	38	0	0	0
39	18427	MD	55	YES	39	0	0	0
40	21777	DP	38	YES	40	0	0	0
41	28939	NC	19	NO	41	0	0	0
42	01300	VB	50	YES	42	0	0	0
43	21996	PS	34	NO	43	0	0	0
44	21600	SS	37	NO	44	0	0	0
45	21268	LV	42	NO	45	0	0	0
46	16440	PN	39	YES	46	0	0	0
47	03047	JB	56	YES	47	0	0	0
48	19844	GS	40	NO	48	0	0	0
49	20974	LW	24	NO	49	0	0	0
50	17385	MV	42	NO	50	0	0	0
51	21191	KH	50	NO	51	0	0	0
52	21339	PE	52	NO	52	0	0	0
53	00005	DM	40	YES	53	0	0	0
54	17109	JB	56	NO	54	0	0	DISC
55	19161	JC	39	NO	55	0	0	0

SCORING SCALE:

0 = None
1 = Mild, Very Slight
2 = Moderate
3 = Severe

DISC = Discontinued

[redacted]

[redacted]

Distributed for Comm[redacted]

Test Material: Facial Moisturizer [redacted]

TABLE III: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: DRYNESS / SCALING

SUBJ #	HRL #	INIT	AGE	SENS SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 28
01	21766	PR	67	NO	01	0	0	0
02	22034	JS	35	NO	02	0	0	0
03	07381	DW	53	YES	03	0	0	0
04	19288	RC	52	YES	04	0	0	0
05	18714	CO	40	YES	05	0	0	0
06	22840	MR	24	YES	06	0	0	0
07	18926	DF	44	NO	07	1*	0	0 (–)
08	07324	EB	47	NO	08	0	0	0
09	07977	DB	21	NO	09	0	0	0
10	28937	CB	31	NO	10	0	0	0
11	15197	KC	44	YES	11	0	0	0
12	16370	KS	60	YES	12	0	0	0
13	01388	CB	51	YES	13	0	0	0
14	22353	LA	30	NO	14	0	0	DISC
15	20083	GD	60	NO	15	0	0	0
16	21818	SF	37	NO	16	0	0	0
17	16515	DC	42	YES	17	0	0	0
18	19099	AR	47	YES	18	0	0	0
19	16364	SK	52	YES	19	0	0	0
20	05120	GP	67	NO	20	0	0	0
21	15198	AD	41	YES	21	1Q	0	0 (–)
22	02993	SB	52	YES	22	1*	1**	0 (–)
23	12991	CS	35	YES	23	0	0	0
24	22074	AF	50	YES	24	0	0	0
25	20611	DS	50	YES	25	0	0	0
26	16463	AT	40	NO	26	0	0	0
27	19985	MG	46	YES	27	0	0	0

SCORING SCALE:

0	=	None	DISC	=	Discontinued
1	=	Mild, Very Slight	*	=	See Data Form
2	=	Moderate	**	=	See Data Form
3	=	Severe	Q	=	See Data Form

[redacted]

[redacted]

Distributed for Comm[redacted]

Test Material: Facial Moisturizer [redacted]

TABLE III: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: DRYNESS / SCALING (CONTINUED)

SUBJ #	HRL #	INIT	AGE	SENS SKIN	TEST MAT'L. #	TEST DAY 0	TEST DAY 14	TEST DAY 28
28	11545	ML	60	YES	28	0	1	0 F
29	13247	PC	50	YES	29	0	0	0
30	15606	EC	22	YES	30	0	0	0
31	16344	JF	27	NO	31	0	1	0 F
32	18143	MB	41	YES	32	0	0	DISC
33	02589	HW	54	YES	33	0	0	0
34	17952	DC	53	NO	34	0	0	0
35	00884	TP	62	NO	35	0	0	0
36	02552	CP	58	YES	36	0	0	0
37	09971	CB	52	YES	37	0	0	0
38	14765	JT	45	NO	38	0	0	0
39	18427	MD	55	YES	39	0	0	0
40	21777	DP	38	YES	40	0	0	0
41	28939	NC	19	NO	41	0	0	0
42	01300	VB	50	YES	42	0	1**	0 F
43	21996	PS	34	NO	43	0	0	0
44	21600	SS	37	NO	44	0	0	0
45	21268	LV	42	NO	45	0	0	0
46	16440	PN	39	YES	46	0	0	0
47	03047	JB	56	YES	47	0	0	0
48	19844	GS	40	NO	48	0	0	0
49	20974	LW	24	NO	49	0	0	0
50	17385	MV	42	NO	50	0	0	0
51	21191	KH	50	NO	51	0	0	0
52	21339	PE	52	NO	52	0	0	0
53	00005	DM	40	YES	53	0	0	0
54	17109	JB	56	NO	54	0	0	DISC
55	19161	JC	39	NO	55	0	1	1 +

SCORING SCALE:

0	=	None	DISC	=	Discontinued
1	=	Mild, Very Slight	**	=	See Data Form
2	=	Moderate			
3	=	Severe			

[redacted]

Test Material: Facial Moisturizer [redacted]

TABLE IV: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: SUBJECTIVE IRRITATION

SUBJ #	HRL #	INIT	AGE	SENSITIVE SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 21
01	21766	PR	67	NO	01	0	0	0
02	22034	JS	35	NO	02	0	0	0
03	07381	DW	53	YES	03	0	0	0
04	19288	RC	52	YES	04	0	0	0
05	18714	CO	40	YES	05	0	0	0
06	22840	MR	24	YES	06	0	0	0
07	18926	DF	44	NO	07	0	0	0
08	07324	EB	47	NO	08	0	0	0
09	07977	DB	21	NO	09	0	0	0
10	28937	CB	31	NO	10	0	0	0
11	15197	KC	44	YES	11	0	0	0
12	16370	KS	60	YES	12	0	0	0
13	01388	CB	51	YES	13	0	0	0
14	22353	LA	30	NO	14	0	0	DISC
15	20083	GD	60	NO	15	0	0	0
16	21818	SF	37	NO	16	0	0	0
17	16515	DC	42	YES	17	0	0	0
18	19099	AR	47	YES	18	0	0	0
19	16364	SK	52	YES	19	0	0	0
20	05120	GP	67	NO	20	0	0	0
21	15198	AD	41	YES	21	0	0	0
22	02993	SB	52	YES	22	0	0	0
23	12991	CS	35	YES	23	0	0	0
24	22074	AF	50	YES	24	0	0	0
25	20611	DS	50	YES	25	0	0	0
26	16463	AT	40	NO	26	0	0	0
27	19985	MG	46	YES	27	0	0	0

SCORING SCALE:

0	=	None	St	=	Stinging	DISC	=	Discontinued
1	=	Mild, Very Slight	B	=	Burning			
2	=	Moderate	It	=	Itching			
3	=	Severe	T	=	Tautness			
			Dr	=	Dryness			

[redacted]

[redacted]

Distributed for Comme [redacted]

Test Material: Facial Moisturizer [redacted]

TABLE IV: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: SUBJECTIVE IRRITATION (CONTINUED)

SUBJ #	HRL #	INIT	AGE	SENSITIVE SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 21
28	11545	ML	60	YES	28	0	0	0
29	13247	PC	50	YES	29	0	0	0
30	15606	EC	22	YES	30	0	0	0
31	16344	JF	27	NO	31	0	0	0
32	18143	MB	41	YES	32	0	0	DISC
33	02589	HW	54	YES	33	0	0	0
34	17952	DC	53	NO	34	0	0	0
35	00884	TP	62	NO	35	0	0	0
36	02552	CP	58	YES	36	0	0	0
37	09971	CB	52	YES	37	0	0	0
38	14765	JT	45	NO	38	0	0	0
39	18427	MD	55	YES	39	0	0	0
40	21777	DP	38	YES	40	0	0	0
41	28939	NC	19	NO	41	0	0	0
42	01300	VB	50	YES	42	0	0	1*
43	21996	PS	34	NO	43	0	0	0
44	21600	SS	37	NO	44	0	0	0
45	21268	LV	42	NO	45	0	0	0
46	16440	PN	39	YES	46	0	0	0
47	03047	JB	56	YES	47	0	0	0
48	19844	GS	40	NO	48	0	0	0
49	20974	LW	24	NO	49	0	0	0
50	17385	MV	42	NO	50	0	0	0
51	21191	KH	50	NO	51	0	0	0
52	21339	PE	52	NO	52	0	0	0
53	00005	DM	40	YES	53	0	0	0
54	17109	JB	56	NO	54	0	0	DISC
55	19161	JC	39	NO	55	0	0	0

SCORING SCALE:

0	=	None	St	=	Stinging	DISC	=	Discontinued
1	=	Mild, Very Slight	B	=	Burning	*	=	See Data Form
2	=	Moderate	It	=	Itching			
3	=	Severe	T	=	Tautness			
			Dr	=	Dryness			

[redacted]

[redacted]

TABLE V: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: GLOBAL EVALUATION

SUBJ #	HRL #	INIT	AGE	SENSITIVE SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 21
01	21766	PR	67	NO	01	0	0	0
02	22034	JS	35	NO	02	1	0	0
03	07381	DW	53	YES	03	0	0	0
04	19288	RC	52	YES	04	0	0	0
05	18714	CO	40	YES	05	0	0	0
06	22840	MR	24	YES	06	2	1	1
07	18926	DF	44	NO	07	0	1	0
08	07324	EB	47	NO	08	0	0	0
09	07977	DB	21	NO	09	1	1	0
10	28937	CB	31	NO	10	1	1	1
11	15197	KC	44	YES	11	0	0	0
12	16370	KS	60	YES	12	0	0	0
13	01388	CB	51	YES	13	1	0	0
14	22353	LA	30	NO	14	1	1	DISC
15	20083	GD	60	NO	15	0	0	0
16	21818	SF	37	NO	16	0	0	0
17	16515	DC	42	YES	17	0	0	0
18	19099	AR	47	YES	18	0	0	0
19	16364	SK	52	YES	19	0	0	0
20	05120	GP	67	NO	20	0	0	0
21	15198	AD	41	YES	21	0	0	0
22	02993	SB	52	YES	22	0	0	0
23	12991	CS	35	YES	23	1	1	1
24	22074	AF	50	YES	24	0	0	0
25	20611	DS	50	YES	25	0	0	0
26	16463	AT	40	NO	26	1	0	1
27	19985	MG	46	YES	27	0	0	0

SCORING SCALE:

0 = None
1 = Only a few lesions
2 = Easily recognizable lesions but most of the face is clear
3 = Moderate involvement, not random
4 = Extensive, heavy concentration but less than half of the face is involved

DISC = Discontinued

[redacted]

[redacted]

Test Material: Facial Moisturizer [redacted]

TABLE V: FACIAL MOISTURIZER USE TEST

DERMATOLOGICAL SCORING: GLOBAL EVALUATION

SUBJ #	HRL #	INIT	AGE	SENSITIVE SKIN	TEST MAT'L #	TEST DAY 0	TEST DAY 14	TEST DAY 21
28	11545	ML	60	YES	28	0	0	0
29	13247	PC	50	YES	29	0	0	0
30	15606	EC	22	YES	30	1	1	1
31	16344	JF	27	NO	31	0	0	0
32	18143	MB	41	YES	32	0	0	
33	02589	HW	54	YES	33	0	0	0
34	17952	DC	53	NO	34	0	0	0
35	00884	TP	62	NO	35	0	0	0
36	02552	CP	58	YES	36	0	0	0
37	09971	CB	52	YES	37	1	0	0
38	14765	JT	45	NO	38	0	1	0
39	18427	MD	55	YES	39	0	0	0
40	21777	DP	38	YES	40	0	0	0
41	28939	NC	19	NO	41	0	0	0
42	01300	VB	50	YES	42	0	0	0
43	21996	PS	34	NO	43	0	0	0
44	21600	SS	37	NO	44	0	0	0
45	21268	LV	42	NO	45	0	0	0
46	16440	PN	39	YES	46	0	0	0
47	03047	JB	56	YES	47	1	0	0
48	19844	GS	40	NO	48	0	0	0
49	20974	LW	24	NO	49	0	0	0
50	17385	MV	42	NO	50	0	0	0
51	21191	KH	50	NO	51	0	1	0
52	21339	PE	52	NO	52	0	0	0
53	00005	DM	40	YES	53	1	1	1
54	17109	JB	56	NO	54	0	0	DISC
55	19161	JC	39	NO	55	1	1	1

SCORING SCALE:

0 = None
1 = Only a few lesions
2 = Easily recognizable lesions but most of the face is clear
3 = Moderate involvement, not random
4 = Extensive, heavy concentration but less than half of the face is involved

DISC = Discontinued

[redacted]

Distributed for Comme[redacted]

Test Material: Facial Moisturizer #[redacted]

Appendix I

WEIGHT SHEET

Subject #	Weight Before Use^	Weight After Use~	Test Material #	Subject #	Weight Before Use^	Weight After Use~	Test Material #
01	151.62	116.54	01	34	150.57	128.85	34
02	151.48	133.98	02	35	149.94	117.12	35
03	152.14	140.35	03	36	151.67	142.28	36
04	151.49	122.32	04	37	151.54	117.77	37
05	152.80	127.56	05	38	149.98	128.38	38
06	150.84	132.26	06	39	151.40	116.38	39
07	151.39	123.40	07	40	151.93	117.72	40
08	151.99	114.61	08	41	150.34	116.85	41
09	152.02	122.58	09	42	151.26	123.13	42
10	151.20	127.57	10	43	150.09	129.79	43
11	151.59	119.57	11	44	150.99	137.07	44
12	151.48	140.33	12	45	149.44	111.22	45
13	150.39	135.26	13	46	150.05	118.94	46
14	151.12	130.70	14	47	151.50	120.84	47
15	151.41	142.65	15	48	149.56	142.53	48
16	151.46	126.27	16	49	150.38	102.71	49
17	152.66	132.77	17	50	150.42	137.24	50
18	151.66	110.49	18	51	150.90	129.82	51
19	152.81	138.08	19	52	151.67	131.05	52
20	150.36	118.11	20	53	151.57	126.33	53
21	151.90	134.42	21	54	151.97	D	54
22	151.65	119.25	22	55	151.30	129.54	55
23	151.67	139.62	23	56	152.46	152.46	NA
24	151.62	136.67	24	57	151.11	151.11	NA
25	151.70	139.18	25	58	152.00	152.00	NA
26	151.55	117.58	26	59	149.97	149.97	NA
27	150.98	119.95	27	60	151.21	151.21	NA
28	151.46	125.94	28	61	152.55	152.55	NA
29	152.50	113.63	29	62	150.05	150.05	NA
30	150.22	116.43	30	63	151.89	151.89	NA
31	151.76	121.67	31	64	150.76	150.76	NA
32	150.29	D	32	65	151.91	137.12	*
33	151.38	138.33	33				

^ = Test Materials #1-65 were weighed by [redacted] on November 5, 2001 on Mettler Balance PE 160.

~ = Test Materials #1-65 were weighed by [redacted] on January 7, 2002 on Mettler Balance PE 160.

D = Subject discontinued and did not return the test material.
NA = Test Material Not Assigned.
* = Used for Patch Testing.

N.B.: All weights are in grams.

[redacted]

Test Material: Facial Moisturizer [redacted]

Appendix II

USE DIRECTIONS

USE THIS PRODUCT TWO TIMES A DAY, IN THE MORNING AND IN THE EVENING!
USE IN PLACE OF YOUR REGULAR FACIAL MOISTURIZER

1. Use the test Facial Moisturizer as your only facial moisturizer.
2. Apply the test Facial Moisturizer TWICE daily, in the morning and in the evening.
3. Cleanse face as usual.
4. Dab small amounts of the product over the forehead, upper and lower cheeks and chin.
5. With your fingertips, smooth over face using **gentle** upward and outward strokes.
6. You may continue to use your regular make-up products, except for your regular facial moisturizer.

REMEMBER:

1. Bring your test Facial Moisturizer with you on the last exam date.
2. This product is for your use only. Do not let other members of your family use it.

YOU MUST REMOVE YOUR MAKE-UP AT LEAST ONE-HALF HOUR BEFORE YOU COME TO THE LAB. YOU MAY WEAR LIPSTICK AND EYE MAKE-UP.

Write your application times (and any comments) on your Daily Diary.

SCHEDULE OF PAYMENTS

All payments are made at the END of the test only.

1) Each visit is paid for at the rate of ONE DOLLAR per visit $ 3 .
2) Upon completion of the test, return of the test Facial Moisturizer and the completed "Daily Diary" form to [redacted] an additional bonus is earned of $ 37 .
3) TOTAL FEE: $ 40 for completion of the test.

It is understood and agreed that if you deviate from the schedule and/or instructions as given to you by [redacted] and/or the Project Manager in charge of the test without their express written consent, you MAY forfeit payment, at the option of [redacted]

Returned:

Test Material: _____ Daily Diary: _____ Pen: _____

FOR OFFICE USE ONLY - PANELIST'S PAYMENT

I hereby acknowledge receipt of $_____ for participation as a volunteer panelist in [redacted]

Panelist's Signature _____ **Date** _____

Witness' Signature _____ **Date** _____

[redacted]

Test Material: Facial Moisturizer [redacted]

Appendix III

PANELIST INSTRUCTIONS

1) When you come to [redacted], please look for a sign for your Panel. Your Panel color is PINK. Your Panel Number is [redacted]

2) You must use the test Facial Moisturizer as your only facial moisturizer.

3) You must use the test Facial Moisturizer TWICE a day in the morning and in the evening. Cleanse face as usual. Dab small amounts of the test Facial Moisturizer over the forehead, upper and lower cheeks and chin. With your fingertips, smooth over face using **gentle** upward and outward strokes. You may continue to use your regular make-up products, except for your regular facial moisturizer.

4) This product is for your use only. Do not let other members of your family use it.

5) No other changes are allowed in your normal daily cosmetic routine. No new cosmetics are to be used during the 4-week test period.

6) You must complete the Daily Diary using the BLACK pen given to you, and return the completed Daily Diary to [redacted] at the end of the test.

7) YOU MUST REMOVE YOUR MAKE-UP AT LEAST ONE-HALF HOUR BEFORE YOU COME TO THE LAB.
YOU MAY WEAR LIPSTICK AND EYE MAKE-UP.

8) You must return the test Facial Moisturizer on the last day of the test or you will not be paid by [redacted]

9) Please do not discuss this test or the test material with anyone other than [redacted] personnel.

10) Any questions, please call [redacted] at [redacted]

COME TO THE LAB	DAY	DATE	TIME	TECH
1.*	TUESDAY	11/06/01	6:15 – 6:45 PM	
2.*	TUESDAY	11/20/01	6:15 – 6:45 PM	
3.*	TUESDAY	12/04/01	6:15 – 6:45 PM	

* Please come to [redacted] on these days between 6:15 PM – 6:45 PM for the Doctor's visit. Please do not be late.

Bring this schedule, the test Facial Moisturizer and your Daily Diary each time you come to [redacted]

[redacted]

[redacted]

Test Material: Facial Moisturizer [redacted]

Appendix IV (Page 1 of 2)

DAILY DIARY - FACIAL MOISTURIZER USE TEST

[redacted]

Weeks: 1 & 2 (_____)

First Name _____ Last Initial_____ Age_____ [redacted]# _____ Panelist # _____

Test Material: Facial Moisturizer #_____

DAY	DATE	APPLICATION TIMES		COMMENTS
				Please use the Black Pen
		1st	**2nd**	
01	11/07/01			
02	11/08/01			
03	11/09/01			
04	11/10/01			
05	11/11/01			
06	11/12/01			
07	11/13/01			
08	11/14/01			
09	11/15/01			
10	11/16/01			
11	11/17/01			
12	11/18/01			
13	11/19/01			
14*	**11/20/01**			

***Please come to [redacted] on this day between 6:15 PM – 6:45 PM for the Doctor's visit.**
Please do not be late!

Additional Comments: _____

_____

_____

[redacted]

Distributed for Comm [redacted]

Test Material: Facial Moisturizer [redacted]

Appendix IV (Page 2 of 2)

DAILY DIARY - FACIAL MOISTURIZER USE TEST

[redacted]

Weeks: 3 & 4 (_____)

DAY	DATE	APPLICATION TIMES		COMMENTS
				Please use the Black Pen
		1st	**2nd**	
15	11/21/01			
16	11/22/01			
17	11/23/01			
18	11/24/01			
19	11/25/01			
20	11/26/01			
21	11/27/01			
22	11/28/01			
23	11/29/01			
24	11/30/01			
25	12/01/01			
26	12/02/01			
27	12/03/01			
28*	**12/04/01**			

***Please come to** [redacted] **on this day between 6:15 PM – 6:45 PM for the Doctor's visit.**
Please do not be late!

Additional Comments: _____

_____

_____

Please remember to bring your test Facial Moisturizer.

[redacted]

[redacted]

Appendix V

DATA FORM: DERMATOLOGICAL EXAMINATION

First Name _____ Last Initial_____ Age_____ [redacted] # _____ Panelist # _____

Telephone # [redacted] _____ Panel # [redacted]

Test Material: FACIAL MOISTURIZER [redacted] / _____

Sensitive Skin: Yes_____ No_____

Test Day	Erythema	Edema	Dryness/ Scaling	Subjective Irritation	Global Evaluation	Initials/ Date
0						
14						
28						

SCORING SCALES:

Erythema, Edema & Dryness / Scaling:

0 = None
1 = Mild, Very Slight
2 = Moderate
3 = Severe

Acne Global Evaluation:

0 = None
1 = Only a few lesions
2 = Easily recognizable lesions but most of the face is clear
3 = Moderate involvement, not random
4 = Extensive, heavy concentration but less than half of the face is involved

Subjective Irritation

0 = None
1 = Mild, Very Slight
2 = Moderate
3 = Severe

St = Stinging
B = Burning
It = Itching
T = Tautness
Dr = Dryness

Comments: _____

_____

_____

_____

[redacted] MD, FAAD
Medical (Dermatological) Investigator

Date

[redacted], PhD
Principal Investigator

[redacted]

QUALITY ASSURANCE MEMORANDUM

FACIAL MOISTURIZER USE TEST

This Final Report was reviewed for accuracy and conformity with both [redacted] Protocol #2119FMDA (including any Sponsor alterations) and [redacted] Standard Operation Procedures (including any Sponsor alterations).

Inspections were accomplished as determined by a random sampling approach and reported to the Project Manager and the [redacted] President immediately following their completion.

The raw data for this study are retained at [redacted]

[redacted]

[redacted]

Quality Assurance Manager
QUALITY ASSURANCE UNIT

Dated: January 11, 2002

[redacted]

[redacted]

Profile [redacted]

CLINICAL SAFETY MEMORANDUM

To: [redacted]

From: [redacted]

Date: **November 7, 2008**

Subject: [redacted] **5-Day Use Test (Lips)**

Background/Purpose:

[redacted] is a product being developed for [redacted] A 5-Day Use Test was conducted to evaluate the formulation for safety.

Conclusion:

[redacted] performed acceptably regarding both clinical and subjective irritation.

Test Materials:

contains 1% Olea Europaea (Olive) Leaf Extract

Test (T): (2076) [redacted]
Control (C): The study included the application of the test sample on the upper and lower lip. There was no control used to maximize product exposure.

Test Date:

October 27- October 31, 2008

Procedure:

An adequate amount applied to the upper and lower lips twice daily for 5 day.

This study followed the procedure outlined in SOP CUT 5.1, dated 4/12/02, with the following specifications:

-**22** female subjects completed the study.
-Subjects reported to the lab twice a day for 5 consecutive days.
-Following a visual exam, the subjects applied an adequate amount.
-Subjects were not permitted to wear any other lip product.
-The afternoon visit consisted of a re-application of the product and completion of a subjective discomfort questionnaire.
-On the last visit of the study, subjects completed a questionnaire rating the gentleness of the product.

Results:

Visible Changes

Clinically, [redacted] performed acceptably. There was three (3) subjects (CL, JS, & TF-K) who exhibited a visible clinical change. CL displayed dryness on upper and lower lips on Day 5 during the morning visit for the duration of the study. JS displayed dryness on upper and lower lips on Day 2 during the afternoon visit for the duration of the study. TF-K displayed dryness on upper and lower lips on Day 3 during the morning visit for the duration of the study. Constant Comfort [redacted] performed acceptably with regard to clinical changes.

Subjective Discomfort

[redacted] performed acceptably. There were no (0) subjects who reported subjective discomfort. [redacted] is acceptable for further pursuit with respect to subjective discomfort.

Gentleness Questionnaire

On the last visit, the subjects rated the gentleness of the product. The entire panel rated [redacted] Very or Somewhat Gentle.

Prepared By: [redacted]
Senior Technician

Approved By: [redacted]
Program Manager

CC: File

[redacted] [redacted]

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1 **TO:** [redacted]

PRODUCT PROFILE NO: [redacted] DATE: October 15, 2008 LAB REF.: [redacted]

1. TEST MATERIAL: [redacted] SIFI [redacted]

2. CONTROL MATERIAL: [redacted] Liquid Lip Color – [redacted]

contains 1% Olea Europaea (Olive) Leaf Extract

3. TEST PROCEDURE:

Single-Insult (24hr.)__X__ Occlusive (Blenderm) Patch__X__ Semi-Occlusive Patch_____.

4. CONCENTRATION:

Full-Strength__X__ Aqueous _____ Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

_____Volatiles were allowed to evaporate on the patch.
_____Patch was hydrated just prior to application to skin.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
		0	±	1	1+	2	2+	3	3+	4	PII
[redacted] SIFI	20	20	0	0	0	0	0	0	0	0	0.00
[redacted] Liquid Lip Color	20	20	0	0	0	0	0	0	0	0	0.00

___ Skin staining noted. Erythematous response was read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). __X__.

B. _____.

Study Conducted By: [redacted] Approved By: [redacted]

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

CC: [redacted]

[redacted]

FINAL REPORT dated December 15, 2008

[redacted]

Sample: Lip Balm coded [redacted]

[redacted]

[redacted]

[redacted]

Title: [redacted] An Evaluation of the Contact-Sensitization Potential of a Topical Coded Product in Human Skin by means of the Maximization Assay

contains 5% Olea Europaea (Olive) Leaf Extract

Sponsor: [redacted]

Commitment Letter dated: October 29, 2008

Principal Investigator: [redacted] M.D. (Board Certified Dermatologist)

Testing Facility: [redacted]

Final Report Date: **December 15, 2008**

[redacted]

[redacted], M.D.
Principal Investigator

15 December 2008
Date

[redacted]

FINAL REPORT

STUDY TITLE:

An assessment of the contact-sensitizing potential of a coded topically-applied test agent using a Human Maximization Assay.

[redacted] PROTOCOL:

[redacted]

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) (21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with [redacted] Standard Operating Procedures (SOP's).

STUDY OBJECTIVE:

The objective of this study was to assess the skin sensitizing potential any preparation designed for topical use by means of the Maximization Test (see references #1 and #2).

DESIGN RATIONALE:

A repeat insult patch test wherein the test product was applied under an occlusive dressing to an SLS (sodium lauryl sulfate) pre-treated site on the upper outer arm repeatedly to the same designated area for five 48-hour induction periods followed 7-10 days later by a single challenge to a naïve skin site on the opposite outer arm.

STUDY SPONSOR:

[redacted]

SPONSOR STUDY:

Commitment Letter dated October 29, 2008

TESTING FACILITY:

[redacted]

PRINCIPAL INVESTIGATOR:

[redacted], M.D. (Board Certified Dermatologist)

Medical Director, [redacted]

[redacted]

[redacted] ADMINISTRATIVE STRUCTURE:

[redacted] (Panel Recruitment/Initial Screening)

[redacted] (Technician /Patch Applications/Removals/Recognize/Report AE's)

[redacted] (Evaluator)

[redacted] (Quality Assurance)

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to read and sign the consent form prior to enrollment. Copies of all consent forms are on file at [redacted].

CONDUCTION DATES:

This study was conducted between November 3, 2008 and December 5, 2008

TEST MATERIAL:

The test product labeled Lip Balm and coded [redacted] was supplied by the sponsor and tested as supplied viz. neat.

TEST PRODUCT ACCOUNTABILITY:

The test sample was received in good condition by our Quality Assurance Department. The test material was checked for (1) amount (2) product number or code (3) material container etc. The material was individually listed on a special sheet (drug/test product log form) signed by the receiver, the laboratory supervisor and the investigator (physician). The test sample was stored under ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test material(s) will be disposed of in accordance with applicable governmental regulations following submission of the final written report or returned to the Sponsor via a traceable method, if requested.

PANEL COMPOSITION:

Healthy, adult volunteers over the age of 18 years were recruited for this study. Panelists had no blemishes, excess hair or other marks on their upper outer arms that would obscure grading of the test site. Both male and female panelists were eligible. None of the subjects had a medical or dermatological illness and none were sensitive to sunscreens or to topical preparations and/or cosmetics. A completed subject was a subject who satisfied the admission criteria and who completed the scheduled study procedures.

Inclusion Criteria:

1. Healthy adult male and female volunteers between the ages of 18 and 65 years.
2. All subjects who were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. Subjects with any significant internal diseases e.g., cardiac, pulmonary, renal, hepatic, etc.
2. History of allergy or hypersensitivity to cosmetics, toiletries or other dermatological products
3. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria
4. Pregnancy or mothers who are breastfeeding or planning a pregnancy
5. Scars, moles or other blemishes over the upper arm(s) or back which can interfere with the study
6. Subjects receiving systemic or topical drugs or medications which can interfere with delayed immunologic responses e.g., corticosteroids, non-steroidal anti-inflammatories, retinoids, immunosuppressants
7. Other conditions considered by the investigator as sound reasons for disqualification from enrollment into the study

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS:

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

STUDY PROCEDURES:

Method and Procedures[1,2]

Patches were applied to the upper outer arm of each subject. The entire test was composed of three distinct phases: (1) an Induction phase and (2) a Rest Phase and (3) a Challenge phase.

(1) **Induction Phase**:

Approximately 0.05ml of aqueous SLS (0.25%) was applied to a designated site under a 15mm disc of Webril cotton cloth and the patch was fastened to the skin with occlusive tape for a period of 24 hours. After 24 hours, the SLS patch was removed and 0.05ml of the test material was applied to the same site before the site was again covered with occlusive tape (induction patch). Since the test material coded [redacted] (Lip Balm) contained volatile ingredients, it was allowed to air-dry for approximately 30 minutes prior to application to the test site before the site was again covered with occlusive tape (induction patch). The induction patch was left in place for 48 hours (or for 72 hours when placed over a weekend) following which it was removed and the site again examined for irritation. If no irritation was present, a 0.25% aqueous SLS patch was again reapplied to the same site for 24 hours, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence viz. 24 hour SLS pre-treatment followed by 48 hours of test material application was continued for a total of 5 induction exposures.

If irritation developed at any time-point during the induction phase as previously outlined, the 24-hour SLS pre-treatment patch was eliminated and only the test material was reapplied to the same site after a 24-hour rest period during which no patch was applied.

The aim during this phase of the study was to maintain at least a minimal degree of irritation in order to enhance penetration through the corneum barrier.

(2) **Rest Period**:

No exposure to the test material was made during this rest period, which lasted for 10 days after the last induction patch.

(3) **Challenge Phase**:

After a ten day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite upper outer arm in order to determine if sensitization had developed.

Pre-treatment with SLS was performed prior to challenge. Approximately 0.05ml of a 5.0% aqueous solution was applied to a fresh skin site under a 15mm disc of Webril cotton and covered with occlusive tape. The SLS patch was left in place for one hour. It was then removed and 0.05ml of the test material was applied to the same site, as outlined above. The challenge patch was then covered by occlusive tape and left in place for 48 hours. After that period, the patch was removed and the site graded 15-30 minutes later and again 24 hours later for any reaction.

SCORING SCALE:

0 = not sensitized

1 = mild sensitization (viz. erythema and a little edema)

2 = moderate sensitization (erythema with infiltration, raised, spreading beyond the borders of the patch, with or without vesiculation)

3 = strong sensitization (large vesiculo-bullous reaction).

Based on these findings the number of subjects with positive responses were tabulated for the test material. The test system shown below was used to classify the allergenic potential of the test substance.

SENSITIZATION RATES:	**GRADES:**	**CLASSIFICATION**:
0 - 2/25	1	Weak
3 - 7/25	2	Mild
8 - 13/25	3	Moderate
14 - 20/25	4	Strong
21 - 25/25	5	Extreme

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions were encountered or reported by any of the panelists.

RESULTS:

A total of twenty-six (26) healthy, adult, volunteers who satisfied the inclusion criteria were enrolled into this study. There were 20 females and 6 males. Their ages ranged from 21 to 64 years. One volunteer (#02, initials G-K, a male) failed to maintain the scheduled study visits and was subsequently dropped from the study. The remaining 25 volunteers completed this investigation, as outlined in the standard protocol. The demographic data are shown in Table 1. No adverse or unexpected reactions were seen in any of the panelists during the induction phase.

The results of the challenge are shown in the enclosed table (Table 2). No instances of contact allergy were recorded at either 48 or 72 hours after the application of the challenge patches.

CONCLUSION:

Under the conditions of this test, the test sample labeled Lip Balm and coded [redacted] does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reactions under normal use conditions.

References:

(1) Kligman, A.M.: The Maximization Test. J.I.D., Vol. 47, No. 5, pp. 393-409, 1966.

(2) Kligman, A.M. and Epstein W.: Updating the Maximization Test for Identifying Contact Allergens. Contact Dermatitis. Vol. 1, 231-239, 1975.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	[redacted]	45	F	C
02	[redacted]	30	M	C
03	[redacted]	27	F	C
04	[redacted]	51	M	C
05	[redacted]	64	F	C
06	[redacted]	50	M	C
07	[redacted]	21	F	B
08	[redacted]	54	F	C
09	[redacted]	45	F	C
10	[redacted]	38	F	C
11	[redacted]	38	F	C
12	[redacted]	52	F	B
13	[redacted]	30	F	C
14	[redacted]	39	F	C
15	[redacted]	62	M	C
16	[redacted]	56	F	C
17	[redacted]	43	F	C
18	[redacted]	43	F	C
19	[redacted]	43	F	C
20	[redacted]	43	M	C
21	[redacted]	50	F	C
22	[redacted]	59	M	C
23	[redacted]	61	F	C
24	[redacted]	22	F	C
25	[redacted]	64	F	C
26	[redacted]	47	F	C

C = Caucasian
B = Black

TABLE 2

MAXIMIZATION TESTING RESULTS

Sample: Lip Balm coded [redacted]

Subject Number:	48-Hour Grading	72-Hour Grading
01	0	0
02	Dropped from the study	
03	0	0
04	0	0
05	0	0
06	0	0
07	0	0
08	0	0
09	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	0
20	0	0
21	0	0
22	0	0
23	0	0
24	0	0
25	0	0
26	0	0

Challenge Readings:

48-Hour Reading – December 4, 2008
72-Hour Reading – December 5, 2008

[redacted]

FINAL REPORT

Final Report Date: September 28, 2010

[redacted]

[redacted]

[redacted]

Title: An Assessment of the Photosensitization Potential of Two Topical Coded Test Products Using a Human Photocontact Allergenicity Assay

product contains 10% Olea Europaea (Olive) Leaf Extract

Sponsor: [redacted]

Sponsor Study: [redacted] Submission Form dated August 2, 2010

Principal Investigator: [redacted], M.D. (Board Certified Dermatologist)

Testing Facility: [redacted]

[redacted] M.D.
Principal Investigator

September 28, 2010
Date

[redacted]

F I N A L R E P O R T

TITLE:

An Assessment of the Photosensitization Potential of Two Topical Test Products Using a Human Photocontact Allergenicity Assay.

[redacted]:

[redacted]

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) ([21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with [redacted] Standard Operating Procedures (SOP's).

OBJECTIVE:

The objective of this study was to determine the photosensitization (photocontact allergenicity) potential of two topical cosmetic products to determine if these materials have a detectable photocontact allergenic potential when topically applied to human skin (see references #1 and #2).

DESIGN RATIONALE:

This was a repeat insult patch test wherein the test materials and ultraviolet radiation (solar simulated radiation) were administered to the same designated test sites over the mid or lower back area repeatedly for a total of six (6) induction exposures over a 3 week period followed by a challenge phase after a rest period of 10 to 14 days. The evaluator was blinded as to the identity of the test products.

CONDUCTION DATES:

This study was conducted from August 9, 2010 through September 10, 2010.

PRINCIPAL INVESTIGATOR:

[redacted], M.D. (Board Certified Dermatologist)

[redacted]

[redacted]

[redacted] **ADMINISTRATIVE STRUCTURE**:

[redacted] (Receptionist/Panel Recruitment/Initial Screening)

[redacted] (Technician/Patch Applications and Removals/UV Irradiation)

[redacted] (Laboratory Supervisor/Expert Grader)

[redacted] (Sr. Associate Director/Quality Assurance)

TESTING FACILITY:

[redacted]

[redacted]

[redacted]

[redacted]

SPONSOR:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

SPONSOR STUDY:

[redacted] Submission Form dated: August 2, 2010

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study.

Each interviewed panelist who qualified was then asked to sign a consent form prior to enrollment. A copy of the study schedule of events, visits and dates was then given to the volunteer.

TEST MATERIALS:

The test samples used in this study were supplied by the sponsor and tested neat. The products consisted of a Green Liquid coded [redacted] and a [redacted]. Both products contained volatiles so the product coded [redacted] was allowed to air-dry for ~30 minutes while the [redacted]. The Green Liquid was also shaken well prior to each application.

TEST DRUG ACCOUNTABILITY:

The test samples were received in good condition by our Quality Assurance Department. The test materials were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet signed by the receiver, the laboratory supervisor and the investigator (physician). The test materials were stored at ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test materials will be disposed of in accordance with established procedures following completion of the study and after the final written report has been issued to the Sponsor.

PANEL COMPOSITION:

Healthy, Caucasian, adult volunteers with no excess hair or other marks on their back that would obscure grading of the test sites were recruited for this study. These were fair skin individuals with skin types I, II, or III defined as follows (Federal Register 43: 38260, 1978):

Type I - Always burns easily; never tans
Type II - Always burns easily; tans minimally
Type III - Burns moderately; tans gradually

None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics.

Inclusion Criteria:

1. Healthy adult male and female volunteers (skin types I to III) between the ages of 18 and 65 years.
2. All subjects were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. History of sun hypersensitivity and photosensitive dermatoses.
2. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria.
3. Subjects with any significant internal diseases, e.g., cardiac, pulmonary, renal, hepatic, etc.
4. History of allergy or hypersensitivity to cosmetics, toiletries, or other dermatological products.
5. History of allergy or hypersensitivity to sunscreens.
6. History of allergy or hypersensitivity to any type of tape.
7. Scars, moles or other blemishes over the lower back, which could have interfered with the study.
8. Subjects receiving systemic or topical drugs including steroidal or non-steroidal anti-inflammatory drugs, or medications which could have interfered with the development of an inflammatory response, e.g., immunosuppressive agents or retinoids.
9. Subjects receiving potentially photosensitizing medications, e.g., thiazides, tetracyclines, phenothiazines, etc.
10. Pregnancy or mothers who were breastfeeding or planning a pregnancy.
11. Other conditions considered by the Investigator as sound reasons for disqualification from enrollment into the study.

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. All scores were recorded on the Case Report Forms. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

TEST SITE:

The test site was the mid or lower back. The test sites were inspected prior to test product application to ensure that the skin was normal in appearance and free of irritation or other blemishes.

METHOD[1,2]:

Test patches were applied to the lower back of each subject. The entire test was composed of three distinct phases: (1) Pre-testing phase (2) Induction phase and (3) Challenge phase.

(1) PRE-TESTING PHASE:

After signing an informed consent form (on Day 1), the Minimal Erythema Dose (MED) of each subject was determined by exposing one side of the midback to a series of exposures (1cm diameter circular areas) in 25% increments from the xenon arc solar simulator, the details of which are listed below. The subject's MED is the shortest exposure time that produces a minimally visible faint erythema 20 to 24 hours later.

(2) INDUCTION PHASE:

Approximately 40mgs. of each test material was applied to 2x2cm square skin sites over the lower back and covered with 2x2cm squares of non-woven cotton cloth (Webril, Curity) and covered with occlusive tape (Blenderm, 3M). The patches were left in place for twenty-four (24) hours. At the end of that period, the patches were then removed and the sites wiped off with dry gauze and exposed to three minimal erythema doses (MED's) from the xenon arc solar simulator. The sites were then left open for a forty-eight (48) hour period, after which the subjects returned to the testing facility and the patches were again reapplied to the same designated test sites under an occlusive dressing as previously outlined. Twenty-four (24) hours later, the patches were removed and the sites re-exposed to 3 MED's of solar simulated radiation. This sequence was repeated to the same test sites twice weekly for a total of three weeks (total of 6 exposures).

(3) CHALLENGE:

Eleven (11) days following the last induction dose, the subjects returned to the testing facility for a single challenge exposure. The test materials were applied as previously specified (40mgs) in **duplicate** to new designated skin sites each measuring 2x2cm on the opposite side of the lower back, under an occlusive dressing for a period of approximately 24 hours. One set of patches was then removed and any excess test material wiped off with dry gauze. The sites were then irradiated with 1/2 an MED of solar simulated radiation (SSR) plus 4J/cm^2 of UVA which was obtained by filtering the beam from the solar simulator to eliminate short (UVB) wavelengths (see Light Source). The duplicate set of patches remained unirradiated and served as control treated sites.

EVALUATION OF SKIN REACTIONS:

All test sites were examined for reactions at 48 and 72 hours following exposure of the sites to UV radiation. Each subject reported back to the testing facility at the two time points to have the responses appraised by an evaluator other than the person applying the test products, and who was unaware of the nature of the test substances.

Skin reactions were scored according to the following scale:

0 = Not sensitized

1 = Mild sensitization (viz. erythema and a little edema)

2 = Moderate sensitization (erythema with infiltration, spreading reaction

beyond the borders of the patch, with or without vesiculation)

3 = Strong sensitization (large vesicula-bullous reaction)

LIGHT SOURCE[3]:

This was a 150-watt compact xenon arc source equipped with UV-reflecting dichroic mirror and a 1mm thick Schott WG-320 filter to produce simulation of the solar spectrum (290nm-400nm). A 1mm thick UG5 filter was added to remove reflected heat and remaining visible radiation. Total irradiance at skin level was measured with a calibrated Eppley Thermopile. The size of the irradiated field was approximately a 1-cm diameter circle. UVA was obtained from this same source by passing the beam through a 1mm Schott WG345 filter (Schott Glass Technologies). This provided a continuous spectrum between 320 and 420nm with a peak between 360-370nm. Total irradiance at skin level was 217.5mW/cm$^{2.}$ The UVA intensity was 112.5mW/cm^2.

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions of any kind were observed or reported during the study.

RESULTS:

A total of 30 healthy, Caucasian panelists who qualified were enrolled into this study. There were 29 females and 1 male ranging in age from 20 to 64 years. The demography is shown in Table 1. Panelists #02, #17 and #22 failed to maintain the scheduled study visits and were subsequently dropped from the study for lack of compliance. Panelists #11 and #13 voluntarily withdrew for personal reasons unrelated to the study. The remaining 25 panelists completed this investigation, as specified in the protocol.

No side-effects or unexpected reactions of any kind were observed. Following the challenge phase, no reactions suggestive of photocontact allergy were seen in any of the panelists at either 48 or 72 hours post exposure. The results of the challenge are summarized in the enclosed tables (Tables 2 through 5).

CONCLUSIONS:

Under the presently described test conditions, the test materials labeled Green Liquid [redacted] and [redacted] do not possess a detectable photocontact-sensitizing potential in human skin.

REFERENCES

(1) Kaidbey, KH and Kligman AM: Photomaximization test for identifying photoallergic contact sensitizers. Contact Dermatitis, 6: 161-169, 1980.

(2) Kaidbey, KH and Kligman AM: Identification of contact photosensitizers by human assay. In "Current concepts in cutaneous toxicity, edited by V.A. Drill and P. Lazar. Academic Press Inc., pp. 55-68, 1980

(3) Berger DS: Specification and design of solar ultraviolet simulators. J.Invest.Dermtol. 53: 192-199, 1969.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	[redacted]	53	F	C
02	[redacted]	34	F	C
03	[redacted]	52	F	C
04	[redacted]	51	F	C
05	[redacted]	39	F	C
06	[redacted]	43	F	C
07	[redacted]	43	F	C
08	[redacted]	29	F	C
09	[redacted]	27	F	C
10	[redacted]	56	F	C
11	[redacted]	28	F	C
12	[redacted]	43	M	C
13	[redacted]	52	F	C
14	[redacted]	50	F	C
15	[redacted]	34	F	C
16	[redacted]	61	F	C
17	[redacted]	34	F	C
18	[redacted]	46	F	C
19	[redacted]	52	F	C
20	[redacted]	45	F	C
21	[redacted]	58	F	C
22	[redacted]	24	F	C
23	[redacted]	39	F	C
24	[redacted]	64	F	C
25	[redacted]	51	F	C
26	[redacted]	46	F	C
27	[redacted]	20	F	C
28	[redacted]	43	F	C
29	[redacted]	50	F	C
30	[redacted]	53	F	C

C = Caucasian

TABLE 2

RESULTS OF PHOTOMAXIMIZATION TESTING (48 Hour Grading)

Sample: Green Liquid coded [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	-	-
003	0	0
004	0	0
005	0	0
006	0	0
007	0	0
008	0	0
009	0	0
010	0	0
011	-	-
012	0	0
013	-	-
014	0	0
015	0	0
016	0	0
017	-	-
018	0	0
019	0	0
020	0	0
021	0	0
022	-	-
023	0	0
024	0	0
025	0	0
026	0	0
027	0	0
028	0	0
029	0	0
030	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 3

RESULTS OF PHOTOMAXIMIZATION TESTING (72 Hour Grading)

Sample: Green Liquid coded [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	-	-
003	0	0
004	0	0
005	0	0
006	0	0
007	0	0
008	0	0
009	0	0
010	0	0
011	-	-
012	0	0
013	-	-
014	0	0
015	0	0
016	0	0
017	-	-
018	0	0
019	0	0
020	0	0
021	0	0
022	-	-
023	0	0
024	0	0
025	0	0
026	0	0
027	0	0
028	0	0
029	0	0
030	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 4

RESULTS OF PHOTOMAXIMIZATION TESTING (48 Hour Grading)

[redacted]

FINAL REPORT

Final Report Date: November 30, 2011

[redacted]

Title: An Assessment of the Photosensitization Potential of Three Topical Coded Test Products Using a Human Photocontact Allergenicity Assay

Sponsor: [redacted]

blend contains 0.01% Olea Europaea (Olive) Fruit Extract

Sponsor Study: [redacted] Submission Form dated: October 5, 2011

Principal Investigator: [redacted] M.D. (Board Certified Dermatologist)

[redacted]

[redacted] M.D.
Principal Investigator

November 30, 2011
Date

[redacted]

FINAL REPORT

TITLE:

An Assessment of the Photosensitization Potential of Three Topical Test Products Using a Human Photocontact Allergenicity Assay.

[redacted] **PROTOCOL**:

[redacted]

GUIDELINES FOR THE CONDUCT OF THE STUDY:

All procedures were conducted in compliance with the regulations of the Food and Drug Administration (FDA) ([21 CFR 50, 56, 312) ICH-GCP Consolidated Guidelines, May 9, 1997 Federal Register) and in accordance with [redacted] Standard Operating Procedures (SOP's).

OBJECTIVE:

The objective of this study was to determine the photosensitization (photocontact allergenicity) potential of three topical cosmetic products to determine if these materials have a detectable photocontact allergenic potential when topically applied to human skin (see references #1 and #2).

DESIGN RATIONALE:

This was a repeat insult patch test wherein the test materials and ultraviolet radiation (solar simulated radiation) were administered to the same designated test sites over the mid or lower back area repeatedly for a total of six (6) induction exposures over a 3 week period followed by a challenge phase after a rest period of 10 to 14 days. The evaluator was blinded as to the identity of the test products.

CONDUCTION DATES:

This study was conducted from October 10, 2011 through November 11, 2011.

PRINCIPAL INVESTIGATOR:

[redacted], M.D. (Board Certified Dermatologist)

[redacted]

[redacted]

[redacted] ADMINISTRATIVE STRUCTURE:

[redacted] (Receptionist/Panel Recruitment/Initial Screening)

[redacted] (Technician/Patch Applications and Removals/UV Irradiation)

[redacted] (Laboratory Supervisor/Expert Grader)

[redacted] (Sr. Associate Director/Quality Assurance)

TESTING FACILITY:

[redacted]

SPONSOR:

[redacted]

[redacted]Submission Form dated: October 5, 2011

INFORMED CONSENT:

Prior to acceptance into the study, each subject was informed by the Investigator or his designee of the nature and purpose of the study, possible side-effects and any other relevant information. The study procedures and possible risks and discomfort were explained to each panelist during the interview using popular understandable language and terms, and the panelists were encouraged to ask questions regarding the study. Each interviewed panelist who qualified was then asked to sign a consent form prior to enrollment. A copy of the study schedule of events, visits and dates was then given to the volunteer.

TEST MATERIALS:

The test samples used in this study were supplied by the sponsor. The products consisted of separate containers labeled [redacted]; [redacted] and Blend coded [redacted]. One jar of each test product was supplied for testing purposes. All three test products were tested as supplied viz. neat.

TEST DRUG ACCOUNTABILITY:

The test samples were received in good condition by our Quality Assurance Department. The test materials were checked for (1) amount (2) product number or code (3) material container etc. The materials were individually listed on a special sheet signed by the receiver, the laboratory supervisor and the investigator (physician). The test materials were stored at ambient conditions in an inaccessible location under the supervision of the investigator.

DISPOSITION OF REMAINING CLINICAL SUPPLIES:

All remaining test materials will be disposed of in accordance with established procedures following completion of the study and after the final written report has been issued to the Sponsor.

PANEL COMPOSITION:

Healthy, Caucasian, adult volunteers with no excess hair or other marks on their back that would obscure grading of the test sites were recruited for this study. These were fair skin individuals with skin types I, II, or III defined as follows (Federal Register 43: 38260, 1978):

Type I - Always burns easily; never tans
Type II - Always burns easily; tans minimally
Type III - Burns moderately; tans gradually

None of the subjects had a medical or dermatological illness and none were sensitive to sunlight or to topical preparations and/or cosmetics.

Inclusion Criteria:

1. Healthy adult male and female volunteers (skin types I to III) between the ages of 18 and 65 years.
2. All subjects were willing to follow the study requirements and voluntarily gave their informed consent.

Exclusion Criteria:

1. History of sun hypersensitivity and photosensitive dermatoses.
2. History of recurrent dermatological diseases, e.g., psoriasis, atopic eczema, chronic urticaria.
3. Subjects with any significant internal diseases, e.g., cardiac, pulmonary, renal, hepatic, etc.
4. History of allergy or hypersensitivity to cosmetics, toiletries, or other dermatological products.
5. History of allergy or hypersensitivity to sunscreens.
6. History of allergy or hypersensitivity to any type of tape.
7. Scars, moles or other blemishes over the lower back, which could have interfered with the study.
8. Subjects receiving systemic or topical drugs including steroidal or non-steroidal anti-inflammatory drugs, or medications which could have interfered with the development of an inflammatory response, e.g., immunosuppressive agents or retinoids.
9. Subjects receiving potentially photosensitizing medications, e.g., thiazides, tetracyclines, phenothiazines, etc.
10. Pregnancy or mothers who were breastfeeding or planning a pregnancy.
11. Other conditions considered by the Investigator as sound reasons for disqualification from enrollment into the study.

SUBJECT ASSIGNMENT:

Volunteer subjects were screened and selected as described above and assigned a study number. The initials of each subject accepted into the study were recorded sequentially as they were enrolled.

RECORDING OF DATA:

The case report forms (CRF's) for this study were provided by the Investigator. All case report forms were completed in actual time, during each subject's visit. All scores were recorded on the Case Report Forms. Copies of the CRF's will be retained by the investigator along with the original signed informed consent forms.

HANDLING OF STUDY DOCUMENTS

All study related documents, case report forms (CRF's), original informed subject consent forms and any data generated were kept under secure lock in the technician's office for the duration of the study.

TEST SITE:

The test site was the mid or lower back. The test sites were inspected prior to test product application to ensure that the skin was normal in appearance and free of irritation or other blemishes.

METHOD[1,2]:

Test patches were applied to the lower back of each subject. The entire test was composed of three distinct phases: (1) Pre-testing phase (2) Induction phase and (3) Challenge phase.

(1) PRE-TESTING PHASE:

After signing an informed consent form (on Day 1), the Minimal Erythema Dose (MED) of each subject was determined by exposing one side of the midback to a series of exposures (1cm diameter circular areas) in 25% increments from the xenon arc solar simulator, the details of which are listed below. The subject's MED is the shortest exposure time that produces a minimally visible faint erythema 20 to 24 hours later.

(2) INDUCTION PHASE:

Approximately 40mgs. of each test material was applied to 2x2cm square skin sites over the lower back and covered with 2x2cm squares of non-woven cotton cloth (Webril, Curity) and covered with occlusive tape (Blenderm, 3M). The patches were left in place for twenty-four (24) hours. At the end of that period, the patches were then removed and

the sites wiped off with dry gauze and exposed to two minimal erythema doses (MED's) from the xenon arc solar simulator. The sites were then left open for a forty-eight (48) hour period, after which the subjects returned to the testing facility and the patches were again reapplied to the same designated test sites under dressings as previously outlined above. Twenty-four (24) hours later, the patches were removed and the sites re-exposed to 2 MED's of solar simulated radiation. This sequence was repeated to the same test sites twice weekly for a total of three weeks (total of 6 exposures).

(3) CHALLENGE:

Ten (10) days following the last induction dose, the subjects returned to the testing facility for a single challenge exposure. The test materials were applied as previously specified (40mgs) in **duplicate** to new designated skin sites each measuring 2x2cm on the opposite side of the lower back, under dressings, as previously described, for a period of approximately 24 hours. One set of patches was then removed and any excess test material wiped off with dry gauze. The sites were then irradiated with 1/2 an MED of solar simulated radiation (SSR) plus 4J/cm^2 of UVA which was obtained by filtering the beam from the solar simulator to eliminate short (UVB) wavelengths (see Light Source). The duplicate set of patches remained unirradiated and served as control treated sites.

EVALUATION OF SKIN REACTIONS:

All test sites were examined for reactions at 48 and 72 hours following exposure of the sites to UV radiation. Each subject reported back to the testing facility at the two time points to have the responses appraised by an evaluator other than the person applying the test products, and who was unaware of the nature of the test substances.

Skin reactions were scored according to the following scale:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesicula-bullous reaction)

LIGHT SOURCE[3]:

This was a 150-watt compact xenon arc source equipped with UV-reflecting dichroic mirror and a 1mm thick Schott WG-320 filter to produce simulation of the solar spectrum (290nm-400nm). A 1mm thick UG5 filter was added to remove reflected heat and remaining visible radiation. Total irradiance at skin level was measured with a calibrated Eppley Thermopile. The size of the irradiated field was approximately a 1-cm diameter circle. UVA was obtained from this same source by passing the beam through a 1mm Schott WG345 filter (Schott Glass Technologies). This provided a continuous spectrum between 320 and 420nm with a peak between 360-370nm. Total irradiance at skin level was 210mW/cm$^{2.}$ The UVA intensity was 75mW/cm^2.

ADVERSE EXPERIENCES:

No adverse experiences or unanticipated reactions of any kind were observed or reported during the study.

RESULTS:

A total of 28 healthy, Caucasian volunteers who qualified were enrolled into this study. There were 25 females and 3 males ranging in age from 20 to 64 years. One subject #06 (initials K-J, a female) failed to maintain the scheduled study visits and was lost to follow-up. She was subsequently dropped from the study for non-compliance. The remaining 27 volunteers completed this investigation, as specified in the protocol. The demography is shown in Table 1.

No side-effects or unexpected reactions of any kind were observed. Following the challenge phase, no reactions suggestive of photocontact allergy were seen in any of the panelists at either 48 or 72 hours post exposure. The results of the challenge are summarized in the enclosed tables (Tables 2 through 7).

CONCLUSIONS:

Under the presently described test conditions, the test materials labeled [redacted], [redacted] and Blend [redacted] do not possess a detectable photocontact-sensitizing potential in human skin.

REFERENCES

(1) Kaidbey, KH and Kligman AM: Photomaximization test for identifying photoallergic contact sensitizers. Contact Dermatitis, 6: 161-169, 1980.

(2) Kaidbey, KH and Kligman AM: Identification of contact photosensitizers by human assay. In "Current concepts in cutaneous toxicity, edited by V.A. Drill and P. Lazar. Academic Press Inc., pp. 55-68, 1980

(3) Berger DS: Specification and design of solar ultraviolet simulators. J.Invest.Dermtol. 53: 192-199, 1969.

TABLE 1

DEMOGRAPHIC DATA

Subject Number:	Subject Initials:	Age:	Sex:	Race:
01	[redacted]	56	F	C
02	[redacted]	29	F	C
03	[redacted]	21	F	C
04	[redacted]	35	M	C
05	[redacted]	37	F	C
06	[redacted]	35	F	C
07	[redacted]	58	F	C
08	[redacted]	63	F	C
09	[redacted]	23	M	C
10	[redacted]	21	F	C
11	[redacted]	41	F	C
12	[redacted]	35	F	C
13	[redacted]	24	F	C
14	[redacted]	20	F	C
15	[redacted]	22	F	C
16	[redacted]	20	F	C
17	[redacted]	62	F	C
18	[redacted]	45	F	C
19	[redacted]	40	F	C
20	[redacted]	37	F	C
21	[redacted]	42	F	C
22	[redacted]	64	F	C
23	[redacted]	42	F	C
24	[redacted]	54	F	C
25	[redacted]	53	F	C
26	[redacted]	55	M	C
27	[redacted]	46	F	C
28	[redacted]	40	F	C

C = Caucasian

TABLE 6

RESULTS OF PHOTOMAXIMIZATION TESTING (48 Hour Grading)

Sample: Blend coded [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	0	0
003	0	0
004	0	0
005	0	0
006	-	-
007	0	0
008	0	0
009	0	0
010	0	0
011	0	0
012	0	0
013	0	0
014	0	0
015	0	0
016	0	0
017	0	0
018	0	0
019	0	0
020	0	0
021	0	0
022	0	0
023	0	0
024	0	0
025	0	0
026	0	0
027	0	0
028	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

TABLE 7

RESULTS OF PHOTOMAXIMIZATION TESTING (72 Hour Grading)

Sample: Blend coded [redacted] (tested as supplied)

Subject Number:	Unirradiated Control	UV Irradiated
001	0	0
002	0	0
003	0	0
004	0	0
005	0	0
006	-	-
007	0	0
008	0	0
009	0	0
010	0	0
011	0	0
012	0	0
013	0	0
014	0	0
015	0	0
016	0	0
017	0	0
018	0	0
019	0	0
020	0	0
021	0	0
022	0	0
023	0	0
024	0	0
025	0	0
026	0	0
027	0	0
028	0	0

GRADING SCALE:

0 = Not sensitized
1 = Mild sensitization (viz. erythema and a little edema)
2 = Moderate sensitization (erythema with infiltration, spreading reaction beyond the borders of the patch, with or without vesiculation)
3 = Strong sensitization (large vesiculo-bullous reaction)

Profile # [redacted]

CLINICAL SAFETY MEMORANDUM

To: [redacted]

From: [redacted]

Date: **June 14, 2013**

Subject: [redacted] **Face Cream: 4 Day Face Use Test**

---

contains 0.0005% Olea Europaea (Olive) Fruit Extract

Background/Purpose:

[redacted] Face Cream [redacted] is a product being developed for the Global market. A 4-Day Facial Use Test was conducted to evaluate the formulation for safety.

Conclusion:

[redacted] Face Cream [redacted] performed acceptably regarding both clinical and subjective irritation and may be pursued further.

Test Materials:

Test (T): (Ref. [redacted]) [redacted] *Face Cream* [redacted]
Control (C): (Ref. [redacted]) [redacted] *Intensive Face Cream* [redacted]
Rationale: The control was selected because it is an inline product with a form and function similar to the test product. It has been previously tested with acceptable results.

Test Date:

May 28 – May 31, 2013

Procedure:

0.2cc applied to each side of the face twice daily for 4 days.

This study followed the procedure outlined in SOP CUT 5.2 dated 5/8/07 with the following specifications:

-**14** subjects completed the study.
-Subjects reported to the lab twice a day for 5 consecutive days.

-Following a visual exam, the subjects washed the entire face; the product was dispensed onto the subject's fingertips and applied to the appropriate side of the face.
-Subjects were not permitted to wear facial make-up or use their own day moisturizers for the duration of the study. They were permitted to use their normal night moisturizer. They were not permitted to use any new products on their face.
-The afternoon visit consisted of a visual exam, re-application of the product, and completion of a subjective discomfort questionnaire.
-On the last visit of the study, subjects completed a questionnaire rating the gentleness of the product.

Results:

Visible Changes

Clinically, [redacted] Face Cream [redacted] performed acceptably. There were no (0) subjects that exhibited visible changes. Clinically, [redacted] Green Olive Face Cream [redacted] performed comparable to the control product with regard to visible changes, and is acceptable for further pursuit.

Subjective Discomfort

Subjectively, [redacted] Face Cream [redacted] performed acceptably. There were no (0) subjects that reported discomfort. Subjectively, [redacted] Green Olive Face Cream [redacted] performed acceptably with regard to subjective discomfort, and is acceptable for further pursuit.

Gentleness Questionnaire

On the last visit the subjects rated the gentleness of the product. The entire panel rated the product as Very Gentle.

Prepared By: [redacted]
Technician III

Approved By: [redacted]
Manager

CC: [redacted], File

[redacted]
Ref. [redacted]

TP

[redacted] **Face Cream** [redacted]
5 Day Use Study: conducted 5/28-5/31/2013
Control: [redacted] Intensive Face Cream [redacted]
n =14

Visible Changes

N = 0

Subjective Discomfort

N = 0

Gentleness Questionnaire

Subjective Perceived Response	No. of Reponses	
	Test	**Control**
Very Gentle	14	14
Somewhat Gentle	0	0
Somewhat Irritating	0	0
Very Irritating	0	0

[redacted]

6/25/13

[redacted]

RESEARCH AND DEVELOPMENT
CLINICAL EVALUATION DEPARTMENT

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1 **TO:** [redacted]

PRODUCT PROFILE NO: [redacted] DATE: April 17, 2013 LAB REF.: [redacted] test material

1. TEST MATERIAL: [redacted] Face Cream [redacted] contains 0.0005% Olea Europea (Olive) Fruit Extract

2. CONTROL MATERIAL: [redacted] Multi Active Face Cream [redacted]

3. TEST PROCEDURE:

Single-Insult (24hr.) X Occlusive (Blenderm) Patch X Semi-Occlusive Patch_____.

4. CONCENTRATION:

Full-Strength X Aqueous _____ Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

_____Volatiles were allowed to evaporate prior to occlusion on the patch.
_____Patch was hydrated just prior to application to skin.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
	n	0	±	1	1+	2	2+	3	3+	4	PII
[redacted] Face Cream [redacted]	19	19	0	0	0	0	0	0	0	0	0.00
[redacted] Multi Active Face Cream [redacted]	19	19	0	0	0	0	0	0	0	0	0.00

____ Skin staining noted. Erythematous response was read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). X .

B. _____.

Study Conducted By: [redacted] Approved By: [redacted]

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

CC:

[redacted]

RESEARCH AND DEVELOPMENT
CLINICAL EVALUATION DEPARTMENT

CLINICAL EVALUATION REPORT: HUMAN PATCH TEST

This test follows the procedure described in SOP, HPT.1 **TO:** [redacted]

PRODUCT PROFILE NO: [redacted] DATE: May 15, 2013 LAB REF.: [redacted]

1. TEST MATERIAL: LE Body Scrub [redacted] test material contains 0.025% Olea Europaea (Olive) Seed Powder
2. CONTROL MATERIAL: PS Vanilla Brown Sugar Scrub [redacted]
3. TEST PROCEDURE:

Single-Insult (24hr.) X Occlusive (Blenderm) Patch X Semi-Occlusive Patch____.

4. CONCENTRATION:

Full-Strength_____ Aqueous X (0.5% T&C) Solution _____ Dispersion_____ Aqueous Paste_____.
Other:_____.

_____Volatiles were allowed to evaporate prior to occlusion on the patch.
_____Patch was hydrated just prior to application to skin.

5. TEST RESULTS:

TEST MATERIAL	*SUBJECTS*	*IRRITATION SCORE**									
	n	0	±	1	1+	2	2+	3	3+	4	PII
LE Body Scrub [redacted]	21	20	1	0	0	0	0	0	0	0	0.02
PS Vanilla Brown Sugar Scrub [redacted]	21	18	3	0	0	0	0	0	0	0	0.07

____ Skin staining noted. Erythematous response was read "through" the Stain.

6. CONCLUSIONS:

A. There were no significant differences in irritancy observed between the Test Material (s) and the Reference Control (s). X .

B. _____.

Study Conducted By: [redacted]. Approved By: [redacted]

* SCORE
0 = No evidence of any effect.
± (Barely Perceptible) = minimal faint uniform or spotty erythema
1 (Mild) = Pink uniform erythema covering most of the contact site.
2 (Moderate) = Pink-red erythema visibly uniform in entire contact area.
3 (Marked) = Bright red erythema with accompanying edema petechiae or papules.
4 (Severe) = Deep red erythema with vesiculation or weeping with or without edema.

+, 1+, 2+ and 3+ = Intermediate scores contributing 0.5, 1.5, 2.5 and 3.5 respectively, to the P.I.I.
P.I.I. - Primary Irritation Index - a value depicting the average skin response of the test panel as a whole. It is calculated by choosing the higher of the two Irritation Scores per panelist, adding them all together and dividing by the total number of test subjects.

CC:

Profile#: [redacted]

CLINICAL SAFETY MEMORANDUM

To: [redacted]

From: [redacted]

Date: **May 1, 2013**

Subject: [redacted] **Tissue Oil Exfoliating Bar Soap: 1-Week Home Use Test**
product contains 1% Olea Europaea Seed Powder

Background/Purpose:

[redacted] Tissue Oil Exfoliating Bar Soap [redacted] is a product being developed for the South Africa market. A 1-Week Home Use Test was conducted to evaluate the formulation for safety.

Conclusion:

[redacted] Tissue Oil Exfoliating Bar Soap [redacted] performed acceptably regarding both visible and subjective irritation.

Test Materials:

Test (T): (Ref. [redacted]) [redacted] *Tissue Oil Exfoliating Bar Soap* [redacted]

Test Date:

December 11 – December 18, 2012

Procedure:

Realistic amount used twice daily for one week.

The study was conducted through [redacted] Clinical Evaluation In-house Testing Program. Thirteen (13) subjects, who met all inclusion/exclusion criteria, were empanelled and twelve (12) subjects completed the study. Subjects were given individual units of the [redacted] Tissue Oil Exfoliating Bar Soap [redacted] to use on their bodies at home, replacing their normal body wash. No new body products were permitted during

the test. Subjects used the test product twice daily during the one-week study and completed a subjective dairy after each use.

Results:

Visible Changes

Clinically, [redacted] Tissue Oil Exfoliating Bar Soap [redacted] performed acceptably. There were no (0) subjects that reported of visible changes. Clinically, [redacted] Tissue Oil Exfoliating Bar Soap [redacted] performed acceptably with regard to visible changes and is acceptable for further pursuit.

Subjective Discomfort

Subjectively, [redacted] Tissue Oil Exfoliating Bar Soap [redacted] performed acceptably. There were no (0) subjects who reported discomfort. Subjectively, [redacted] Tissue Oil Exfoliating Bar Soap [redacted] performed acceptably with regard to subjective discomfort and is acceptable for further pursuit.

Gentleness Questionnaire:

On the last day of the study the subjects rated the gentleness of the product. The entire panel rated the product as either Very or Somewhat Gentle.

Prepared By [redacted]

Approved By: [redacted]

CC: [redacted], File

TP

[redacted]
Ref. [redacted]

[redacted] Tissue Oil Exfoliating Bar Soap[redacted]
1-Week Home Use Study: conducted 12/11-12/18/2012
n =12

Visible Changes
N =0

Subjective Discomfort
N=0

Gentleness Questionnaire

Subjective Perceived Response	No. of Reponses **Test**
Very Gentle	11
Somewhat Gentle	1
Somewhat Irritating	0
Very Irritating	0

[redacted]

7/16/13

[redacted]

REPEATED INSULT PATCH STUDY

[redacted]

product contains 0.0025% Olea Europaea (Olive) Fruit Extract and 0.035% Olea Europaea (Olive) Seed Powder

CONDUCTED FOR:

[redacted]

Attention: [redacted]

DATE OF ISSUE:

September 5, 2014

Version 1.0

[redacted]

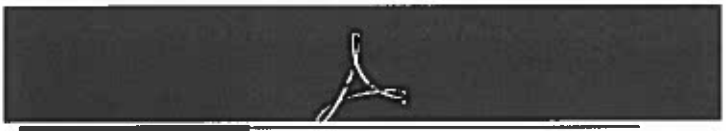
[redacted] [redacted]

TABLE OF CONTENTS

APPENDICES

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and [redacted] Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.



[redacted], MD
Dermatologist
Principal Investigator

September 5, 2014
Date

[redacted], CCRP
Vice President, Clinical Operations

September 5, 2014
Date

[redacted]
Manager, Dermatologic Safety Testing

September 5, 2014
Date

STATEMENT OF 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, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIAL

Scrub B, [redacted]

DATE STUDY INITIATED

June 30, 2014

DATE STUDY COMPLETED

August 8, 2014

DATE OF ISSUE

September 5, 2014

INVESTIGATIVE PERSONNEL

[redacted] - Dermatologist
Principal Investigator

[redacted], CCRP
Vice President, Clinical Operations

[redacted]
Manager, Dermatologic Safety Testing

CLINICAL SITE

[redacted]

SUMMARY

One product, [redacted], was evaluated as a 0.5% w/v aqueous solution to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. One hundred (100) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to product, [redacted].

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

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. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified 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. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 100 completed subjects. In the absence of any sensitization reactions in this sample size (100 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 3.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 years of age or older, in general good health;
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 (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease 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 active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. Patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2]

Following the 9th evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last Induction Visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading). Subjects who missed the 9th evaluation (N9G) but have had 9 patch applications were considered to have completed the Induction Phase.

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Following a negative Induction, a 48/72-hour sequence of "-/+," "?/+," or "+/+"

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

resulted in an additional reading being performed at the 96-hour interval. Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1[3]	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

1-6	Same as Week 2

WEEK 4

1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU induction patches
3	Staff graded MU induction sites at MU visit
2-7	Rest Period

WEEK 5

1-7	Rest Period

WEEK 6

1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

[3] Study flow starting with Week 1, Day 1, will be altered when enrollment occurs other than on Monday. Study flow could be altered when a holiday occurs during the study.

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

- = No reaction
? = Minimal or doubtful response, slightly different from surrounding normal skin
+ = Definite erythema, no edema
++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema
S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p = Papular response > 50%
pv = Papulovesicular response > 50%
D = Damage to epidermis: oozing, crusting and/or superficial erosions
I = Itching
X = Subject absent
PD = Patch dislodged
NA = Not applied
NP = Not patched (due to reaction achieved)
N9G = No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting [redacted] strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : Scrub B, [redacted]
Amount Applied : 0.2 mL
Special Instructions : Prepared fresh daily as a 0.5% w/v aqueous solution. Mixed well until dissolved prior to patch preparation.

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, 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. A sample of the study material was reserved and will be stored for a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm. Unless otherwise directed by the Sponsor, the study material was discarded upon completion of the study.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. [redacted] preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization

reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a [redacted] facility in a secured room accessible only to [redacted] employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of [redacted].

7.0 RESULTS AND DISCUSSION

One hundred eleven (111) subjects between the ages of 18 and 70 were enrolled and 100 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition:

Number enrolled:		111
Number discontinued:		11
Lost to follow-up:	6	
Voluntary withdrawal:	5	
Number completed:		100

Source: Table 1, Appendix I

There were no AEs reported during the study.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to product, [redacted].

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

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Marzulli FN, Maibach HI. Contact allergy: predictive testing in man. Contact Dermatitis 1976; 2:1.

Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

APPENDIX I

SUMMARY TABLES

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	111
Subjects completed induction phase	101 (91.0)
Subjects completed all phases	100 (90.1)
Total subjects discontinued	11 (9.9)
Lost to follow-up	6 (5.4)
Voluntary withdrawal	5 (4.5)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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[redacted]

Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	47 (42.3)
N (%) 45 to 65	53 (47.7)
N (%) 66 and up	11 (9.9)
Mean (SD)	47.1 (14.3)
Median	48.2
Range	18.5 to 70.4
Gender	
N (%) Male	29 (26.1)
N (%) Female	82 (73.9)
Race	
Amer Ind	1 (0.9)
Black	37 (33.3)
Caucasian	60 (54.1)
Hispanic	11 (9.9)
Other	2 (1.8)

See data listing 2 for further detail.

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[redacted]

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = [redacted]

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	102	100	99	102	102	101	101	101	101	3	100	100	
?	0	1	0	0	0	0	0	0	0	0	0	0	
Total evaluable	102	101	99	102	102	101	101	101	101	3	100	100	
Number absent	2	2	4	0	0	0	0	0	0		0	0	
Number discontinued	7	8	8	9	9	10	10	10	10		11	11	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=101)

Response	n(%) Subjects
-	100 (99.0%)
?	1 (1.0%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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[redacted]

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

APPENDIX II

DATA LISTINGS

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
002	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
003	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
004	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
005	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
006	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
007	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
008	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
009	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
010	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
011	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
012	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
013	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
014	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
015	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
016	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
017	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
018	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
019	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
020	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
021	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
022	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
023	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
024	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
025	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
026	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
027	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
028	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
029	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
030	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
031	06/30/14	06/30/14	08/05/14	08/08/14	C	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)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
033	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
034	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
035	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
036	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
037	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
038	06/30/14	06/30/14	08/05/14	08/08/14	C	C	40
039	06/30/14	06/30/14	--	07/03/14	I0	S	4
040	06/30/14	06/30/14	--	07/03/14	I0	S	4
041	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
042	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
043	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
044	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
045	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
046	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
047	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
048	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
049	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
050	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
051	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
052	07/03/14	07/03/14	--	07/07/14	I1	S	5
053	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
054	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
055	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
056	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
057	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
058	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
059	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
060	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
061	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
062	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37

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)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
064	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
065	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
066	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
067	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
068	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
069	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
070	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
071	07/03/14	07/03/14	--	07/09/14	I0	L	7
072	07/03/14	07/03/14	--	07/09/14	I0	L	7
073	07/03/14	07/03/14	--	07/09/14	I0	L	7
074	07/03/14	07/03/14	--	08/05/14	I9	S	34
075	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
076	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
077	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
078	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
079	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
080	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
081	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
082	07/03/14	07/03/14	--	07/09/14	I0	L	7
083	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
084	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
085	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
086	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
087	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
088	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
089	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
090	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
091	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
092	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
093	07/03/14	07/03/14	--	07/16/14	I3	L	14

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)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
095	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
096	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
097	07/03/14	07/03/14	--	07/18/14	I5	L	16
098	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
099	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
100	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
101	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
102	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
103	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
104	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
105	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
106	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
107	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
108	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
109	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
110	07/03/14	07/03/14	08/05/14	08/08/14	C	C	37
111	07/03/14	07/03/14	--	07/09/14	I0	S	7

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)

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[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
001	53.3	Female	Caucasian
002	24.5	Female	Caucasian
003	65.3	Male	Amer Ind
004	62.0	Female	Black
005	30.7	Female	Black
006	48.2	Female	Black
007	57.8	Female	Caucasian
008	53.6	Female	Caucasian
009	50.1	Female	Caucasian
010	62.6	Female	Black
011	59.4	Female	Caucasian
012	51.1	Male	Caucasian
013	68.4	Male	Caucasian
014	61.9	Female	Caucasian
015	61.8	Male	Caucasian
016	54.3	Female	Black
017	67.4	Female	Caucasian
018	68.8	Female	Caucasian
019	46.7	Female	Caucasian
020	63.5	Male	Caucasian
021	21.7	Female	Black
022	47.2	Female	Caucasian
023	30.6	Female	INDIAN
024	62.4	Female	Caucasian
025	59.5	Female	Caucasian
026	63.7	Female	Black
027	33.9	Female	Black
028	44.3	Male	Caucasian
029	56.4	Male	Black
030	40.7	Female	Caucasian
031	48.9	Female	Black
032	68.1	Female	Caucasian
033	44.9	Female	Black
034	70.3	Male	Hispanic
035	52.7	Female	Black
036	47.7	Female	Caucasian
037	59.2	Female	Caucasian

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
038	60.3	Female	Hispanic
039	19.9	Female	Black
040	19.9	Female	Black
041	56.6	Male	Black
042	58.8	Female	Caucasian
043	54.1	Female	Caucasian
044	40.1	Female	Caucasian
045	26.4	Female	Caucasian
046	57.7	Female	Black
047	38.5	Female	Black
048	47.2	Female	Black
049	61.2	Female	Caucasian
050	49.1	Female	Caucasian
051	56.9	Female	Caucasian
052	39.0	Male	Hispanic
053	31.6	Female	Hispanic
054	38.7	Female	Black
055	38.5	Female	Hispanic
056	54.8	Male	Caucasian
057	60.2	Female	Black
058	18.5	Male	Hispanic
059	70.3	Female	Caucasian
060	21.4	Female	Hispanic
061	55.8	Female	Hispanic
062	54.0	Female	Caucasian
063	61.4	Female	Caucasian
064	44.0	Female	BI-RACIAL
065	50.4	Male	Black
066	38.5	Female	Black
067	45.8	Male	Black
068	59.4	Male	Caucasian
069	41.5	Female	Black
070	36.0	Female	Caucasian
071	22.1	Male	Hispanic
072	61.0	Female	Caucasian
073	36.8	Female	Caucasian
074	49.0	Female	Black

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[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
075	54.4	Female	Black
076	45.6	Female	Caucasian
077	53.6	Male	Caucasian
078	54.1	Female	Caucasian
079	53.6	Male	Caucasian
080	20.0	Female	Caucasian
081	41.2	Female	Caucasian
082	23.4	Female	Caucasian
083	39.9	Male	Caucasian
084	69.1	Female	Caucasian
085	68.7	Female	Caucasian
086	30.6	Male	Black
087	31.9	Female	Caucasian
088	38.7	Female	Caucasian
089	39.8	Female	Caucasian
090	50.4	Male	Caucasian
091	41.2	Female	Black
092	47.2	Male	Black
093	50.4	Female	Black
094	70.4	Female	Caucasian
095	44.5	Male	Black
096	26.1	Female	Caucasian
097	35.9	Female	Caucasian
098	56.6	Female	Caucasian
099	45.5	Male	Black
100	44.5	Female	Caucasian
101	28.9	Female	Black
102	39.6	Male	Black
103	37.3	Male	Caucasian
104	19.6	Female	Black
105	21.9	Male	Caucasian
106	28.6	Female	Black
107	35.5	Male	Hispanic
108	24.7	Male	Black
109	70.0	Female	Hispanic
110	66.5	Female	Caucasian
111	37.0	Female	Caucasian

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[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	-	-	-	-	-		-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	-	-	-	-	-	-	-	-	-		-	-	
007	-	-	-	-	-	-	-	-	-		-	-	
008	-	-	-	-	-	-	-	-	-		-	-	
009	-	?	-	-	-	-	-	-	-		-	-	
010	-	-	-	-	-	-	-	-	-		-	-	
011	-	-	-	-	-	-	-	-	-		-	-	
012	-	-	-	-	-	-	-	-	-		-	-	
013	-	-	-	-	-	-	-	-	-		-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	-	-	-	-	-	-	-	-		-	-	
017	-	-	-	-	-	-	-	-	-		-	-	
018	-	-	-	-	-	-	-	-	-		-	-	
019	-	-	-	-	-	-	-	-	-		-	-	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	-	-	-	-	-	-	-	-		-	-	
023	-	-	-	-	-	-	-	-	-		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

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[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	-	-	-	-	-	-	-	-		-	-	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	X	-	-	-	-	-	-	-	-	-	-	
029	-	-	-	-	-	-	-	-	-		-	-	
030	-	X	-	-	-	-	-	-	-	-	-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	-	-	-	-	-		-	-	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	X	-	-	-	-	-	-	-	-	-	
039	X	X	X	X	X	X	X	X	X		X	X	
040	X	X	X	X	X	X	X	X	X		X	X	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	-	X	-	-	-	-	-	-	N9G	-	-	

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[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	-	-	-	-	-		-	-	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	X	X	X	X	X	X	X	X		X	X	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	-	-	-	-	-	-	-	-	-		-	-	
056	-	-	X	-	-	-	-	-	-	N9G	-	-	
057	-	-	-	-	-	-	-	-	-		-	-	
058	-	-	-	-	-	-	-	-	-		-	-	
059	-	-	-	-	-	-	-	-	-		-	-	
060	-	-	-	-	-	-	-	-	-		-	-	
061	-	-	-	-	-	-	-	-	-		-	-	
062	-	-	-	-	-	-	-	-	-		-	-	
063	-	-	-	-	-	-	-	-	-		-	-	
064	-	-	-	-	-	-	-	-	-		-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	-	-	-	-	-	-		-	-	
067	-	-	-	-	-	-	-	-	-		-	-	
068	-	-	-	-	-	-	-	-	-		-	-	
069	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
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[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	-	-	-	-	-	-		-	-	
071	X	X	X	X	X	X	X	X	X		X	X	
072	X	X	X	X	X	X	X	X	X		X	X	
073	X	X	X	X	X	X	X	X	X		X	X	
074	-	-	-	-	-	-	-	-	-		X	X	
075	-	-	-	-	-	-	-	-	-		-	-	
076	-	-	-	-	-	-	-	-	-		-	-	
077	-	-	-	-	-	-	-	-	-		-	-	
078	-	-	-	-	-	-	-	-	-		-	-	
079	-	-	-	-	-	-	-	-	-		-	-	
080	-	-	-	-	-	-	-	-	-		-	-	
081	-	-	-	-	-	-	-	-	-		-	-	
082	X	X	X	X	X	X	X	X	X		X	X	
083	-	-	-	-	-	-	-	-	-		-	-	
084	-	-	-	-	-	-	-	-	-		-	-	
085	-	-	-	-	-	-	-	-	-		-	-	
086	X	-	-	-	-	-	-	-	-	N9G	-	-	
087	X	-	-	-	-	-	-	-	-	N9G	-	-	
088	-	-	-	-	-	-	-	-	-		-	-	
089	-	-	-	-	-	-	-	-	-		-	-	
090	-	-	-	-	-	-	-	-	-		-	-	
091	-	-	-	-	-	-	-	-	-		-	-	
092	-	-	-	-	-	-	-	-	-		-	-	

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[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	X	X	X	X	X	X		X	X	
094	-	-	-	-	-	-	-	-	-		-	-	
095	-	-	-	-	-	-	-	-	-		-	-	
096	-	-	-	-	-	-	-	-	-		-	-	
097	-	-	X	-	-	X	X	X	X		X	X	
098	-	-	-	-	-	-	-	-	-		-	-	
099	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	-	-		-	-	
101	-	-	-	-	-	-	-	-	-		-	-	
102	-	-	-	-	-	-	-	-	-		-	-	
103	-	-	-	-	-	-	-	-	-		-	-	
104	-	-	-	-	-	-	-	-	-		-	-	
105	-	-	-	-	-	-	-	-	-		-	-	
106	-	-	-	-	-	-	-	-	-		-	-	
107	-	-	-	-	-	-	-	-	-		-	-	
108	-	-	-	-	-	-	-	-	-		-	-	
109	-	-	-	-	-	-	-	-	-		-	-	
110	-	-	-	-	-	-	-	-	-		-	-	
111	X	X	X	X	X	X	X	X	X		X	X	

(*) When required
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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: August 17, 2022

SUBJECT: Olea Europaea (Olive) Leaf Extract and Olea Europaea (Olive) Seed Powder

Anonymous. 2010. Verification of the absence of sensitizing potential and of the good cutaneous compatibility of a cosmetic investigational product, by repeated epicutaneous applications under occlusive patch, in 110 (or 109) healthy adult subjects (product contains 0.3% Olea Europaea (Olive) Leaf Extract).

Anonymous. 2007. Human repeat insult patch test with challenge (product contains 25% Olea Europaea (Olive) Seed Powder).

[redacted]

[redacted]

REPORT: SENSITISATION AND CUTANEOUS COMPATIBILITY STUDY

[redacted]

VERIFICATION OF THE ABSENCE OF SENSITISING POTENTIAL AND OF THE GOOD CUTANEOUS COMPATIBILITY OF A COSMETIC INVESTIGATIONAL PRODUCT, BY REPEATED EPICUTANEOUS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 110 (OR 109) HEALTHY ADULT SUBJECTS
(modified Marzulli and Maibach method)

INVESTIGATIONAL PRODUCT : [redacted]

PROTOCOLS :

REPORT :

BEGINNING OF THE OBSERVATIONS : 14 September 2010
END OF OBSERVATIONS : 23 October 2010

test material contains 0.3% Olea Europaea (Olive) Leaf Extract

SAFETY ASSESSOR	LABORATORY DIRECTOR / TECHNICAL AND SCIENTIFIC MANAGER	DERMATOLOGISTS
[redacted]		

Document of 60 pages

[redacted]

TABLE OF CONTENTS

AUTHENTICATION

[redacted]

I have read this report, I certify that these data are an accurate reflection of the results obtained and I agree with its content.

[redacted]

[redacted]

ENGLISH SUMMARY OF THE REPORT

[redacted]

SENSITISATION AND CUTANEOUS COMPATIBILITY STUDY

VERIFICATION OF THE ABSENCE OF SENSITISING POTENTIAL AND OF THE GOOD CUTANEOUS COMPATIBILITY OF A COSMETIC INVESTIGATIONAL PRODUCT, BY REPEATED EPICUTANEOUS APPLICATIONS UNDER OCCLUSIVE PATCH, IN 110 (OR 109) HEALTHY ADULT SUBJECTS (modified Marzulli and Maibach method)

INTRODUCTION	The study consists in the application of the investigational product under maximized application conditions according to the modified Marzulli and Maibach method. It is carried out on cosmetic product whose safety had 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.
STUDY OBJECTIVE	To confirm that the repeated application, under patch, of investigational product, on the subject's back, does not induce an allergic reaction and to evaluate its good cutaneous compatibility.
STUDY RELEVANCE	Cutaneous allergy is an individual phenomenon, of immune origin, of which setting off activating 3 phases (penetration of the foreign substance in the skin and forming of the allergen; development of the immune reaction; activating of the reaction, by a new application of the allergenic molecule to the skin). These 3 phases are thus required to check, in 50 or 100 subjects, the absence of sensitising potential of an investigational product, and are the basis of the method described by Marzulli and Maibach *(protocol in conformity to note dated 4 August 1997 of the French "Répression des Fraudes" to the "Fédération Française des Industries de la Parfumerie").*

INCLUSION CRITERIA SPECIFIC TO THE STUDY (*in addition to the criteria given in the standard study protocol*)	To be eligible, each subject must satisfy all the criteria written in the standard study [redacted] and the specific following ones: . *Number of subjects:* 100 subjects divided in two panels of 50 subjects receiving each 12 investigational products (the product distribution being indicated in the application scheme of the Case Report Form). . *Selection of subjects:* exclusive selection of 100 valid cases (a valid case will be defined as a subject who has completed a full procedure (9 applications and 9 readings during the induction phase followed by a double application (induction and virgin sites) and 2 readings during the challenge phase [or more if this is necessary in order to fully evaluate observed reaction]). However, a subject who has presented with significant reactions (moderate erythema and/or infiltration and/or papules and/or vesicles) twice during the induction phase, inducing a stop of application, but who received the challenge phase application after decision of the Dermatologist Investigator and the Sponsor, will be considered as a valid case even though he had not followed the previous procedure. . *Sex:* female and male . *Age:* 18 to 70 years old (the 60-70 age bracket should not exceed 10% of the total number of subjects) . *Origin:* Caucasian . *Phototypes:* I, II or III . *Healthy subjects:* 100% without "atopic" background.
NON-INCLUSION CRITERIA SPECIFIC TO THE STUDY (*in addition to the criteria given in the standard study protocol*)	To be eligible, each subject must not meet any criterion written in the standard protocol cited above. Subjects having participated to the Study [redacted] must not participate to this study.
METHODOLOGY	**- Modes of application:** . *area:* back . *quantity:* 0.02 ml over a 50 mm² surface (occlusive patch: Small Finn Chambers on Scanpor), or 0.2 ml over a 4 cm² surface (semi-occlusive patch Brady, U.S.A.), in case of reaction. . *conditions of application:* the investigational product as supplied. . *frequency and duration:* . induction phase: 9 applications spread out over 3 weeks as follows: 1st week: Day 0 (Tuesday: 1st application), Day 2 (Thursday), Day 4 (Saturday), 2nd week: Day 7 (Tuesday), Day 9 (Thursday), Day 11 (Saturday), 3rd week: Day 14 (Tuesday), Day 16 (Thursday), Day 18 (Saturday) Duration of exposure: 48 ± 4 hours for the 1st, 2nd, 4th, 5th, 7th and 8th applications, 72 ± 4 hours for the week-ends (3rd, 6th and 9th applications). . rest phase: the subjects are not submitted to any application from Day 22 (Wednesday) to Day 34 (Monday) inclusive, i.e. for a 13-day period. . challenge phase: single application on 2 sites (virgin and induced sites) on Day 35 (Tuesday) for 48 ± 4 hours. N.B.: the patches are removed by the Laboratory staff.

METHODOLOGY *(con't)*	- **Modes of evaluation:** - *Clinical observations*: readings performed, according to the Sponsor's specificities (D2, D35, D37 and D39), by the Dermatologist Investigator: . *Induction phase:* 15 to 30 minutes, after removal of the patches . *"challenge" phase:* between 30 to 35 min, and 48 ± 4 hours, after removal of the patches or more if this is necessary in order to fully evaluate observed reactions. - *Grading*, according to a given numerical scale (irritation scale: 0 to 4 & scale of the International Contact Dermatitis Research Group (I.C.D.R.G.): 0 to 3 [+++]).
ANALYSIS OF THE RESULTS AND EVALUATION CRITERIA	- *Determination of the Mean Irritation Index (M.I.I.):* equal to the sum of the quotations of the 9 readings of the induction phase divided by the number of subjects and of readings performed. - *Interpretation of the results obtained,* under the experimental conditions adopted: . **for cumulative irritation**: arbitrary classification ("non-irritating" to "severely irritating"); . **for sensitising potential**: An erythema, of intensity higher than or equal to 2 during the "challenge" phase, with or without palpable lesions, must be evaluated in the following days to determine if the reaction decreases or increases in order to precise if the reaction observed is of allergical or irritative type. A quick decrease of the reaction indicates an irritation (decrescendo reaction). A reaction with presence of infiltration/oedema, which persists and/or which increases within time generally indicates a reaction of allergical type, and additional studies ("rechallenge" and/or R.O.A.T.: Repeated Open Application Test) could be performed 3 to 6 weeks after the first appearance of the challenge reaction and after all reactions have ceased. [redacted]

M.I.I.	Classification of the investigational product
lower than 0.25	non-irritant
0.25 to 1 not included	slightly irritant
1 to 2 not included	moderately irritant
2 to 3 not included	very irritant
3 to 4	severely irritant

RESULTS AND CONCLUSION

STUDIED POPULATION

Number of subjects recruited	140
Number of subjects who came to [redacted]	120
Number of subjects included by the Dermatologist Investigator	110
Number of subjects discontinued from the study	1
Number of subjects for the analysis of the results . for the evaluation of Primary Cutaneous Irritation . for the evaluation of Cumulative Irritation . for the evaluation of Cutaneous Sensitisation	 110 109 109

The physical characteristics of the subjects are summarized in the following table:

Subjects	Primary Cutaneous Irritation	Cumulative Irritation	Cutaneous Sensitisation
Number	110	109	109
Females	100	100	100
Males	10	9	9
Age minimum (y.o.)	27	27	27
Age maximum (y.o.)	70	70	70

RESULTS

Percentage of subjects having presented with one or several well visible to severe irritation reactions (score ≥ 2), during the induction	0%
Mean Irritation Index (M.I.I.) of the induction Classification of the investigational product	0.01 ■ non-irritant: M.I.I. < 0.25 □ slightly irritant: M.I.I. [0.25 - 1[□ moderately irritant: M.I.I. [1 - 2[□ very irritant: M.I.I. [2 - 3[□ severely irritant: M.I.I. [3 - 4[
Percentage of the sensitisation reactions observed	0%
Reactions considered as serious adverse events linked to the investigational product	0%

CONCLUSION

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of the investigational product designated as [redacted], under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitization.

[redacted]

QUALITY CONTROL

This study was conducted in conformity with the Standard Operating Procedures of the Clinical Research Centre, the signed protocols and "in the spirit" of the general principles of the Good Clinical Practices (ICH topic E6 – CPMP/ICH/135/95).

The quality control of the clinical studies is carried out periodically. It is designed to ensure that all critical phases (investigational product applications and examinations or measurements) of a particular study type are controlled, at least once quarterly, for the studies carried out during this time period. Types and dates of quality controls are given below. When the quality control of a critical phase has been conducted on another study (of the same type) than the study concerned by the present report, the sentence "on identical study" is added to the "Type of quality control".

The results of these quality controls were reported to the Investigator, to the Dermatologist and to the General Management.

Type of quality control	Dates of quality controls	Dates of reports to the Dermatologist Investigator	Dates of reports to the General Management
. Critical phase(s) (on identical study)	21 September 2010	23 September 2010	28 September 2010
. Raw data: Induction	7 October 2010	8 October 2010	14 October 2010
. Raw data: Challenge	26 October 2010	27 October 2010	2nd November 2010

[redacted]

	Date of quality control	Dates of reports to the Dermatologist Investigator	Date of report to the General Management
Report (vs. compiled data):	15 December 2010	15 December 2010	15 December 2010

Signature:

[redacted]

1. INTRODUCTION

The study consists in the application of the investigational product under maximized application conditions according to the modified Marzulli and Maibach method. It is carried out on cosmetic product whose safety had 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.

2. STUDY OBJECTIVE

To confirm that the repeated application, under patch, of investigational product, on the subject's back, does not induce an allergic reaction and to evaluate its good cutaneous compatibility.

3. STUDY RELEVANCE

Cutaneous allergy is an individual phenomenon, of immune origin, which triggering requires 3 phases:
. penetration of the foreign substance (hapten) into the skin and forming of the allergen;
. development of the immune reaction;
. triggering of the reaction, by a new application of the allergenic molecule to the skin.
These 3 phases are thus required to check the absence of sensitising potential of an investigational product, and are at the root of the method described by Marzulli and Maibach *(protocol in compliance with the note of 4 August 1997 of the "Répression des Fraudes" à la "Fédération Française des Industries de la Parfumerie"):* repeated applications of the investigational product, by occlusive epicutaneous route, for 48± 4 or 72 ± 4 hours and for 3 consecutive weeks (induction phase), followed by a rest phase and by a new application under occlusion, for 48 ± 4hours (challenge phase, during which cutaneous macroscopic examinations are performed according to the International Contact Dermatitis Research Group scale: I.C.D.R.G.).

The realisation of this study under medical control, on a limited number of people thus enables to complete the data relative to the safety of a product by studying it under maximized exposure conditions.
The maximization of the test conditions (occlusivity, leaving time, etc ...) moreover enables to determine better the substances with a very weak allergenic potential.

4. PRINCIPLE

- Induction phase: during which the "preparing" or "sensitising" contacts between epidermis and investigational product may occur, which will possibly induce the allergical process without showing evidence of any clinical manifestation of hypersensitivity:

. 9 consecutive applications, to the same area, of about 0.02 ml, per subject, of the investigational product, by occlusive epicutaneous route (Finn Chambers on Scanpor), for 48 ± 4 hours or 72 ± 4 hours for the first 3 week-ends, to the skin of the back of healthy adult subjects, of both sexes.

- Rest phase: or incubation period during which the cells' transformations possibly go on, leading to the modification of reactivity:

. 13 days without any application.

- "Challenge" phase: corresponding to the contact between the epidermis and the investigational product applied during the induction phase and which aim is to reveal a clinical manifestation of induced immunological hypersensitivity:

. single application of about 0.02 ml, per subject, of the investigational product, by occlusive epicutaneous route (Finn Chambers on Scanpor) for 48 ± 4 hours, on 2 areas on the skin of the back of the subjects (i.e., the same area as the one used for the induction and on an untreated symmetrical area).

The cutaneous reaction, control of the primary and cumulative irritations, is evaluated by the macroscopic examination of the reactions possibly observed 15 to 30 minutes after removal of each patch corresponding to the induction phase.

The cutaneous reaction, control of the sensitisation, is evaluated by the macroscopic examination of the reactions possibly noted, between 30 to 35 minutes and 48 ± 4 hours after removal of the patches corresponding to the "challenge" application.

These examinations are performed by comparison to the reactions possibly obtained with a patch alone (without investigational product), or if necessary with a vehicle known as neutral, non irritant, non sensitising and non comedogenic, applied in parallel under the same conditions, as a "negative" control.

Analysis and interpretation of the results are performed depending on the data obtained under the experimental conditions adopted.

5. INVESTIGATIONAL PRODUCT

Designation	[redacted]
Formula	
Batch n°	
Physical form	
[redacted]	
Colour	beige
Packaging	glass pot
Quantity supplied (packaging included)	161 g + 165 g+ 2 x 166 g
Quantity used	75 g
Date of receipt	1st September 2010
Storage	Under lock and key, protected from heat (between + 5°C and + 25° C). [redacted]
Particular precaution	In the absence of information from the Sponsor about a possible interaction with the other investigational products, no particular precaution was taken during the positioning of this product on the subjects' back.

6. SUBJECTS

6.1. Principle of selection, recruitment, admission and inclusion

The procedure for selection, recruitment and admission of the subjects who accepted to participate in this study, after signed informed consent form, was elaborated to give him/her clear and precise information, enabling him/her to appreciate the aim and the consequences of his/her consent.

[redacted]

The final inclusion of the subject in the present study was determined by the Dermatologists, from a pre-study medical auto-questionnaire and from a clinical medical examination specific to the study, performed just before its start, on the basis of the inclusion and non-inclusion criteria specific to the study, as well as the prohibition and restriction concepts defined in the protocol.

6.2. Number of subjects requested for the study

The number of subjects in the study at D0 must be at least 105 in order to obtain at Day end a minimum of 100 valid cases.

Justification: sensitisation being an individual phenomenon, of immune origin, the test being performed under medical control and maximized conditions, this number corresponds to a minimum acceptable number, to put into evidence the sensitising potential of an investigational product.

This study was carried out on an exclusive selection of 109 valid cases:
- 110 subjects for the evaluation of Primary Cutaneous Irritation,
- 109 subjects for the evaluation of Cumulative Irritation and of Cutaneous Sensitisation.

A valid case was defined as a subject who has completed the following procedure:
- 9 applications and 9 readings during the induction phase;
- 2 applications (on the induction and virgin sites) and 2 readings during the "challenge" phase (or more if this is necessary in order to fully evaluate observed reaction).

However, a subject who had presented with significant reactions (moderate erythema and/or infiltration and/or papules and/or vesicles) twice during the induction phase, inducing a stop of application, but who received the challenge phase application after decision of the Investigator Dermatologist and the Sponsor, could be considered as a valid case even though he had not followed the previous procedure.

6.3. Inclusion criteria

6.3.1. General inclusion criteria [redacted]

- Origin: Caucasian
  Justification for origin: the white colour of Caucasians' skin allows easier evaluation of the cutaneous reactions.

- Weight: included within the limits of the scale indicated in the Standard Operating Procedure of [redacted]

- Understanding of the [redacted] language: subjects able to read the documents they are presented with and to hold to what they are explained.

- Subject whose medical examination performed during the inclusion visit allows him/her to participate to clinical studies.

- Subject able to justify a fixed abode.

6.3.2. Inclusion criteria specific to the study

These criteria were evaluated on the basis of a questionnaire and clinical examination listed in the case report form.

- Weight: included within the limits of the scale indicated in the Standard Operating Procedure of [redacted]

- Civil contract: it was signed by the subject for each study.

- Female subjects: having taken the necessary precautions to make sure not to be pregnant at least 3 months before the beginning of the study, during the whole study, and 3 months after its completion.

- Subject whose medical examination at D0 confirmed his/her suitability for participation in this study.

- Age: adults from 18 to 70 years old (the 60-70 age bracket should not exceed 10% of the total number of subjects).

- Sex: male and female.

- Origin: Caucasian.

- Healthy subject without "atopic" background: 100%.

- Phototypes: I to III.

- Provide signed Informed Consent.

6.4. Non-inclusion criteria

6.4.1. General non-inclusion criteria [redacted]

- Subject deprived from liberty by a judiciary or administrative decision, sick subject in situation of emergency.

- Under age or of age, subject protected by law, as well as those admitted to sanitary or social facilities, ever since the research can be performed in another manner.

- Subject being an [redacted]

- Subject who cannot be contacted in case of emergency.

- Subject who participed in another clinical study of any kind.

- Health condition: these selection criteria have been strictly adhered to, in order to minimise risks to the subject (criteria evaluated on the basis of a questionnaire):

. Subject either lactating or pregnant or breastfeeding mother, or not using a medically acceptable contraceptive method;

. Subject having bilateral mastectomy, mastectomy within the last year; axillary lymph nodes (both arms) removed for any reason;

. Subject having undergone organ excision (kidney, lung, spleen, liver ...), an organ transplant, a skull concussion with extended loss of consciousness in the last 5 years or with present after-effects;

. Subject having at least one of the following disorders: cardiovascular, pulmonary, digestive, neurologic, psychiatric, genital, urinary, haematological or endocrine;

. Subject having or being in the course of a long-term treatment, in particular with antihistaminic, steroids, beta blockers (including collyrium) and/or desensitisation;

. Subject having an asthma crisis;

. Subject having an Insulino-dependent diabetes;

. Subject having a background of drug intolerance (in particular local or general anaesthetics) or of allergy to products for professional use, such as colophane, rubber (gloves, adhesives, plasters);

. Subject having *a skin disease,* and in particular: skin cancer or history of skin cancer, urticaria, œdema, eczema, recurrent herpes, herpes zoster having erupted in the last 3 months, pityriasis versicolour, common acne with a sudden rise of inflammation or nodular or kystic acne, psoriasis, ichthyosis, lichen planus, chronic lupus erythematosis, keloid scars, severe pigmentation disorders (vitiligo, chloasma, multiple lentigines, numerous or congenital nevi, especially if they are of large size), hyperhidrosis, dorsal hyperpilosity;

. Subject having a disease of the immune system or under immunosuppressive treatment;

. Subject having a treatment for malignancy (of any kind) within the last six months;

. Subject smoking more than the equivalent of 10 cigarettes a day or consuming more than 3 glasses of alcoholic drink a day.

6.4.2. Non-inclusion criteria specific to the study

These criteria were evaluated on the basis of a questionnaire and clinical examinations listed in the case report form:
- Subject not meeting with the above-mentioned inclusion criteria.
- Subject having refused to give his/her agreement by not signing the informed consent form.
- Subject not covered by a civil contract or without a fixed abode.
- Subject deprived from liberty by a judiciary or administrative decision, sick subject in situation of emergency.
- Subject who cannot be contacted in case of emergency.

- Subject not having respected:
  . the prohibition concerning the simultaneous acceptance of several biomedical research projects;
  . the grace period during which a person may not be involved in any other biomedical research projects: subject having participated in acceptability study in the last week and/or in a sensitisation study and/or in a photo-irritation or photo-sensitisation study in the last 3 months.

- Subject presenting with an "atopic" background, that is to say presenting with:
  . either TWO familial past history (among: mother, father, brother(s) and sister(s)) for the following affections: (1) atopic dermatitis, (2) allergic asthma in the 1st half of life, (3) recognised pollinosis, (4) dermo-respiratory syndrome;
  . or personal past history (at least ONE criterion) among the following affections: (1) constitutional eczema, mostly appearing during the childhood and mostly located into the skin folds, (2) recurrent periodic asthma in the childhood or pre-teenage years (no asthma crisis should have occurred during the last 6 months), (3) recurrent periodic (chronic) conjunctivitis, (4) documented (allergological examination + prick tests) or non documented pneumallergen related (pollens, acaridae, animals) allergic rhinitis.

- Subject of whom the health condition has changed since the inclusion visit in the [redacted] and/or makes, in the Dermatologist Investigator judgement, the subject ineligible or places the subject at undue risk (if the potential subject is under the care of a physician, approval to participate may be sought from that physician, at the Dermatologist Investigator's discretion and/or in accordance with regulatory requirements):
  . Subject either lactating or pregnant or breastfeeding mother, or not using a medically acceptable contraceptive method for at least 3 months before the beginning of the study, during the study and for 3 months after its completion;
  . Subject having bilateral mastectomy, mastectomy within the last year; axillary lymph nodes (both arms) removed for any reason;
  . Subject having undergone organ excision, an organ transplant, a skull concussion with extended loss of consciousness in the last 5 years or with present after-effects;
  . Subject having a disease of the immune system or under immunosuppressive treatment;
  . Subject having a treatment for malignancy (of any kind) within the last six months;
  . Subject having an asthma crisis during the last 6 months;
  . Subject having an Insulino-dependent diabetes;
  . Subject having been to the hospital or to a physician for at least one of the following disorders during the last 6 months: cardiovascular, pulmonary, digestive, neurologic, psychiatric, genital, urinary, haematological, endocrine or immunologic;
  . Subject having or being in the course of a long-term treatment, in particular with antihistaminic, steroids, beta blockers (including collyrium) and/or desensitisation;
  . Subject having intensive treatment with retinoids less than 3 months before the current HRIPT
  . Subject having a background of drug intolerance (in particular local or general anaesthetics) or of allergy to products for professional use, such as colophane, rubber (gloves, adhesives, plasters);

- Subject having *a skin disease,* and in particular: skin cancer or history of skin cancer, urticaria, œdema, eczema, recurrent herpes, herpes zoster having erupted in the last 3 months, pityriasis versicolour, common acne with a sudden rise of inflammation or nodular or kystic acne, psoriasis, ichthyosis, lichen planus, chronic lupus erythematosis, keloid scars, severe pigmentation disorders (vitiligo, chloasma, multiple lentigines, numerous or congenital nevi, especially if they are of large size), hyperhidrosis, dorsal hyperpilosity, residual hyperpigmentation on the back following photobiology studies (photo-irritation ...), keratosis pilaris, severe dermographism that could compromise evaluation of skin reactions.

- Subject smoking more than the equivalent of 10 cigarettes a day or consuming more than 3 glasses of alcoholic drink.

- Subject having macroscopic traces of irritation or any other abnormality (scars, moles or other blemishes) on the concerned areas of product application which could interfere in the analysis of the results.

- Subject currently taking or having taken, in the past 3 months, medical treatment which is, in the Dermatologist Investigator judgement, inconsistent with the participation in the study and that thus makes him/her ineligible, in particular for topical or systemic anti inflammatory drugs (e.g. aspirin, ibuprofen, corticosteroids) used currently or during the month before the beginning of the study, intensive treatment with systemic retinoids or topical retinoids to the back within the last month.

- Subject currently receiving anti-allergy injections, with final injection within the last 8 days, or expecting to begin injections during the study.

- Subject having had a febrile illness: more than 24 hours of fever within the 8 days prior to the first application of the investigational product.

- Subject being vaccinated in the last month or 3 weeks preceeding the start of the study or intention to be vaccinated during the course of the study.

- Subject having modified his/her cosmetic habits (on the areas concerned by the study) during the last 2 weeks.

- Subject with excessive skin reactivity to patch materials.

- Subject with documented history of contact allergy.

- Subject having a skin recently exposed to sunlight (natural or artificial), or having followed heliotherapy during the month preceding the start of the study.

- Subject having a phototype IV, V or VI, or abnormal pigmentation of the skin.

- Subjects having participated to the Study [redacted]

6.5. Prohibition and Restriction

Aspirin, products containing aspirin, anti-inflammatory drugs or antihistaminic or systemic steroids by general route, were forbidden throughout the duration of the study (paracetamol accepted). Vaccination and immunisation were not permitted during the whole study. Throughout the duration of the applications (except during the rest phase), the subjects should not wet the treated area or apply adhesives. They should not use other products on the body (except for water and soap or the usual cleansing product) during the study.
Moreover, the subject were instructed not to change as far as possible their routine lifestyle, e.g. food, smoking, exercise, etc. and to absolutely avoid UV exposure of the test sites (natural or artificial) throughout the entire test and for 2 weeks after the study in case of persisting reactions during the challenge phase.

7. CLINICAL STUDY (EXPERIMENTAL DESIGN)

7.1. Application

7.1.1 Application area

The applications of the investigational product were performed on a surface of about 50 mm² (8 mm in diameter) on the one hand, for the induction on the left side of the spine, and on the other hand, for the challenge phase, on one side and the other of the spine (induction area and "blank" area), between the hips and shoulders. These areas had been submitted beforehand to a specific examination, at the occasion of the final inclusion **by the Dermatologist Investigator**, that is to say just before the start of the study on D0, **as well as on D35** (before the application of the challenge phase), in order to keep only surfaces free from any macroscopic trace of irritation or from any abnormality which could interfere with the interpretation of the results.

7.1.2. Preparation of the application area

The surface defined above was previously cleaned with distilled water, then dried with cotton-wool cellulose paper.

7.1.3. Patches

The applications of the investigational product were performed under occlusive patches (Small Finn Chambers on Scanpor, delivered by Epitest Ltd. OY Finland) during the whole study. The "Finn Chamber" makes an isolation chamber which ensures a good occlusion limited to the application area of the investigational product: it is composed of an 8 mm-diameter aluminium cupule covering a contact surface of 50 mm².

Each cupule is individually mounted onto an adhesive tape (Scanpor: Norgesplaster A/S Norway) applied in order to create the same pressure on the whole cupule.

Being under a cream form, the investigational product was put directly into the cupule which was filled to the 2/3 of its volume.

7.1.4. Dose level and concentration

- About 0.02 ml, per subject, of the investigational product as supplied, measured with an automatic micropipette ("Brand" - Handy Step).

- Justification for the dose level: it is the capacity of the cupule indicated by the manufacturer of the patches.

7.1.5. Administration route

- Route: local epicutaneous

- Justification for the route: normal route for this type of study.

7.1.6. Application modalities

7.1.6.1. Induction phase

- **Application area**: back, between the hips and the shoulders, on the left side of the spine and always on the same area.

- **Investigational products applied**: the previously identified patches were carefully applied to the skin of the back, using several "ribbons" composed of 2 parallel rows, having a number of several isolation chambers corresponding to the number of investigational products.
Isolation chamber alone (without investigational product) was also affixed under the same conditions to act as a negative control.

- **Frequency and administration time**: 9 applications spread out over 3 weeks as follows:

1st week	:	Day 0 (Tuesday: 1st application), Day 2 (Thursday), Day 4 (Saturday),
2nd week	:	Day 7 (Tuesday), Day 9 (Thursday), Day 11 (Saturday),
3rd week	:	Day 14 (Tuesday), Day 16 (Thursday), Day 18 (Saturday).

- **Duration of exposure**: 48 ± 4 hours (1st, 2nd, 4th, 5th, 7th and 8th applications) or 72 ± 4 hours (3rd, 6th and 9th applications). During the last patch removal, the application area of each product was marked off on the skin (using transparent cards with anatomic marks), in order to find the precise areas for the "challenge" phase.

7.1.6.2. Rest phase

The subjects were not submitted to any application from Day 22 (Wednesday) to Day 34 (Monday) inclusive, i.e. for a 13 day period.

7.1.6.3. "Challenge" phase

- **Application area**: back, between the hips and the shoulders, on the left and right side of the spine, on the same area as the one for the induction, precisely marked off, as well as on a symmetric area (on the right of the spine), having never received any product.

- **Investigational product applied**: the investigational product (left and right side of the spine), as well as one patch alone (without investigational product) applied under the same conditions, to act as "negative" control.

- **Frequency and administration time point**: single application on D35 (Tuesday).

- **Duration of exposure:** 48 ± 4 hours.

7.1.7. Security

If the adhesive of the patch provokes an intolerance leading to the stop of the applications to the concerned area, the patch is not applied to the same site as the one used for the previous application, but to a site located near it.

When, during the induction and as of the 2nd application, a clear sign of intolerance (moderate to severe erythema: score ≥ 2) is observed on the application area of an investigational product, when removing the patches, its application is done on another site, located close to the previous one and the readings are performed on the 1st site until reversibility of the effects and on the 2nd site until the end of the induction (the changing of area can only be performed once). If an intolerance sign reappears on this 2nd site, the case is immediately discussed with the Sponsor and the application is interrupted until the "challenge" phase.

If the investigational product turns out to be very irritant, the Sponsor is informed of this in order to examine another study protocol (application in open, reduction of the leaving time...).

In the case where there is suspicion of an allergic type of reaction, the investigational product is not applied again and the case is discussed, in the shortest delay with the Sponsor.

The decision of reapplying or not the investigational product during the challenge stage is taken by both the Investigator and the Sponsor.

A photograph is taken and sent to the Sponsor in the case of a marked reaction (induction or challenge).

If the applications provoke a severe or unforeseeable intolerance, the subject must immediately inform the Dermatologist Investigator: this one will proceed, in the shortest delay, to a medical examination and [redacted] the Sponsor of the consequences on the evolution of the study.

7.2. Observations and clinical examinations

7.2.1. Reading times

The cutaneous examinations were performed on the one hand, during the induction, about 15 to 30 minutes after removal of the patches of the investigational product, in order to appraise their possible irritation potential and on the other hand, between 30 to 35 minutes and 48 ± 4 hours after removal of the patches corresponding to the "challenge" phase (i.e. on D37 and D39: examinations performed by the Dermatologist) to evaluate their possible sensitising potential.

In all cases, during the challenge phase, any late cutaneous reaction on the test area, after the reading at time point 96 hours (that is to say 48 hours after the removal), must be reported by the subject who must come back to the laboratory for an evaluation of the site by the Dermatologist Investigator.

7.2.2. Evaluation of the sensitising potential and of the cutaneous compatibility

The cutaneous reactions possibly observed during the induction and the "challenge" phase were evaluated, for each subject and for each product, according to the 3 following scales (provided by the Sponsor of the Study):

(E) Erythema

No visible erythema..... 0
Slight (slightly pinkish) erythema 1
Moderate (well defined) erythema 2
Severe erythema 3
Caustic erythema - erosive aspect and/or necrotic aspect 4

(A) Scale of the International Contact Dermatitis Research Group: I.C.D.R.G.

No reaction* 0
Slightly positive reaction: erythema, infiltration, possibly papules ..... 1 (+)
Strongly positive reaction: erythema, infiltration, papules, vesicles..... 2 (++)
Extreme positive reaction: intense erythema, infiltration,
coalescent vesicles leading to the forming of a bullae ..... 3 (+++)

** no reaction according to the I.C.D.R.G.*
for the doubtful reactions (±), score the Erythema only.

(M) Supplementary mentions / other reactions

H = Homogeneous infiltration / oedema from 1 to 3 [1 = slight; 2 = moderate; 3 = severe]
P = Papule (to precise the number)
V = Vesicle (to precise the number)
B = Bullae (to precise the number)
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 (to precise the colour)
Hy = Hypopigmentation
Fr = Follicular reaction
NA = Non applied product
T = Tape reaction
I = Itching at the test site
Er = Erosion
* = Additionals free comments
N9G = No 9th reading
Cr = Exudation and/or surface encrustation
X = The following patch is not applied; indication of the residual reactions between brackets
- = Absent subject
° = Discontinuation during the study
MU = Make-up patch.

7.3. Removal of subjects from study or data analysis

Reasons for which a subject could be discontinued from the clinical study or withdrawn from the data analysis will be one of the following:
- Adverse event,
- Serious adverse event,
- Concomitant treatment(s) incompatible with the study,
- Consent withdrawal by the subject*,
- Lost to follow up,
- Emergence of a non inclusion criterion,
- Decision of the Dermatologist Investigator,
- Violation of the protocol.

** All the subjects were informed of the fact that they can willingly and freely withdraw from the study, if they wish to do so.*

Any discontinuation in the participation of a subject during the study was mentioned in the report and the reasons for this discontinuation were precised.

Any premature discontinuation linked to a Serious Adverse Event had to be followed-up (until final outcome) and this information had to be sent to the Sponsor within 24 hours.

If the number of discontinuation or non presentations at the beginning of the study was higher than 10%, the subjects were replaced so that the data are available in at least 90% of the subjects, except if this discontinuation was due to a severe intolerance to the investigational product.

7.4. Data analysis and interpretation of the results

Analysis and interpretation of the results were performed according to the data obtained under the experimental conditions adopted.

7.4.1. Sensitising potential

For the analysis of the sensitising potential, only the subjects having participated in the challenge stage and having respected the protocol were taken into account.
The interpretation of the sensitising potential was made from results in compliance to the I.C.D.R.G. scale (see chapter. 7.2.2.).
An erythema, of intensity higher or equal to 2 during the challenge phase, with or without palpable lesions, must be evaluated in the following days to determine if the reaction decreases or increases, in order to precise if the reaction observed is of allergical or irritative type. A reaction with presence of infiltration/oedema, which persists and/or increases within time generally indicates a reaction of allergical type.

7.4.2. Cutaneous compatibility

All the subjects included were taken into account for the analysis of the cutaneous compatibility, whatever the number of times they visited the Investigator, during the induction stage.

This analysis was completed by the calculation of the Mean Irritation Index (M.I.I.), equal to the sum of the quotations of the 9 readings corresponding to the induction divided by the number of subjects included in this study and the number of readings performed:

$$M.I.I. = \frac{\Sigma \text{ quotations of the 9 readings (all the subjects)}}{\text{Number of subjects x 9 (readings)}}$$

For this index calculation, it was defined that:

- if a subject is absent for an examination, the quotation of the day of absence is identical to the one of the day before;
- if an application is stopped because of a too severe reaction, the maximum quotation (4) is attributed on the day following the stop of the investigational product application for the considered area and this, until the end of the tolerance test;
- if the applications are stopped for any other reason, the quotations of the subject are excluded of the indices calculation.

The M.I.I. thus obtained enabled arbitrary classification of the investigational products as follows (taking into account the reactions and the M.I.I. calculated on the control area):

M.I.I.	Classification of the investigational product
lower than 0.25	non-irritant
0.25 to 1 not included	slightly irritant
1 to 2 not included	moderately irritant
2 to 3 not included	very irritant
3 to 4	severely irritant

7.4.3. Adverse Events

7.4.3.1. Definition

An adverse event (AE) is defined as:
- any unfavourable and unintended event or degradation of the medical conditions (in comparison with those noted during the initial examination), occurring during the period of application of the investigational product(s) (between the inclusion in the study and the end of the study), not related to the investigational product(s) application: disease, accident, food intoxication, ...
- any reaction or event related to the application of the investigational product(s) (definitely related (very probable or certain), probably related, possibly related or unlikely related (doubtful)) or unrelated to investigational product(s) application, which by its nature, its intensity or its appearance frequency leads to a modification of the application modalities of the investigational product(s) (rhythm, quantity, application area, ...), and/or a discontinuation from the study (withdrawal of the consent by the subject or discontinuation on decision of the Dermatologist Investigator).

As soon as [redacted] that an AE has occurred, the Sponsor must be informed of the AE either immediately for a serious adverse event or within 48 hours for a non serious adverse event.
The AEs should be collected in the appropriate form at the end of the case report form along with the date of onset, site and duration of event, any action taken, outcome and an assessment of causality and severity. If the AE is still going on the final visit, the Dermatologist Investigator has to follow-up the event until complete outcome.

7.4.3.2. Causality

The Dermatologist Investigator assesses the relationship (causality) of an AE to the investigational product according to the following definitions:

- **Definitely related (very probable or certain)**
  No uncertainty about the relationship between the event and investigational product application.
  The event follows a definite reasonable temporal sequence from the time of the investigational product application and improves upon stopping the dose of the investigational product. A re-challenge is positive. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject. The event follows a known response pattern to the investigational product.

- **Probably related**
  High degree of certainty about the relationship between the event and investigational product application.
  The event follows a reasonable temporal sequence from the time of the investigational product application and improves upon stopping the dose of the investigational product. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject.

- **Possibly related**
  Unlikely but cannot rule out with certainty the relationship between the event and investigational product application.
  The event may follow a reasonable temporal sequence from the time of the investigational product application. The event may be produced by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.

- **Unlikely related (doubtful)**
  Clinical event has an unlikely relationship with the investigational product application.
  There is no reasonable temporal association between the investigational product and the suspected event and the event could be reasonably produced by the subject's clinical state or other modes of therapy administered to the subject.

- **Unrelated (not linked)**
  Clinical event is clearly not due to investigational product application.
  There is no reasonable temporal relationship between the investigational product application and the suspected event (e.g., event occurs before investigational product application) or no reasonable causality, such as an accident, which cannot remotely be related to study participation (e.g., injuries sustained in a car accident).

7.4.3.3. Severity

The Dermatologist Investigator assesses the severity of each AE according to the following definitions:

- **Slight**
  Subject is aware (fully or partly) of the sign or symptom, but it is easily tolerated and does not interfere at all with the subject's daily activity.

- **Mild**
  Subject is aware of the sign or symptom, but it is rather well tolerated and does not interfere with the subject's daily activity.

- **Moderate**
  Event causes discomfort enough to interfere with the subject's usual activities.

- **Severe**
  Incapacitating; subject is unable to perform usual activity.

7.4.3.4. Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse event, regardless of cause or relationship to the investigational product, which:
- Results in death.
- Is life-threatening (i.e., an event which, in the view of the Dermatologist Investigator, places the subject at immediate risk of death from the reaction as soon as it occurs; it does not refer to an event which hypothetically may cause death if it had been more severe).
- Requires hospitalisation or prolonged hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly.
- Also considered an SAE is any other important medical event that jeopardises the subject or requires intervention to prevent one of the outcomes listed in this definition above.

8. REGULATIONS, CONFIDENTIALITY AND LEGAL FORMALITIES

8.1. Regulations

This study was performed in agreement with the most recent recommendations of the World Medical Association (Declaration of Helsinki 1964, last amendement in force).

8.2. Confidentiality

Any information regarding the health condition of the subjects and the results of the clinical examinations, performed before the start of treatment, for their recruitment, their selection and inclusion, were submitted to the rules of the medical secrecy: in no case this information was given to the Sponsor with their identity.
To ensure preservation of the subjects' anonymity, they were identified by a code using 5 letters (and 2 digits if necessary when the letter code is already given to another subject), corresponding to the first 3 letters of their surname, then the first 2 letters of their first name, and for the study, by a number corresponding to their inclusion order in the study.
At the end of the study, the page named "Subject Identification Form", in which the name and address of the subject were mentioned, was taken from the case report form and destroyed.
The Dermatologist Investigator/Institution should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority(ies).
The Monitor(s), the Auditor(s), the IRB/IEC, and the Regulatory Authority(ies) were granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
Should the raw data be sent to the Sponsor, the confidential data of the informed consent form, as well as of the the information sheet, were masked.

8.3. Legal formalities

[redacted]

8.3.3. Information sheet and informed consent form

An information sheet was given to each subject, in order to inform him/her, in particular of:
- the aim of the research, its methodology and its duration;
- the constraints linked to the study and the foreseeable risks, even in case of stop of the research before its end;
- the non-inclusion period, the amount of the indemnity, the possibility for him/herself to check the exactitude of the data contained in his/her medical file and their subsequent destruction.

Prior to a subject's participation in a study:
- the subject dated and signed the information sheet and the informed consent form, with full knowledge of the facts. The information sheet and an original copy of the signed and dated informed consent form were kept by the subject.
- the Dermatologist Investigator dated and signed the information consent form.

8.3.4. Data recording and archiving

[redacted]

[redacted]

8.3.8. Opinion from the Independent Ethical Committee

A favourable opinion of the Independent Ethical Committee was obtained before the start of the study (Cf. Appendix 2).

9. BIBLIOGRAPHICAL REFERENCES

- Marzulli F.N. and Maibach H.I. Contact allergy, predictive testing in man. Contact Dermatitis, 1976, 2, 1 - 17

- I.C.D.R.G. = The International Contact Dermatitis Research Group., Fregert S. Manual of Contact Dermatitis 2nd Edition

- ICH topic E6 – CPMP/ICH/135/95.

- Declaration of Helsinki 1964, last amendement in force.

10. RESULTS

10.1. Amendments and protocol compliance

10.1.1 Amendments

One amendment to the protocol was issued during the course of this study.

Amendment No	Date	Reason for the amendment
1	14/12/2010	[redacted]

10.1.2 Protocol compliance

- Analysis of the results was carried out on a panel of 110 (or 109) subjects, instead of the 100 stated in the protocol.

- 25 subjects (i.e. 23 %) were aged of 60 years old and above instead of the 10 % maximum stated in the protocol and the [redacted]

- The Independent Ethical Committee gave its opinion for the realization of the study on D6 instead of on D0 the latest.

These deviations are not considered to have affected, in a notable way, the quality or the interpretation of the results obtained.

10.2. Subjects

Number of subjects recruited	140
Number of subjects who came to [redacted]	120
Number of subjects included by the Dermatologist Investigator	110
Number of subjects discontinued from the study	1 (n° 41)
. before the 1st reading	/
. during the induction phase	1 (n° 41)
. during the rest phase	/
- Non related adverse event	/
- Non related serious adverse event	/
- Related adverse event	/
- Related serious adverse event	/
- Concomitant treatment(s) incompatible with the study	1 (n° 41)
- Consent withdrawal by the subject	/
- Lost to follow up	/
- Emergence of a non inclusion criterion	/
- Decision of the Dermatologist Investigator	/
- Violation of the protocol	/
Number of subjects for the analysis of the results	
. for the evaluation of Primary Cutaneous Irritation	110
. for the evaluation of Cumulative Irritation	109
. for the evaluation of Cutaneous Sensitisation	109

The physical characteristics of the subjects are summarized in the following table:

Subjects	Primary Cutaneous Irritation	Cumulative Irritation	Cutaneous Sensitisation
Number	110	109	109
Females	100	100	100
Males	10	9	9
Age minimum (y.o.)	27	27	27
Age maximum (y.o.)	70	70	70

Results

The observations and clinical examinations are listed in the following appendix (Tables I to VII).

Percentage of subjects having presented with one or several well visible to severe irritation reactions (score ≥ 2), during the induction	0%
Mean Irritation Index (M.I.I.) of the induction Classification of the investigational product	0.01 ■ non-irritant: M.I.I. < 0.25 □ slightly irritant: M.I.I. [0.25 - 1[□ moderately irritant: M.I.I. [1 - 2[□ very irritant: M.I.I. [2 - 3[□ severely irritant: M.I.I. [3 - 4[
Percentage of the sensitisation reactions observed	0%
Reactions considered as serious adverse events linked to the investigational product	0%

11. CONCLUSION

In conclusion and given the results obtained under the experimental conditions adopted, the single and repeated epicutaneous applications of the investigational product designated as [redacted], under occlusive patch, in the healthy adult subject, did not provoke any primary or cumulative irritation reaction, nor any cutaneous sensitization.

APPENDIX 1: RESULTS

TABLE II

INDUCTION PHASE: CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJ. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS DAYS																										Σ QUOT	
	2			4			7			9			11			14			16			18			21				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
01	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
02	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
03	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
04	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
05	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
06	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
07	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
08	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
09	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
10	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
11	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
12	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
13	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
14	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
15	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
16	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
17	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
18	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
19	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
20	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
21	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
22	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
23	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
24	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
25	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
26	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
27	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
28	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
29	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
30	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0

TABLE II (con't)

INDUCTION PHASE: CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJ. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS DAYS																											Σ QUOT	
	2			4			7			9			11			14			16			18			21				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
31	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
32	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
33	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
34	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
35	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
36	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
37	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
38	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
39	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
40	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
41	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	°	°	°	°	°
42	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
43	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
44	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
45	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
46	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
47	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
48	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
49	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
50	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
51	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
52	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
53	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
54	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
55	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
56	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
57	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
58	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
59	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
60	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0

TABLE II (con't)

INDUCTION PHASE: CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJ. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS DAYS																											Σ QUOT	
	2			4			7			9			11			14			16			18			21				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
61	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
62	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
63	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
64	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
65	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
66	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
67	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
68	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
69	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
70	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
71	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
72	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
73	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
74	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
75	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
76	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
77	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
78	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
79	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
80	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
81	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
82	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
83	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
84	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
85	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
86	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
87	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
88	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
89	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
90	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0

TABLE II (con't)

INDUCTION PHASE: CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJ. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS DAYS																										Σ QUOT	
	2			4			7			9			11			14			16			18			21				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
91	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
92	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
93	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
94	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
95	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
96	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
97	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
98	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
99	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
100	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
101	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
102	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
103	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
104	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
105	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
106	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
107	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
108	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
109	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
110	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0

TOTAL [E] = 0
M.I.I. = 0

SUPPLEMENTARY MENTION [M]:

° = Discontinuation during the study.

OTHER OBSERVATION: Nothing to report.

TABLE III

INDUCTION PHASE: INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUBJ. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																										Σ QUOT	
	DAYS																											
	2			4			7			9			11			14			16			18			21				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
01	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
02	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
03	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
04	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
05	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
06	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
07	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
08	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
09	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
10	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
11	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
12	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
13	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
14	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
15	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
16	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
17	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
18	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
19	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
20	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
21	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
22	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
23	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
24	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
25	0	0	/	0	0	/	0	1	/	0	1	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	2
26	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
27	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
28	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
29	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
30	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0

TABLE III (con't)

INDUCTION PHASE: INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUBJ. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS DAYS																										Σ QUOT	
	2			4			7			9			11			14			16			18			21				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
31	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
32	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	1	/	0	0	/	0	0	/	0	0	/	-	1
33	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
34	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
35	0	0	/	0	0	/	0	0	/	0	0	/	0	1	/	0	0	/	0	0	/	0	0	/	0	0	/	-	1
36	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
37	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
38	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
39	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
40	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
41	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	°	°	°	°	°
42	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
43	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
44	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
45	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
46	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
47	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
48	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
49	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
50	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
51	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
52	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
53	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
54	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
55	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
56	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
57	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
58	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
59	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
60	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0

TABLE III (con't)

INDUCTION PHASE: INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUBJ. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS DAYS																										Σ QUOT	
	2			4			7			9			11			14			16			18			21				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
61	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
62	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
63	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
64	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
65	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
66	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
67	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
68	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
69	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
70	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
71	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
72	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
73	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
74	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
75	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
76	0	0	/	0	0	/	0	0	/	0	0	/	0	1	/	0	1	/	0	0	/	0	0	/	0	0	/	-	2
77	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
78	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
79	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
80	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
81	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
82	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
83	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
84	0	0	/	0	0	/	0	1	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	1
85	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
86	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
87	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
88	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
89	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
90	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0

TABLE III (con't)

INDUCTION PHASE: INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUBJ. N°	SENSITISATION (0 to 3) and IRRITATION (0 to 4) REACTIONS																										Σ QUOT	
	DAYS																											
	2			4			7			9			11			14			16			18			21				
	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E	M	A	E
91	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
92	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
93	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
94	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
95	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
96	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
97	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
98	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
99	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
100	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
101	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
102	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
103	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
104	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
105	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
106	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
107	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
108	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
109	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	0	0	/	-	0
110	0	0	/	0	0	/	0	1	/	0	1	/	0	1	/	0	0	/	0	0	/	0	0	/	0	0	/	-	3

TOTAL [E] = 10
M.I.I. = 0.01

SUPPLEMENTARY MENTION [M]:

° = Discontinuation during the study.

OTHER OBSERVATION: Nothing to report.

TABLE IV

CHALLENGE PHASE: CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (absence of sensitisation)
	between 30 to 35 minutes						48 ± 4h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
01	0	0	-	0	0	-	0	0	-	0	0	-	-
02	0	0	-	0	0	-	0	0	-	0	0	-	-
03	0	0	-	0	0	-	0	0	-	0	0	-	-
04	0	0	-	0	0	-	0	0	-	0	0	-	-
05	0	0	-	0	0	-	0	0	-	0	0	-	-
06	0	0	-	0	0	-	0	0	-	0	0	-	-
07	0	0	-	0	0	-	0	0	-	0	0	-	-
08	0	0	-	0	0	-	0	0	-	0	0	-	-
09	0	0	-	0	0	-	0	0	-	0	0	-	-
10	0	0	-	0	0	-	0	0	-	0	0	-	-
11	0	0	-	0	0	-	0	0	-	0	0	-	-
12	0	0	-	0	0	-	0	0	-	0	0	-	-
13	0	0	-	0	0	-	0	0	-	0	0	-	-
14	0	0	-	0	0	-	0	0	-	0	0	-	-
15	0	0	-	0	0	-	0	0	-	0	0	-	-
16	0	0	-	0	0	-	0	0	-	0	0	-	-
17	0	0	-	0	0	-	0	0	-	0	0	-	-
18	0	0	-	0	0	-	0	0	-	0	0	-	-
19	0	0	-	0	0	-	0	0	-	0	0	-	-
20	0	0	-	0	0	-	0	0	-	0	0	-	-
21	0	0	-	0	0	-	0	0	-	0	0	-	-
22	0	0	-	0	0	-	0	0	-	0	0	-	-
23	0	0	-	0	0	-	0	0	-	0	0	-	-
24	0	0	-	0	0	-	0	0	-	0	0	-	-
25	0	0	-	0	0	-	0	0	-	0	0	-	-
26	0	0	-	0	0	-	0	0	-	0	0	-	-
27	0	0	-	0	0	-	0	0	-	0	0	-	-
28	0	0	-	0	0	-	0	0	-	0	0	-	-
29	0	0	-	0	0	-	0	0	-	0	0	-	-
30	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE IV (con't)

CHALLENGE PHASE: CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (absence of sensitisation)
	between 30 to 35 minutes						48 ± 4h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
31	0	0	-	0	0	-	0	0	-	0	0	-	-
32	0	0	-	0	0	-	0	0	-	0	0	-	-
33	0	0	-	0	0	-	0	0	-	0	0	-	-
34	0	0	-	0	0	-	0	0	-	0	0	-	-
35	0	0	-	0	0	-	0	0	-	0	0	-	-
36	0	0	-	0	0	-	0	0	-	0	0	-	-
37	0	0	-	0	0	-	0	0	-	0	0	-	-
38	0	0	-	0	0	-	0	0	-	0	0	-	-
39	0	0	-	0	0	-	0	0	-	0	0	-	-
40	0	0	-	0	0	-	0	0	-	0	0	-	-
42	0	0	-	0	0	-	0	0	-	0	0	-	-
43	0	0	-	0	0	-	0	0	-	0	0	-	-
44	0	0	-	0	0	-	0	0	-	0	0	-	-
45	0	0	-	0	0	-	0	0	-	0	0	-	-
46	0	0	-	0	0	-	0	0	-	0	0	-	-
47	0	0	-	0	0	-	0	0	-	0	0	-	-
48	0	0	-	0	0	-	0	0	-	0	0	-	-
49	0	0	-	0	0	-	0	0	-	0	0	-	-
50	0	0	-	0	0	-	0	0	-	0	0	-	-
51	0	0	-	0	0	-	0	0	-	0	0	-	-
52	0	0	-	0	0	-	0	0	-	0	0	-	-
53	0	0	-	0	0	-	0	0	-	0	0	-	-
54	0	0	-	0	0	-	0	0	-	0	0	-	-
55	0	0	-	0	0	-	0	0	-	0	0	-	-
56	0	0	-	0	0	-	0	0	-	0	0	-	-
57	0	0	-	0	0	-	0	0	-	0	0	-	-
58	0	0	-	0	0	-	0	0	-	0	0	-	-
59	0	0	-	0	0	-	0	0	-	0	0	-	-
60	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE IV (con't)

CHALLENGE PHASE: CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (absence of sensitisation)
	between 30 to 35 minutes						48 ± 4h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
61	0	0	-	0	0	-	0	0	-	0	0	-	-
62	0	0	-	0	0	-	0	0	-	0	0	-	-
63	0	0	-	0	0	-	0	0	-	0	0	-	-
64	0	0	-	0	0	-	0	0	-	0	0	-	-
65	0	0	-	0	0	-	0	0	-	0	0	-	-
66	0	0	-	0	0	-	0	0	-	0	0	-	-
67	0	0	-	0	0	-	0	0	-	0	0	-	-
68	0	0	-	0	0	-	0	0	-	0	0	-	-
69	0	0	-	0	0	-	0	0	-	0	0	-	-
70	0	0	-	0	0	-	0	0	-	0	0	-	-
71	0	0	-	0	0	-	0	0	-	0	0	-	-
72	0	0	-	0	0	-	0	0	-	0	0	-	-
73	0	0	-	0	0	-	0	0	-	0	0	-	-
74	0	0	-	0	0	-	0	0	-	0	0	-	-
75	0	0	-	0	0	-	0	0	-	0	0	-	-
76	0	0	-	0	0	-	0	0	-	0	0	-	-
77	0	0	-	0	0	-	0	0	-	0	0	-	-
78	0	0	-	0	0	-	0	0	-	0	0	-	-
79	0	0	-	0	0	-	0	0	-	0	0	-	-
80	0	0	-	0	0	-	0	0	-	0	0	-	-
81	0	0	-	0	0	-	0	0	-	0	0	-	-
82	0	0	-	0	0	-	0	0	-	0	0	-	-
83	0	0	-	0	0	-	0	0	-	0	0	-	-
84	0	0	-	0	0	-	0	0	-	0	0	-	-
85	0	0	-	0	0	-	0	0	-	0	0	-	-
86	0	0	-	0	0	-	0	0	-	0	0	-	-
87	0	0	-	0	0	-	0	0	-	0	0	-	-
88	0	0	-	0	0	-	0	0	-	0	0	-	-
89	0	0	-	0	0	-	0	0	-	0	0	-	-
90	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE IV (con't)

CHALLENGE PHASE: CONTROL

ALLERGY [A] AND IRRITATION [E]

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (absence of sensitisation)
	between 30 to 35 minutes						48 ± 4h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
91	0	0	-	0	0	-	0	0	-	0	0	-	-
92	0	0	-	0	0	-	0	0	-	0	0	-	-
93	0	0	-	0	0	-	0	0	-	0	0	-	-
94	0	0	-	0	0	-	0	0	-	0	0	-	-
95	0	0	-	0	0	-	0	0	-	0	0	-	-
96	0	0	-	0	0	-	0	0	-	0	0	-	-
97	0	0	-	0	0	-	0	0	-	0	0	-	-
98	0	0	-	0	0	-	0	0	-	0	0	-	-
99	0	0	-	0	0	-	0	0	-	0	0	-	-
100	0	0	-	0	0	-	0	0	-	0	0	-	-
101	0	0	-	0	0	-	0	0	-	0	0	-	-
102	0	0	-	0	0	-	0	0	-	0	0	-	-
103	0	0	-	0	0	-	0	0	-	0	0	-	-
104	0	0	-	0	0	-	0	0	-	0	0	-	-
105	0	0	-	0	0	-	0	0	-	0	0	-	-
106	0	0	-	0	0	-	0	0	-	0	0	-	-
107	0	0	-	0	0	-	0	0	-	0	0	-	-
108	0	0	-	0	0	-	0	0	-	0	0	-	-
109	0	0	-	0	0	-	0	0	-	0	0	-	-
110	0	0	-	0	0	-	0	0	-	0	0	-	-

SUPPLEMENTARY MENTION [M]: Nothing to report.

OTHER OBSERVATION: Nothing to report.

TABLE V

CHALLENGE PHASE: INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (absence of sensitisation)
	between 30 to 35 minutes						48 ± 4h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
01	0	0	-	0	0	-	0	0	-	0	0	-	-
02	0	0	-	0	0	-	0	0	-	0	0	-	-
03	0	0	-	0	0	-	0	0	-	0	0	-	-
04	0	0	-	0	0	-	0	0	-	0	0	-	-
05	0	0	-	0	0	-	0	0	-	0	0	-	-
06	0	0	-	0	0	-	0	0	-	0	0	-	-
07	0	0	-	0	0	-	0	0	-	0	0	-	-
08	0	0	-	0	0	-	0	0	-	0	0	-	-
09	0	0	-	0	0	-	0	0	-	0	0	-	-
10	0	0	-	0	0	-	0	0	-	0	0	-	-
11	0	0	-	0	0	-	0	0	-	0	0	-	-
12	0	0	-	0	0	-	0	0	-	0	0	-	-
13	0	0	-	0	0	-	0	0	-	0	0	-	-
14	0	0	-	0	0	-	0	0	-	0	0	-	-
15	0	0	-	0	0	-	0	0	-	0	0	-	-
16	0	0	-	0	0	-	0	0	-	0	0	-	-
17	0	0	-	0	0	-	0	0	-	0	0	-	-
18	0	0	-	0	0	-	0	0	-	0	0	-	-
19	0	0	-	0	0	-	0	0	-	0	0	-	-
20	0	0	-	0	0	-	0	0	-	0	0	-	-
21	0	0	-	0	0	-	0	0	-	0	0	-	-
22	0	0	-	0	0	-	0	0	-	0	0	-	-
23	0	0	-	0	0	-	0	0	-	0	0	-	-
24	0	0	-	0	0	-	0	0	-	0	0	-	-
25	0	0	-	0	0	-	0	0	-	0	0	-	-
26	0	0	-	0	0	-	0	0	-	0	0	-	-
27	0	0	-	0	0	-	0	0	-	0	0	-	-
28	0	0	-	0	0	-	0	0	-	0	0	-	-
29	0	0	-	0	0	-	0	0	-	0	0	-	-
30	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V (con't)

CHALLENGE PHASE: INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (absence of sensitisation)
	between 30 to 35 minutes						48 ± 4h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
31	0	0	-	0	0	-	0	0	-	0	0	-	-
32	0	0	-	0	0	-	0	0	-	0	0	-	-
33	0	0	-	0	0	-	0	0	-	0	0	-	-
34	0	0	-	0	0	-	0	0	-	0	0	-	-
35	0	0	-	0	0	-	0	0	-	0	0	-	-
36	0	0	-	0	0	-	0	0	-	0	0	-	-
37	0	0	-	0	0	-	0	0	-	0	0	-	-
38	0	0	-	0	0	-	0	0	-	0	0	-	-
39	0	0	-	0	0	-	0	0	-	0	0	-	-
40	0	0	-	0	0	-	0	0	-	0	0	-	-
42	0	0	-	0	0	-	0	0	-	0	0	-	-
43	0	0	-	0	0	-	0	0	-	0	0	-	-
44	0	0	-	0	0	-	0	0	-	0	0	-	-
45	0	0	-	0	0	-	0	0	-	0	0	-	-
46	0	0	-	0	0	-	0	0	-	0	0	-	-
47	0	0	-	0	0	-	0	0	-	0	0	-	-
48	0	0	-	0	0	-	0	0	-	0	0	-	-
49	0	0	-	0	0	-	0	0	-	0	0	-	-
50	0	0	-	0	0	-	0	0	-	0	0	-	-
51	0	0	-	0	0	-	0	0	-	0	0	-	-
52	0	0	-	0	0	-	0	0	-	0	0	-	-
53	0	0	-	0	0	-	0	0	-	0	0	-	-
54	0	0	-	0	0	-	0	0	-	0	0	-	-
55	0	0	-	0	0	-	0	0	-	0	0	-	-
56	0	0	-	0	0	-	0	0	-	0	0	-	-
57	0	0	-	0	0	-	0	0	-	0	0	-	-
58	0	0	-	0	0	-	0	0	-	0	0	-	-
59	0	0	-	0	0	-	0	0	-	0	0	-	-
60	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V (con't)

CHALLENGE PHASE: INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (absence of sensitisation)
	between 30 to 35 minutes						48 ± 4h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
61	0	0	-	0	0	-	0	0	-	0	0	-	-
62	0	0	-	0	0	-	0	0	-	0	0	-	-
63	0	0	-	0	0	-	0	0	-	0	0	-	-
64	0	0	-	0	0	-	0	0	-	0	0	-	-
65	0	0	-	0	0	-	0	0	-	0	0	-	-
66	0	0	-	0	0	-	0	0	-	0	0	-	-
67	0	0	-	0	0	-	0	0	-	0	0	-	-
68	0	0	-	0	0	-	0	0	-	0	0	-	-
69	0	0	-	0	0	-	0	0	-	0	0	-	-
70	0	0	-	0	0	-	0	0	-	0	0	-	-
71	0	0	-	0	0	-	0	0	-	0	0	-	-
72	0	0	-	0	0	-	0	0	-	0	0	-	-
73	0	0	-	0	0	-	0	0	-	0	0	-	-
74	0	0	-	0	0	-	0	0	-	0	0	-	-
75	0	0	-	0	0	-	0	0	-	0	0	-	-
76	0	0	-	0	0	-	0	0	-	0	0	-	-
77	0	0	-	0	0	-	0	0	-	0	0	-	-
78	0	0	-	0	0	-	0	0	-	0	0	-	-
79	0	0	-	0	0	-	0	0	-	0	0	-	-
80	0	0	-	0	0	-	0	0	-	0	0	-	-
81	0	0	-	0	0	-	0	0	-	0	0	-	-
82	0	0	-	0	0	-	0	0	-	0	0	-	-
83	0	0	-	0	0	-	0	0	-	0	0	-	-
84	0	0	-	0	0	-	0	0	-	0	0	-	-
85	0	0	-	0	0	-	0	0	-	0	0	-	-
86	0	0	-	0	0	-	0	0	-	0	0	-	-
87	0	0	-	0	0	-	0	0	-	0	0	-	-
88	0	0	-	0	0	-	0	0	-	0	0	-	-
89	0	0	-	0	0	-	0	0	-	0	0	-	-
90	0	0	-	0	0	-	0	0	-	0	0	-	-

TABLE V (con't)

CHALLENGE PHASE: INVESTIGATIONAL PRODUCT

ALLERGY [A] AND IRRITATION [E]

SUBJECTS N°	SENSITISATION [A] (0 to 3) and IRRITATION [E] (0 to 4) REACTIONS												CONCLUSION + (sensitisation) - (absence of sensitisation)
	between 30 to 35 minutes						48 ± 4h						
	Induction area			Blank site (having never received any product)			Induction area			Blank site (having never received any product)			
	A	E	M	A	E	M	A	E	M	A	E	M	
91	0	0	-	0	0	-	0	0	-	0	0	-	-
92	0	0	-	0	0	-	0	0	-	0	0	-	-
93	0	0	-	0	0	-	0	0	-	0	0	-	-
94	0	0	-	0	0	-	0	0	-	0	0	-	-
95	0	0	-	0	0	-	0	0	-	0	0	-	-
96	0	0	-	0	0	-	0	0	-	0	0	-	-
97	0	0	-	0	0	-	0	0	-	0	0	-	-
98	0	0	-	0	0	-	0	0	-	0	0	-	-
99	0	0	-	0	0	-	0	0	-	0	0	-	-
100	0	0	-	0	0	-	0	0	-	0	0	-	-
101	0	0	-	0	0	-	0	0	-	0	0	-	-
102	0	0	-	0	0	-	0	0	-	0	0	-	-
103	0	0	-	0	0	-	0	0	-	0	0	-	-
104	0	0	-	0	0	-	0	0	-	0	0	-	-
105	0	0	-	0	0	-	0	0	-	0	0	-	-
106	0	0	-	0	0	-	0	0	-	0	0	-	-
107	0	0	-	0	0	-	0	0	-	0	0	-	-
108	0	0	-	0	0	-	0	0	-	0	0	-	-
109	0	0	-	0	0	-	0	0	-	0	0	-	-
110	0	0	-	0	0	-	0	0	-	0	0	-	-

SUPPLEMENTARY MENTION [M]: Nothing to report.

OTHER OBSERVATION: Nothing to report.

TABLE VI

DISCONTINUATION(S) / EXIT(S) OF THE STUDY NOT LINKED TO THE INVESTIGATIONAL PRODUCT

SUBJECT(S) N°	REASON(S)
41	Concomitant treatment(s) incompatible with the study

TABLE VII

RELATED ADVERSE EVENTS

Subjects N°	Description	Serious Y/N	Imputability	Severity	Action taken	Outcome
/	/	/	/	/	/	/

/ = Nothing to report

APPENDIX 2:
STUDY ACCEPTABILITY FORM

STUDY ACCEPTABILITY FORM

DOCUMENTS EXAMINED BY THE DERMATOLOGIST INVESTIGATOR

	NO	YES
- Qualitative composition of the investigational product:	|___|	|_X_|
- The "sum up" from the investigational product and the application conditions (type of patch, concentration)	|___|	|_X_|
- Prerequisite: . Engagement certificate signed by the Sponsor	|___|	|_X_|
- Specific study protocol: N° B101360PE of 9 September 2010 which refers to the Standard Protocol N° EN_P_STD_CLITP_5021_01 (submitted to the Independent Ethical Committee on 26 May 2010)	|___|	|_X_|

OPINION OF THE "INDEPENDENT ETHICAL COMMITEE":
(in relation with the information sent by I.E.C. before the beginning of the observations)

FAVOURABLE \|_X_\| UNFAVOURABLE \|___\|

On: \|_2_\|_0_\| \|_0_\|_9_\| \|_1_\|_0_\|

DERMATOLOGIST INVESTIGATOR APPROVAL:

Study accepted \|_X_\| Study refused \|___\|

Reason for the refusal (if there is no refusal, put: /): /

In Sofia, on: \|_1_\|_4_\| \|_1_\|_2_\| \|_1_\|_0_\|

Dr. E. BONINSKA, M.D.
Dermatologist Investigator

[redacted]

Human Repeat Insult Patch Test with Challenge

product contains 25% Olea Eurpaea (Olive) Seed Powder

Sponsor: [redacted]

Document type: Clinical Study Report

Investigational Product: [redacted]

Batch No.:

Product Type:

Study Monitor:

Investigator:

Document Version: Final Date: October 15, 2007

[redacted]

[redacted]

Study Title: Human Repeat Insult Patch Test with Challenge

Sponsor: [redacted]

Protocol #:

Contract Research Organization:

Study Site:

Dates of Study: August 6, 2007 – September 14, 2007

STUDY PERSONNEL

Principal Investigator

Clinical Research Coordinator,
Director, Dermatological Safety Testing

Assistant Clinical Research Coordinator

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

SUMMARY

One investigational product, [redacted] was evaluated as an aqueous solution to determine if the application of the investigational product, [redacted] did not cause a delayed contact allergic response in normal volunteers using a semi-occlusive human repeat insult patch test. Fifty-four (54) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization or significant irritation to [redacted]

1 INTRODUCTION

The test consists in the repeated dermal application of the investigational product to human volunteer subjects under conditions which exaggerate the normal conditions of product use.

2 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.

3 STUDY DESIGN

3.1 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 allergic response.

If a cutaneous response observed in the challenge phase indicated possible sensitization, or at the discretion of the dermatologist 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 dermatologist investigator as to whether such reactions were felt to be indicative of contact allergic response.

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

3.2 DISCUSSION OF DESIGN

This study design is based on the Modified Draize procedure (Marzulli & Maibach 1974), and is accepted standard methodology used for assessment of skin sensitization [2, 3].

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 investigational product can be applied safely to human skin without significant risk of adverse reactions [4].

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.

3.3 STUDY PROCEDURES

3.3.1 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/non-inclusion criteria. If the subject fulfilled all the inclusion and none of the non-inclusion criteria, he/she was allowed to participate in the study, and received a unique enrollment number in order to preserve the subject's confidentiality. 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.

3.3.2 Induction

The induction phase consisted of a series of 9 consecutive applications of the investigational product 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 dermatologist investigator-trained evaluator removed any remaining excess investigational product to avoid transference of products between sites. The sites were evaluated 15 to 30 minutes after patch removal by a dermatologist investigator-trained evaluator using the scoring system detailed in Table 3.1 in Appendix I. 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.

3.3.3 Rest Period

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

3.3.4 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.

3.3.5 Rechallenge

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

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

3.3.6 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

[redacted]

3.4 SELECTION OF SUBJECTS

A sufficient number of subjects were enrolled in order to provide 50 completed subjects evaluable for analysis; an individual subject was allowed to participate in the study 1 time only.

To be considered a **completed case**, a subject must have had 9 applications of the investigational product and 9 subsequent readings during induction and 1 application followed by 2 subsequent readings during challenge. Only completed cases were used to assess sensitization.

3.4.1 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 able to give written consent

3. were informed of the test procedures, were capable of reading the documents presented to them, and were capable of understanding them in the language used,

4. were subjects who benefited from social security or medical insurance (according to the legislation in force in the country where the test takes place),

5. were subjects selected according to the procedures established by the Investigating Laboratory. These criteria will be evaluated using the questionnaires recorded in the Investigator's CRF.

3.4.2 Non-inclusion Criteria

Subjects excluded from the study were those who:

1. refused to undertake to refrain from participating simultaneously in other bio-medical studies,

2. did not comply with the non-inclusion period stipulated at the time of their participation in the previous test,

3. had been deprived of their freedom by a legal or administrative decision, or people undergoing an emergency medical treatment [redacted]

4. were minors or subjects protected by law, as well as those admitted into a health, social or mental institution [redacted]

5. refused to give their agreement by not signing the informed consent declaration,

6. had an organ removed (kidney, lung, spleen, hepatic lobe etc), a transplant, or suffered from a cranial trauma with after-effects;

7. pregnant or nursing women, or those who have not taken contraceptive precautions,

8. presented a condition which is considered unacceptable for the study: such as skin marks at the test site that may interfere with the evaluation of the skin reactions (pigmentation problems, scarring, excessive hair growth, excessive numbers of freckles and moles, sunburn etc), an immune deficiency, a previous history of contact allergies, immediate allergic reactions currently under treatment (asthma, periodic spasmodic rhinitis, conjunctivitis etc), a fever lasting for more than 24 hours, in the 8 days preceding the product application,

9. had undergone long-term treatment or who were currently undergoing long-term treatment involving insulin, antihistamines, corticoids, beta-blockers (including eye drops), antibiotics, immunosuppressive drugs (cyclosporine) and/or in a period of de-sensitisation,

10. had treatment with vitamin A or its derivatives less than 3 months before the beginning of the study,

11. had been vaccinated in the 3 weeks prior to the study or intend to be vaccinated during the study,

12. had been presenting cutaneous hyperactivity or skin disorder,

13. had strong reactions to sticking plaster to patches,

14. had been exposed to natural sunshine or UV lamp on the test area, during the month preceding the study,

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

3.4.3 Informed Consent

A properly executed informed consent document in compliance with FDA regulations (21 CFR Part 50) and the Helsinki Declaration (1964) and subsequent amendments [5] was obtained from each subject prior to entering the study. Each subject dated and signed an informed consent document, which was witnessed and dated and signed by the dermatologist investigator's designee. 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).

3.4.4 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 dermatologist 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 non-inclusion criteria, he/she was to be withdrawn immediately.

[redacted]

The subject may have been withdrawn from the study at any time at the discretion of the dermatologist 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 Table 3.1 in Appendix I for interpretation of scores) 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 dermatologist investigator) of any of the study products:

- withdrawal of informed consent,
- serious adverse events,
- allergic reactions to the investigational products,
- subject's request,
- occurrence of one of the safety criteria for non-inclusion 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
- dermatologist 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.

3.5 INVESTIGATIONAL PRODUCT (IP)

3.5.1 Investigational Product Specifications

IP Category	:	[redacted]
Formula No.	:	
Batch No.	:	
Description	:	
Amount Applied	:	20 µL
Patch Type	:	Semi-occlusive
Evaporation	:	No
Dilution	:	Yes (Mix 5 g of masque 765005 07 with 14 mL of water)
Special Instructions	:	No

[redacted]

3.5.2 Description of Patch Conditions

Products evaluated under semi-occlusive patch conditions are applied under a 1 cm x 1 cm Webril patch. An amount of investigational product sufficient to cover the patch (usually 20 µL or mg) is applied. Liquids are applied to the patch using an Eppendorf single channel adjustable pipette set at the appropriate amount to be applied to the patch, usually 20 µL. Creams, semi-solids, and solids are weighed by applying product to a patch that has been pre-weighed on a pre-calibrated weight balance. The product and patch are then weighed on the pre-calibrated weight balance to determine the appropriate amount of product, usually 20 mg. The weighed patch is used as a visual guide to prepare patches.

The patches were affixed with Micropore 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.

3.5.3 Storage, Handling, and Documentation of the Investigational Product

[redacted]

3.5.4 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 3.3.1). A dermatologist investigator -trained, experienced evaluator assessed study compliance. Records of patch applications and visit schedule compliance were recorded on the subjects' CRFs.

3.6 SAFETY EVALUATIONS

3.6.1 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 examination of the treated sites was carried out under an artificial type D65 North daylight illuminator. The scores outlined in Table 3.1, Appendix I were used to express the response observed at the time of examination. Allergy was evaluated according to the International Contact Dermatitis Research Group [6].

3.6.2 Adverse Events

An adverse event is defined as an occurrence of a new symptom(s) of a medical nature during use of the investigational product whether or not considered related to the investigational product, 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

[redacted]

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 Table 3.1 was not considered an AE. Likewise, any tape-related irritation was not noted as an AE.

3.7 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

3.8 QUALITY ASSURANCE

[redacted] Quality Assurance Unit conducted a systematic and independent examination of study-related 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.

4 DATA MANAGEMENT

4.1 DOCUMENTATION

[redacted]

4.2 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.

5 INTERPRETATION OF THE RESULTS

5.1 SAMPLE SIZE

With a sample size of 50, in the absence of any sensitization reactions, a 95% upper confidence bound on the population rate of sensitization would be 4.9% [7].

5.2 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.

5.3 CRITERIA OF EVALUATION OF SKIN COMPATIBILITY

Skin compatibility was evaluated from the skin reactions observed (number, intensity, frequency) and compared with that established for the chosen investigational product as a reference with the untreated control site. The analysis of skin compatibility include all subjects in the test, however many times they were evaluated during the induction phase.

5.4 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 dermatologist investigator as to whether such reactions were felt to be indicative of contact allergic response.

6 RESULTS

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

6.1 SUBJECTS EVALUATED

6.1.1 Subject Disposition

Subject disposition is shown in Table 1 and summarized in Text Table 6-1; these data are supported by Data Listing 1.

[redacted]

Text Table 6-1 Subject Disposition

Number of subjects enrolled	58
Number of subjects treated	58
Number of subjects discontinued	4
Voluntarily withdrew consent	1
Lost to follow-up	1
Adverse events (pneumonia)	1
Other reasons (inadvertently enrolled)	1
Number of subjects completed	54

Source: Appendix I, Table 1

6.1.2 Protocol Deviations

The following protocol deviation occurred: 12 (21%) subjects were between the ages of 60 to 65 years, a deviation from not more than 10%. This deviation did not affect the validity of the study.

6.1.3 Baseline Demographic and Background Characteristics

All subjects met the inclusion and non-inclusion criteria. Demographic information is summarized in Table 2, these data are supported by Data Listing 2. The study population was comprised of 49 (84.5%) females and 9 (15.5%) males, of whom 32 (55%) were Caucasian, 25 (43%) were Hispanic, and 1 (2%) was Asian. Subject ages ranged from 18 to 65 years; the mean was 48 years.

6.2 SAFETY RESULTS

6.2.1 Induction and Challenge Responses

Fifty-four (54) subjects completed the induction phase and were included in determining the presence of significant irritation. Fifty-four subjects completed the challenge phase of the study and were included in the sensitization analysis. There was no requirement for a rechallenge phase to be conducted. 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.

6.2.2 Overall Experience of Adverse Events

One serious adverse event occurred that was not product related: Subject 29 was admitted to the hospital with pneumonia. See Data Listing 4, Appendix I.

7 CONCLUSIONS

Under the conditions employed in this study, there was no evidence of sensitization or significant irritation to [redacted]

8 REFERENCES

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2. Jordan, WP. 24-, 48-, and 48/48-hour Patch Tests. *Contact Dermatitis* 1980. 6: 151-152.
3. Marzulli F. N.; Maibach H. I. Contact Allergy: Predictive Test in Man. *Contact Dermatitis* 1976. 2:1-17
4. 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.
5. Declaration of Helsinki adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; 41st World Medical Assembly, Hong Kong, September, 1989; 48th General Assembly, Somerset West, Republic of South Africa, October 1996; 52th General Assembly, Edinburgh, 2000; AMM General Assembly, Washington, 2002 and the AMM General Assembly, Tokyo, 2004.
6. CDRG = The International Contact Dermatitis Research Group, Fregert S. Manual of Contact Dermatitis, 2nd Edition
7. Mood AM, Graybill FA, Boes DC. Introduction to the Theory of Statistics. 3rd ed. New York: McGraw-Hill Higher Ed; 1974:Chapter 7.

APPENDIX I

SUMMARY TABLES

[redacted]

TABLE 1: SUMMARY OF SUBJECT ENROLLMENT AND DISPOSITION

	n	(%)
Subjects enrolled	58	
Subjects completed induction phase	54	(93.1)
Subjects completed all phases	54	(93.1)
Total subjects discontinued	4	(6.9)
Lost to follow-up	1	(1.7)
Voluntary withdrawal	1	(1.7)
Adverse events	1	(1.7)
Other reasons	1	(1.7)

Note: All percentages are relative to total subjects enrolled

See Data Listing 1 for further detail

Program: DISPSMY.SAS/USES: FINAL/21SEP07:09:19:52

[redacted]

TABLE 2: SUMMARY OF SUBJECT DEMOGRAPHICS
ALL ENROLLED SUBJECTS

Age	
n (%) 18 to 44	21 (36.2)
n (%) 45 to 59	25 (43.1)
n (%) 60 to 65	12 (20.7)
Mean (SD)	48.4 (13.1)
Median	49.7
Range	18.4 to 65.3
Gender	
n (%) Male	9 (15.5)
n (%) Female	49 (84.5)
Race	
n (%) Asian	1 (1.7)
n (%) Caucasian	32 (55.2)
n (%) Hispanic	25 (43.1)

See Data Listing 2 for further detail

Program: DEMOSMY1.SAS/USES: DEMOGS/21SEP07:09:19:54

[redacted]

TABLE 3: SUMMARY OF DERMATOLOGIC RESPONSE GRADES
NUMBER OF SUBJECTS BY PRODUCT

[redacted]

	Induction Reading										Challenge Phase			
										Make-	-48h--		-96h--	
Response (EAM)	1	2	3	4	5	6	7	8	9	Up	L	R	L	R
00	58	56	55	55	55	54	54	54	54	0	54	54	54	54
10	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Total evaluable	58	56	56	55	55	54	54	54	54	0	54	54	54	54
Number absent	0	0	0	0	0	0	0	0	0		0	0	0	0
Number discontinued	0	2	2	3	3	4	4	4	4		4	4	4	4

MAXIMUM ELICITED RESPONSE DURING INDUCTION
ALL SUBJECTS COMPLETING INDUCTION (N= 54)

Response	n(%) Subjects
00	53 (98.1%)
10	1 (1.9%)

See Table 3.1 for key to symbols and scores

Program: SUMMARY4.SAS/Uses: LRESPONS, PRODLIST, FINAL/21SEP07:09:20:02

[redacted]

TABLE 3.1: KEY TO SYMBOLS AND SCORES

ERYTHEMA RESULTS (E)

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

ALLERGIC RESULTS (A)

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

ADDITIONAL COMMENTS (M)

Symbol	Response
E	- Edema from 0 to 3
P	- Papules
V	- Vesicles
B	- Bullae
S	- Spreading of reaction beyond the patch area
Pe	- Petichiae
SV	- Soap effect
F	- Fissuring
D	- Desquamation
Dr	- Dryness
C	- Skin coloration - hyperpigmentation
H	- Hypopigmentation
Fr	- Follicular reaction
NA	- Not applied
T	= Tape reaction
*	= Additional free comments
N9G	= No ninth grading
Cr	= Exudation and/or surface encrustation
X	= Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction
--	= Subject absent

[redacted]

APPENDIX II

DATA LISTINGS

[redacted]

DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

Subject No.	Study Dates: Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days on Study
1	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
2	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
3	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
4	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
5	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
6	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
7	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
8	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
9	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
10	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
11	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
12	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
13	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
14	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
15	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
16	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
17	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
18	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
19	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
20	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
21	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
22	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
23	08/06/07	08/06/07		08/15/07	I3	L	10
24	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
25	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
26	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
27	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
28	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
29	08/06/07	08/06/07		08/20/07	I5	AE	15
30	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
31	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
32	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
33	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
34	08/06/07	08/06/07		08/08/07	I1	O	3
35	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
36	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
37	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
38	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
39	08/06/07	08/06/07	09/10/07	09/14/07	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/21SEP07:09:19:34

[redacted]

DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION

Subject No.	Study Dates: Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days on Study
40	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
41	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
42	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
43	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
44	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
45	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
46	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
47	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
48	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
49	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
50	08/06/07	08/06/07		08/10/07	I1	S	5
51	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
52	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
53	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
54	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
55	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
56	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
57	08/06/07	08/06/07	09/10/07	09/14/07	C2	C	40
58	08/06/07	08/06/07	09/10/07	09/14/07	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/21SEP07:09:19:34

[redacted]

DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

[redacted]

	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
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	00	00		00	00	00	00		
4	00	00	00	00	00	00	00	00	00		00	00	00	00		
5	00	00	00	00	00	00	00	00	00		00	00	00	00		
6	00	00	00	00	00	00	00	00	00		00	00	00	00		
7	00	00	00	00	00	00	00	00	00		00	00	00	00		
8	00	00	00	00	00	00	00	00	00		00	00	00	00		
9	00	00	00	00	00	00	00	00	00		00	00	00	00		
10	00	00	00	00	00	00	00	00	00		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	00	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	00	00	00	00	00		00	00	00	00		
16	00	00	00	00	00	00	00	00	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	00	00	00		00	00	00	00		
23	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/21SEP07:09:19:38

[redacted]

DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

[redacted]

Subject No.	Induction Reading 1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	MU	Challenge Phase 48-hour L EAM	48-hour R EAM	96-hour L EAM	96-hour R EAM	120-hour(*) L EAM	120-hour(*) R 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	00	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	00	00		00	00	00	00		
29	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	00	00	00		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	--	--	--	--	--	--	--	--		--	--	--	--		
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	10	00	00	00	00	00	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	00	00	00	00	00	00	00	00		00	00	00	00		
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/21SEP07:09:19:38

[redacted]

DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES
BY PRODUCT AND SUBJECT

[redacted]

Subject No.	Induction Reading 1 EAM	2 EAM	3 EAM	4 EAM	5 EAM	6 EAM	7 EAM	8 EAM	9 EAM	MU	Challenge Phase 48-hour L EAM	48-hour R EAM	96-hour L EAM	96-hour R EAM	120-hour(*) L EAM	120-hour(*) R 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	--	--	--	--	--	--	--	--		--	--	--	--		
51	00	00	00	00	00	00	00	00	00		00	00	00	00		
52	00	00	00	00	00	00	00	00	00		00	00	00	00		
53	00	00	00	00	00	00	00	00	00		00	00	00	00		
54	00	00	00	00	00	00	00	00	00		00	00	00	00		
55	00	00	00	00	00	00	00	00	00		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	00	00		00	00	00	00		
58	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/21SEP07:09:19:38

[redacted]

DATA LISTING 4: ADVERSE EVENTS

==========

Subject No. 29

Adverse Event: PNEUMONIA

Date of Onset: 08/19 Date of Resolution: 08/30
Frequency: Single episode Severity: Severe
Duration: Outcome: Resolved
Rel. to Study Product: Unrelated
Action Taken/Study Product: Discontinued
Action Taken/Treatment?: YES
Serious? YES

Comment: WENT TO THE EMERGENCY ROOM ON 8/19 FOR PNEUMONIA AND WAS ADMITTED INTO HOSPITAL. SUBJECT WAS RELEASED FROM THE HOSPITAL AND WAS TOLD TO TAKE TOBRAMYCIN FOR TEN DAYS FOR COMPLETE RECOVERY.

==========

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: September 1, 2022

SUBJECT: Olea Europaea (Olive) Leaf Extract and Olea Europaea (Olive) Fruit Extract

Anonymous. 2022. Olea Europaea (Olive) Leaf Extract – Summary information.

Anonymous. 2022. Olea Europaea (Olive) Fruit Extract - Summary information.

- **Olea Europaea (Olive) Leaf Extract**

Manufacturing Process:

The **leaf** is extracted with specified **eluent(s) under appropriate temperature conditions,** to yield a **concentrate**. The concentrate containing the phytochemical constituents is then blended with the desired diluent(s) and preservation system to produce the final ingredient. The ingredient is evaluated for physiochemical properties according to the specification requirements for the batch to be released. In addition, the concentrate is also evaluated for contaminants and physiochemical properties as needed.

Typical eluents include Water, Butylene Glycol, Carthamus Tinctorius (Safflower) Seed Oil, Glycerin, and Propylene Glycol.

Heavy Metal & Pesticides/ Allergens/ Impurities:

The following heavy metal testing was conducted on the concentrate in an Alcohol base:

	Heavy Metal	Detection	Reporting Limit	Heavy Metal	Detection	Reporting Limit
Heavy metals:	Antimony	Not Detected	0.25 mg/L	Iron	Not Detected	5.0 mg/L
	Arsenic	Not Detected	0.050 mg/L	Lead	Not Detected	0.050 mg/L
	Cadmium	Not Detected	0.010 mg/L	Mercury	Not Detected	0.0040 mg/L
	Chromium	Not Detected	0.050 mg/L	Nickel	Not Detected	0.050 mg/L

There were no residual pesticides detected. (Parameters: 8081 GCS Pesticides and 8141 GCS, O/P Pesticides)

Additional information:

- A typical product with the **Olea Europaea (Olive) Leaf Extract** prepared in Water has the following specifications:

Analysis:

Specification	Range	Actual
APPEARANCE	Colorless to light yellow liquid	PASS
MICROBIAL PLATE COUNT	Less than 100 organisms per gram	PASS
ODOR	Characteristic	PASS
PH	4.0 - 6.5 at 25° C	4.2
REFRACTIVE INDEX	1.3300 - 1.3400 at 25° C	1.3340
SOLUBILITY	Soluble in any proportion in water	PASS
SPECIFIC GRAVITY	0.99 - 1.01 at 25° C	1.00

- **Olea Europaea (Olive) Fruit Extract**

Manufacturing Process:

The **fruit** is extracted with specified **eluent(s) under appropriate temperature conditions,** to yield a **concentrate**. The concentrate containing the phytochemical constituents is then blended with the desired diluent(s) and preservation system to produce the final ingredient. The ingredient is evaluated for physiochemical properties according to the specification requirements for the batch to be released. In addition, the concentrate is also evaluated for contaminants and physiochemical properties as needed.

Typical eluents include Water, Butylene Glycol, Carthamus Tinctorius (Safflower) Seed Oil, Glycerin, and Propylene Glycol.

Additional information:

- A typical product with the **Olea Europaea (Olive) Fruit Extract** prepared in Butylene Glycol and Water has the following specifications:

Analysis:

Specification	Range	Actual
APPEARANCE	Colorless to light yellow liquid	PASS
MICROBIAL PLATE COUNT	Less than 100 organisms per gram	PASS
ODOR	Characteristic	PASS
PH	4.0 - 6.5 at 25° C	4.7
REFRACTIVE INDEX	1.3800 - 1.4000 at 25° C	1.3954
SOLUBILITY	Soluble in any proportion in water	PASS
SPECIFIC GRAVITY	1.00 - 1.04 at 25° C	1.02

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: October 11, 2022

SUBJECT: Olea Europaea (Olive) Fruit Juice Extract and Olea Europaea (Olive) Leaf Extract

Anonymous. 2022. Summary information Olea Europaea (Olive) Fruit Juice Extract and Olea Europaea (Olive) Leaf Extract.

October 2022

Summary Information

Olea Europaea (Olive) Fruit Juice Extract as Olive Fruit Juice Extract BG

Olea Europaea (Olive) Leaf Extract as Olive Leaf Extract BG and Olive Leaf Extract(B)-BG

1. Chemical properties

Trade name	The chemical properties
Olive Fruit Juice Extract BG	<Composition> Saccharides and tannin
Olive Leaf Extract BG	<Composition> Organic acid and tannin
Olive Leaf Extract(B)-BG	

2. Method of manufacturing, relevant to ingredients as used in cosmetic products

Trade name	The method of manufacture
Olive Fruit Juice Extract BG	Concentrated juice ⇒extract with 50vol% 1,3-butylene glycolic solution ⇒sedimentation⇒filtrate⇒adjustment⇒packaging
Olive Leaf Extract BG	Dried raw material ⇒extract with 50vol% ethanol solution⇒concentration ⇒dissolve in 50vol% 1,3-butylene glycolic solution ⇒sedimentation⇒filtrate⇒adjustment⇒packaging
Olive Leaf Extract(B)-BG	

3. Composition and impurities, relevant to ingredients as used in cosmetic products

Trade name	Composition and impurities
Olive Fruit Juice Extract BG	<Composition> Please refer to the answer 1. <Impurities> Heavy metals: not more than 20ppm Arsenic: not more than 2ppm
Olive Leaf Extract BG	
Olive Leaf Extract(B)-BG	

Trade name	Content [w/v%]
Olive Fruit Juice Extract BG	
Olive Leaf Extract BG	
Olive Leaf Extract(B)-BG	Oleuropein (not less than 0.03w/v%)

4. Toxicological studies, especially on plant parts not traditionally eaten

Trade name	Test Item	Result	Method
Olive Leaf Extract BG	Acute toxicity*	LD_{50}＞2000mg/kg	20 Mice (10/sex)

* The test was conducted in our laboratory.

5. Dermal irritation and sensitization at maximum use concentrations

Trade name	Test Item	Concentration of test solution	Result	Method
Olive Leaf Extract BG	Primary skin irritation*	100%, 10%	non irritant	3 Rabbits
	Cumulative skin irritation*	100%, 50%, 25%, 12.5%	non irritant	3 Rabbits
	Skin sensitization*	1st induction : 25% 2nd induction : 100% challenge : 100%, 10%	Negative	5 guinea pigs per group
	Human patch test	100%	non irritant	Closed patch 46 subjects
Olive Leaf Extract(B)-BG	Primary skin irritation	100%	Non irritant	LabCyte method
	Human skin sensitization test (Repeated Insult Patch Test)	20%	Mild material, Not induce delayed contact sensitization	Modified Shelanski Method 54 subjects

* The tests were conducted in our laboratory.

2022 FDA VCRP Raw Data

OLEA EUROPAEA (OLIVE) FRUIT	05G	Tonics, Dressings, and Other Hair Grooming Aids	1
OLEA EUROPAEA (OLIVE) FRUIT	10A	Bath Soaps and Detergents	3
OLEA EUROPAEA (OLIVE) FRUIT	12A	Cleansing	2
OLEA EUROPAEA (OLIVE) FRUIT	12C	Face and Neck (exc shave)	3
OLEA EUROPAEA (OLIVE) FRUIT	12D	Body and Hand (exc shave)	2
OLEA EUROPAEA (OLIVE) FRUIT	12F	Moisturizing	4
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	02D	Other Bath Preparations	2
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	03D	Eye Lotion	1
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	03G	Other Eye Makeup Preparations	2
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	04E	Other Fragrance Preparation	1
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	05A	Hair Conditioner	6
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	05F	Shampoos (non-coloring)	4
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	05G	Tonics, Dressings, and Other Hair Grooming Aids	1
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	05I	Other Hair Preparations	3
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	07B	Face Powders	3
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	07C	Foundations	1
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	07E	Lipstick	11
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	07F	Makeup Bases	1
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	07I	Other Makeup Preparations	1
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	10A	Bath Soaps and Detergents	4
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	10D	Feminine Deodorants	1
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	10E	Other Personal Cleanliness Products	2
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	12A	Cleansing	10
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	12C	Face and Neck (exc shave)	9
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	12D	Body and Hand (exc shave)	12

OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	12F	Moisturizing	20
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	12G	Night	2
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	12H	Paste Masks (mud packs)	1
OLEA EUROPAEA (OLIVE) FRUIT EXTRACT	12J	Other Skin Care Preps	6
OLEA EUROPAEA (OLIVE) FRUIT UNSAPONIFIABLES	12C	Face and Neck (exc shave)	8
OLEA EUROPAEA (OLIVE) FRUIT UNSAPONIFIABLES	12D	Body and Hand (exc shave)	1
OLEA EUROPAEA (OLIVE) FRUIT UNSAPONIFIABLES	12F	Moisturizing	4
OLEA EUROPAEA (OLIVE) FRUIT UNSAPONIFIABLES	12J	Other Skin Care Preps	1
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	01A	Baby Shampoos	1
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	03D	Eye Lotion	6
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	03G	Other Eye Makeup Preparations	5
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	05A	Hair Conditioner	3
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	05F	Shampoos (non-coloring)	4
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	05I	Other Hair Preparations	4
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	07B	Face Powders	1
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	07E	Lipstick	1
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	07I	Other Makeup Preparations	1
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	08G	Other Manicuring Preparations	1
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	10A	Bath Soaps and Detergents	23
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	10E	Other Personal Cleanliness Products	5
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	11B	Beard Softeners	1
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	12A	Cleansing	5

OLEA EUROPAEA (OLIVE) LEAF EXTRACT	12B	Depilatories	1
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	12C	Face and Neck (exc shave)	31
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	12D	Body and Hand (exc shave)	22
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	12F	Moisturizing	41
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	12G	Night	2
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	12H	Paste Masks (mud packs)	4
OLEA EUROPAEA (OLIVE) LEAF EXTRACT	12J	Other Skin Care Preps	20
OLEA EUROPAEA (OLIVE) LEAF POWDER	12F	Moisturizing	1
OLEA EUROPAEA (OLIVE) LEAF WATER	12C	Face and Neck (exc shave)	1
OLEA EUROPAEA (OLIVE) SEED POWDER	10E	Other Personal Cleanliness Products	1
OLEA EUROPAEA (OLIVE) SEED POWDER	12A	Cleansing	3
OLEA EUROPAEA (OLIVE) SEED POWDER	12C	Face and Neck (exc shave)	1
OLEA EUROPAEA (OLIVE) SEED POWDER	12D	Body and Hand (exc shave)	2
OLEA EUROPAEA (OLIVE) SEED POWDER	12H	Paste Masks (mud packs)	1
OLEA EUROPAEA (OLIVE) SEED POWDER	12J	Other Skin Care Preps	2
OLIVE EXTRACT	08C	Nail Creams and Lotions	5
OLIVE EXTRACT	10A	Bath Soaps and Detergents	1
OLIVE EXTRACT	10E	Other Personal Cleanliness Products	2
OLIVE EXTRACT	12C	Face and Neck (exc shave)	3
OLIVE EXTRACT	12F	Moisturizing	1
OLIVE EXTRACT	12J	Other Skin Care Preps	2
OLIVE STONE	12J	Other Skin Care Preps	2