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

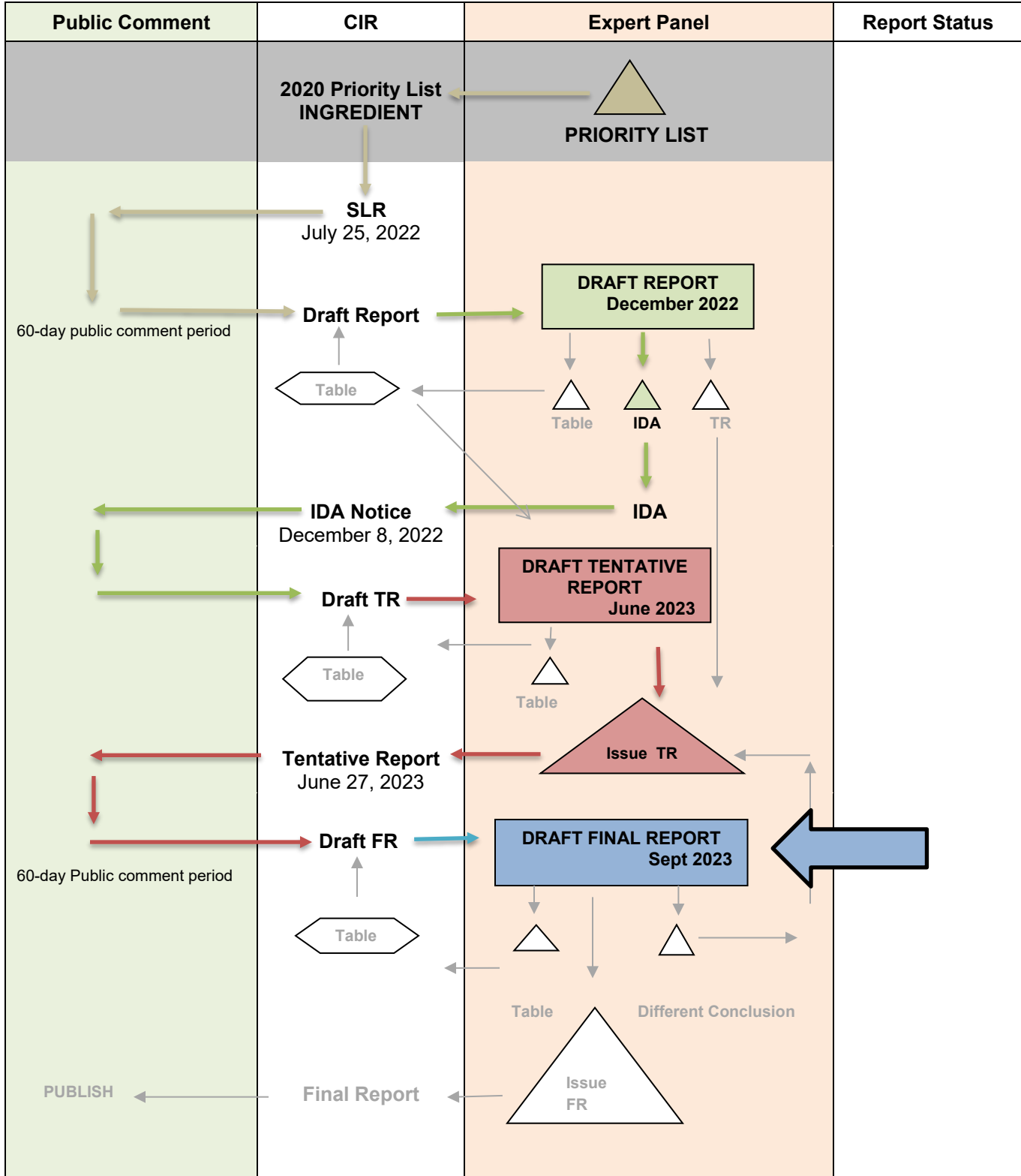
Status: Draft Final Report for Panel Review
Release Date: August 18, 2023
Panel Meeting Date: September 11-12, 2023

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., and the Senior Director is Monice Fiume. This safety assessment was prepared by Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

SAFETY ASSESSMENT FLOW CHART

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

MEETING September 2023





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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR
Date: August 18, 2023
Subject: Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics. (It is identified as *report_Olive_092023* in the pdf document.) At the June 2023 meeting, the Panel issued a Tentative Report with the conclusion concluded that the following 16 *Olea europaea* (olive)-derived ingredients are safe in cosmetics in the present practice of use and concentration described in this safety assessment:

Hydrolyzed Olive Fruit	Olea Europaea (Olive) Fruit Water
Hydrolyzed Olive Fruit Extract	Olea Europaea (Olive) Husk Powder
Hydrolyzed Olive Leaf Extract	Olea Europaea (Olive) Leaf
Olea Europaea (Olive) Fruit	Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Fruit Extract	Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Fruit Juice	Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Fruit Juice Extract	Olea Europaea (Olive) Seed
Olea Europaea (Olive) Fruit Unsaponifiables	Olea Europaea (Olive) Seed Powder

Additionally, the Panel also concluded that the available data are insufficient to make a determination of safety for the following 7 *Olea europaea* (olive)-derived ingredients under the intended conditions of use in cosmetic formulations:

Olea Europaea (Olive) Bark Extract	Olea Europaea (Olive) Flower Water
Olea Europaea (Olive) Branch Extract	Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Bud Extract	Olea Europaea (Olive) Wood Extract
Olea Europaea (Olive) Flower Extract	

The additional data needed to determine the safety of these ingredients in cosmetics are:

- Method of manufacture for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
- Composition and impurities data for Olea Europaea (Olive) Branch Extract and Olea Europaea (Olive) Flower Water
- 28-day dermal toxicity data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
 - If positive, additional data (e.g., DART and genotoxicity data) may be needed
- Dermal irritation and sensitization data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract

Since the June meeting, CIR has received no new unpublished data. Comments from the Council on the Tentative Report have been addressed (*PCPCcomments_Olive_092023* and *response-PCPCcomments_Olive_092023*).

Additional supporting documents for this report package include a flow chart (*flow_Olive_092023*), report history (*history_Olive_092023*), a search strategy (*search_Olive_092023*), meeting transcripts (*transcripts_Olive_092023*), and a data profile (*datapofile_Olive_092023*).

The Panel should review the Abstract, Discussion, and Conclusion, and issue a Final Report.



Memorandum

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

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

DATE: July 25, 2023

SUBJECT: Tentative Report: Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics (release date June 27, 2023)

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

Method of Manufacture; Table 2 – The description of olive husk in the method of manufacture section (“solid residue obtained after olive oil extraction”) does not match the definition given in Table 2 (“A dry outer covering of a fruit or seed”). Perhaps the definition used in the method of manufacture section should be added to Table 2 in addition to the general definition.

DART; Summary – Please provide more information about the reproductive toxicity study in the text. The text should state that both male and female rats were treated, and note when in relation to gestation they were treated.

Dermal Irritation and Sensitization; Summary – Since only 1 product (containing 2 olive-derived ingredients) was tested, “In human repeated-insult patch tests” should be changed to “In a human repeated-insult patch test”.

Table 1 – The CAS number for the bud extract needs to be corrected (period needs to be replaced with a dash).

Table 10 – The protocol column for the first study indicates that histopathological exams were completed, but the outcomes of these examinations are not included in the results column. In the description of the second study, the results column suggests that microscopic examinations of the forestomach were completed, but neither the protocol nor the results column indicates if any other organs were examined microscopically.

Table 11 – In the results column for the first study, it is not clear what the p values represent as the effects were reported in all treatment groups. Are the p values for the high dose group compared to controls? If the p values were the same for all treatment groups compared to controls, it should be noted that there was not a dose-response relationship.

<i>Olea europaea</i> (Olive)-Derived Ingredients - September 2023 – Christina Burnett	
Comment Submitter: Alexandra Kowcz, Personal Care Products Council	
Date of Submission: July 25, 2023	
Comment	Response/Action
Method of Manufacture; Table 2 – The description of olive husk in the method of manufacture section (“solid residue obtained after olive oil extraction”) does not match the definition given in Table 2 (“A dry outer covering of a fruit or seed”). Perhaps the definition used in the method of manufacture section should be added to Table 2 in addition to the general definition.	Added suggested definition to Table 2.
DART; Summary – Please provide more information about the reproductive toxicity study in the text. The text should state that both male and female rats were treated, and note when in relation to gestation they were treated.	Detail added.
Dermal Irritation and Sensitization; Summary – Since only 1 product (containing 2 olive-derived ingredients) was tested, “In human repeated-insult patch tests” should be changed to “In a human repeated-insult patch test”.	Correction made.
Table 1 – The CAS number for the bud extract needs to be corrected (period needs to be replaced with a dash).	Correction made.
Table 10 – The protocol column for the first study indicates that histopathological exams were completed, but the outcomes of these examinations are not included in the results column. In the description of the second study, the results column suggests that microscopic examinations of the forestomach were completed, but neither the protocol nor the results column indicates if any other organs were examined microscopically.	Additional detail added where available. No detail available on organs studied in second study.
Table 11 – In the results column for the first study, it is not clear what the p values represent as the effects were reported in all treatment groups. Are the p values for the high dose group compared to controls? If the p values were the same for all treatment groups compared to controls, it should be noted that there was not a dose-response relationship.	Further detail on the results added.

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.

December 2022 – The Panel issued an Insufficient Data Announcement. The additional data needed to determine safety for these 23 cosmetic ingredients are:

- Method of manufacture for Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, Hydrolyzed 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) Husk Powder, Olea Europaea (Olive) Leaf, Olea Europaea (Olive) Sap Extract, Olea Europaea (Olive) Seed Powder, and Olea Europaea (Olive) Wood Extract
- Composition and impurities data for Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, Hydrolyzed Olive Leaf Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Flower Water, Olea Europaea (Olive) Fruit Unsaponifiables, Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) Leaf Water, and Olea Europaea (Olive) Seed Powder
- 28-day dermal toxicity data on Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) Sap Extract, Olea Europaea (Olive) Seed, Olea Europaea (Olive) Seed Powder, and Olea Europaea (Olive) Wood Extract
 - If positive, additional data (e.g., DART and genotoxicity data) may be needed
- Dermal irritation and sensitization data for Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, Hydrolyzed 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) Fruit Extract (at maximum use concentration), Olea Europaea (Olive) Husk Powder, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
- Ocular irritation data for Olea Europaea (Olive) Fruit Extract and Olea Europaea (Olive) Leaf Extract, if available

February/March 2023 – Additional unpublished data received.

June 2023 - The Panel issued a Tentative Report with the conclusion concluded that the following 16 *Olea europaea* (olive)-derived ingredients are safe in cosmetics in the present practice of use and concentration described in this safety assessment:

Hydrolyzed Olive Fruit	Olea Europaea (Olive) Fruit Water
Hydrolyzed Olive Fruit Extract	Olea Europaea (Olive) Husk Powder
Hydrolyzed Olive Leaf Extract	Olea Europaea (Olive) Leaf
Olea Europaea (Olive) Fruit	Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Fruit Extract	Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Fruit Juice	Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Fruit Juice Extract	Olea Europaea (Olive) Seed
Olea Europaea (Olive) Fruit Unsaponifiables	Olea Europaea (Olive) Seed Powder

Additionally, the Panel also concluded that the available data are insufficient to make a determination of safety for the following 7 *Olea europaea* (olive)-derived ingredients under the intended conditions of use in cosmetic formulations:

Olea Europaea (Olive) Bark Extract	Olea Europaea (Olive) Flower Water
Olea Europaea (Olive) Branch Extract	Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Bud Extract	Olea Europaea (Olive) Wood Extract
Olea Europaea (Olive) Flower Extract	

The additional data needed to determine the safety of these ingredients in cosmetics are:

- Method of manufacture for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
- Composition and impurities data for Olea Europaea (Olive) Branch Extract and Olea Europaea (Olive) Flower Water

- 28-day dermal toxicity data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract
 - If positive, additional data (e.g., DART and genotoxicity data) may be needed
- Dermal irritation and sensitization data for Olea Europaea (Olive) Bark Extract, Olea Europaea (Olive) Branch Extract, Olea Europaea (Olive) Bud Extract, Olea Europaea (Olive) Flower Extract, Olea Europaea (Olive) Sap Extract, and Olea Europaea (Olive) Wood Extract

Olea Europaea (Olive)-Derived Ingredients* - September 2023 - 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	
Hydrolyzed Olive Fruit																													
Hydrolyzed Olive Fruit Extract							X				X			X	X														
Hydrolyzed Olive Leaf Extract																													
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	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																									

* "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		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	

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
 ((hydrolyzed) AND (olive)) NOT (oil) – 45 hits, 2 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/opthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - <http://www.cdc.gov/niosh/>
- NTIS (National Technical Information Service) - <http://www.ntis.gov/>
 - technical reports search page: <https://ntrl.ntis.gov/NTRL/>
- NTP (National Toxicology Program) - <http://ntp.niehs.nih.gov/>
- Office of Dietary Supplements <https://ods.od.nih.gov/>
- FEMA (Flavor & Extract Manufacturers Association) GRAS: <https://www.femaflavor.org/fema-gras>
- EU CosIng database: <http://ec.europa.eu/growth/tools-databases/cosing/>
- ECHA (European Chemicals Agency – REACH dossiers) – <http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1>
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - <http://www.ecetoc.org>
- European Medicines Agency (EMA) - <http://www.ema.europa.eu/ema/>
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- <http://webnet.oecd.org/hpv/ui/Search.aspx>
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- <https://www.industrialchemicals.gov.au/>
- International Programme on Chemical Safety <http://www.inchem.org/>
- FAO (Food and Agriculture Organization of the United Nations) - <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/>
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

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/>

DECEMBER 2022 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – December 5, 2022

DR. BELSITO: Okay. Olive. Oh, time for a martini.

MS. BURNETT: After all those hair dyes.

DR. BELSITO: I probably should recuse myself from this as an Italian, right? I have a certain bias. Okay. This is the first time we're looking at this; is that right?

MS. BURNETT: Yes.

DR. BELSITO: Lots of data. We had some comments -- or questions first. Hydrolyzed compounds? Sure, add them in.

DR. SNYDER: I agree.

DR. BELSITO: So that would be the hydrolyzed fruit leaf.

DR. SNYDER: Fruit extract.

DR. BELSITO: Fruit extract.

DR. SNYDER: Yup.

DR. BELSITO: So, we need to add those into the introduction. On PDF, Page 17, the second paragraph in composition and impurities on the olive bark extract, you say the primary metabolites of the powdered bark, do you mean constituents?

DR. RETTIE: Must be.

MS. BURNETT: Probably. I'll check that.

DR. RETTIE: Primary comes in there because the next sentence you have a yield of secondary metabolites, if we're talking about secondary metabolites for plants. But I'm not sure that's really what the sense is here either. Maybe they are because they're flavonoids.

MS. BURNETT: I'll go find my source and I can share it.

DR. RETTIE: I'm not used to hearing primary metabolites when you talk about plant materials. Secondary metabolites for sure, maybe that's a white swath. Maybe reconsider metabolites all around.

MS. FIUME: Curt has his hand raised.

DR. BELSITO: Curt? Can't hear you.

DR. KLAASSEN: No, I don't need anything.

DR. BELSITO: Okay. No Vicks VapoRub or anything?

DR. KLAASSEN: No, I have Kleenex.

DR. BELSITO: Okay. In the genotox studies, I just had a question. There are positive and negative results here for the hydrolyzed olive fruit extract, especially, what did you gentlemen make of that?

DR. SNYDER: I had put genotox negative, so it must not have bothered me. But I did have a question, Christina, on page 21. There's a 90-day study where the NOAEL was 1000 milligrams per kilogram tested. But on Table 11, the only 90-day studies we have are on leaf extracts, not on fruit extracts. Is that a typo there? It's right above --

MS. BURNETT: Let me find the table.

DR. BELSITO: There's a 42-day study with leaf extract.

DR. SNYDER: No, it's the 90-day --

DR. BELSITO: The NOAEL for the 90-day rat study?

DR. SNYDER: Yes.

DR. BELSITO: That's the one you're talking about?

DR. SNYDER: Yeah.

DR. BELSITO: That was olive leaf extract.

DR. SNYDER: Olive leaf extract, but in Table 11, it says fruit extracts.

MS. BURNETT: I see it on PDF, Page 33.

DR. SNYDER: There's a leaf or a fruit?

MS. BURNETT: It's a leaf extract proprietary product.

DR. SNYDER: Oh, is it? Maybe I was looking at the wrong 90-day study then.

MS. BURNETT: Yeah, there is one with the hydrolyzed olive fruit extract. Yes, there's two.

DR. SNYDER: Okay.

MS. BURNETT: One was a NOAEL of 2000, and the one with the leaf extract was a NOAEL of 1000.

DR. SNYDER: Those two 90 days at the top of that -- oral 90 days at the top there are both fruit extracts. On Table 11, the first one is a 90-day fruit extract, and the second one is a 90-day hydrolyzed fruit extract. So where is the 90-day --

MS. BURNETT: At the end of the table.

DR. SNYDER: Oh, you put them there. Okay. Okay. I got you. All right. Thank you.

DR. RETTIE: So, looking at the table on Page 9, PDF 9, just going by that. While we had a very good method of manufacture for leaf and fruit extracts product, it seem to be missing it all for bark extract, branch extract. Are they the same thing? Bud extract, flower extract and sap extract, so there's a few of those that were missing, we could ask for, I guess.

DR. BELSITO: Right. But I thought the fruit, leaf and seed were safe as used.

DR. RETTIE: Yeah, certainly fruit and leaf. Seed, seed? Why did you include seed in there? Because the seed powder was good.

DR. BELSITO: We have seed powder and then we have the composition and impurities for seed.

DR. RETTIE: Yes. Okay.

DR. BELSITO: So, we have the bark is homeopathic but not -- and the branch and wood are also in homeopathic uses, but the bud and flower don't. And I have a question whether the composition is sufficient for the bud and the flower?

We have composition data for the bud extract and the flower extract, but we don't we don't have method of manufacture for either. I had fruit, leaf and seed safe as used. In discussion, the fruit extract has been reported that some skin bleaching would not be a cosmetic effect, yada, yada, yada, we've dealt with that before.

Bud and flower, additional method of manufacture. And I wasn't sure whether you felt the composition and purity data was sufficient, but a 28-day dermal tox and, if positive, other endpoints of the bud and flower. Sensitization and irritation on the bark, branch, wood, flower and wood.

And I guess we must have gotten some Wave data because I said, not yet completely inserted, composition, manufacturing and impurities.

DR. SNYDER: No, we didn't get any Wave data.

MS. BURNETT: No.

DR. BELSITO: Okay. Not yet completely inserted, composition, manufacturing and impurities, I have. I reviewed this a long time ago. I don't know what I mean by that. See if I can figure that out.

And for the bark, you're going to check whether it's metabo- -- but then it says, "The yield of secondary metabolite." So what were they doing here?

MS. BURNETT: I used the terms as stated in the document. So, I can send you the reference.

DR. BELSITO: Bud extract and flower extract, they're phenolic compounds. Flower extract in ethanol, phenolic acids. A little bit more detail there. Are you okay with a list of those compositions without concentrations? Is there anything that jumps out at you that worries you?

DR. RETTIE: It's olive. It's kind of hard to be worried about, what I imagine must be enolic under --

DR. BELSITO: Yeah, but I'm talking here, specifically. I mean, we don't eat the flower.

DR. RETTIE: Yeah.

DR. BELSITO: And we don't eat the -- the bark has been reported to be used as a homeopathic agent.

DR. RETTIE: So, if it's a homeopathic agent, how does that change our outcome?

DR. BELSITO: I think we agreed that we're not going to consider that GRAS.

DR. RETTIE: Well, I mean, this is the first time through looking at this, my notes say we should ask for bark extract, bud extract, sap extract.

DR. BELSITO: What are we asking for, manufacturing and composition?

DR. RETTIE: Yeah, manufacturing and composition. Well, not necessarily composition, we have composition for some of them but not all of them.

DR. SNYDER: Well, leaf extract -- well, leaf and fruit we're good on. Oh, composition, no.

DR. BELSITO: I have fruit, leaf and seed, safe as used.

DR. RETTIE: Yes, that's what I have.

DR. BELSITO: I have bud and flower, not sure if composition is sufficient. So we must have some composition data. So do we have manufacturing for those?

DR. SNYDER: No.

DR. BELSITO: So we need manufacturing --

DR. SNYDER: And composition and 28-day dermal.

DR. BELSITO: But we have some composition data. That's my question. Is it sufficient?

DR. RETTIE: Well, composition is not listed for branch extract or flower water. Fruit juice, but I guess fruit extract covers that?

DR. BELSITO: So, bud and flower, we need manufacturing?

DR. RETTIE: Yes.

DR. BELSITO: Okay.

DR. RETTIE: What did we decide about the wood extracts and the bark and branch extracts?

DR. BELSITO: Can we just go through bud and flower, the needs for those? So, bud and flower we want manufacturing, but the composition we're okay with. We want 28-day dermal tox. And if positive or if absorbed, then other endpoints, DART, genotox are needed.

Okay. So for the bark, I have sensitization, irritation on bark, branch wood, flower and wood. So let's go to -- so the flower, we need sensitization on -- which, I guess, means that the bud we have some sensitization data?

DR. RETTIE: No.

DR. BELSITO: So flower and bud we need sensitization and irritation?

DR. RETTIE: Yeah.

DR. BELSITO: Okay. So, now let's go to the bark, branch wood, and wood. So, I have sensitization and irritation on all three of those.

DR. RETTIE: Yep.

DR. BELSITO: What else do we need on them?

DR. RETTIE: We need method of manufacturing on bark, branch and bud.

DR. BELSITO: Bark, branch and --

DR. RETTIE: And bud.

DR. BELSITO: -- and bud. Yeah, well I have manufacturing for the bud. So we need manufacturing -- do we need impurities?

DR. RETTIE: I don't think so.

DR. BELSITO: Manufacturing, sensitization and irritation on bark, branch wood and wood.

DR. RETTIE: Yes.

DR. BELSITO: Okay. Do we need anything else on the bark, branch wood and wood?

DR. RETTIE: Yes, sensitization, I think we're good.

DR. BELSITO: You had sensitization. I got manufacturing, sensitization and irritation. That's it?

DR. SNYDER: But we don't have any absorption, so we got to have a 28-day dermal, right?

DR. BELSITO: Okay. 28-day dermal.

DR. RETTIE: Did we talk about the sap extract?

DR. BELSITO: Nope.

DR. RETTIE: On the seed we don't have method of manufacturing for either of those. We do have some composition and impurities, but we're missing method of manufacture for sap extract and seed.

DR. BELSITO: Well, we have method of manufacturing for seed powder.

DR. RETTIE: Oh, yes, we do. That's right, just below it. So, that just leave sap extract.

DR. BELSITO: So, let's get to the sap extract. For sap extract we need manufacturing, composition and impurities?

DR. SNYDER: We have composition. Oh, no we don't. Yeah, we do. We have composition and impurities for the sap extract.

DR. RETTIE: Just need the method of manufacturing. And then there's nothing else listed.

DR. BELSITO: Do we need sensitization and irritation on the sap extract?

DR. SNYDER: Yes, 28-day dermal.

DR. BELSITO: Okay.

MS. FIUME: Can I clarify for the ingredients for method of manufacturer? Some of the method of manufactures that are listed are basically just based on the definition from the monographs. Are those acceptable as the method of manufacturer?

DR. BELSITO: Yep.

DR. SNYDER: Yeah.

DR. RETTIE: We need to go through them all?

MS. FIUME: Sorry.

DR. SNYDER: Maybe in that table -- it looks like we're all looking at that table. Maybe we could put an asterisk that says that those are only -- in the future, we can just put asterisks so this --

MS. FIUME: Sure.

DR. SNYDER: We're very table driven for looking at these last data sets. So if that's all it is, no, that's not adequate.

MS. BURNETT: So that applies to the flower, water, fruit unsaponifiable, fruit water, the husk powder.

DR. RETTIE: Fruit water is through steam distillation.

MS. BURNETT: Correct.

DR. RETTIE: Are we going to get much more than that?

MS. BURNETT: Probably not.

DR. RETTIE: And husk powder is drying and grinding the husks?

MS. BURNETT: Probably. Yeah, leaf water and seed powder.

DR. SNYDER: Leaf water and seed powder.

MS. BURNETT: Oh, wait. We did get a confirmation from the supplier on the leaf water. So that was okay.

DR. SNYDER: So the only one would be the seed powder. What does that one say?

MS. BURNETT: According to the dictionary, seed powder is obtained from drying and grinding the seeds of *olea europaea*.

DR. SNYDER: But we have composition on the seed.

DR. BELSITO: Yeah. So, I have currently fruit, leaf and seed are safe as used with a discussion that the fruit extract, skin bleaching, would not be a cosmetic effect.

Bud and flower, we need manufacturing, 28-day dermal tox and, if absorbed, then other endpoints, DART, genotox are needed and sensitization and irritation.

For the bark, branch wood and wood we need manufacturing, 28-day dermal and, if absorbed, other tox endpoints. And for the sap extract we need manufacturing, 28-day dermal, if absorbed, other tox endpoints and sensitization and irritation.

DR. SNYDER: The only one you forgot was the husk powder.

DR. BELSITO: Husk powder is the same as the --

DR. SNYDER: As the bark and branch wood and all that.

MS. BURNETT: So we won't run into the next time, we added three ingredients.

DR. BELSITO: Hydrolyzed.

DR. SNYDER: Hydrolyzed, yes.

MS. BURNETT: Hydrolyzed. We do have some data on the hydrolyzed fruit -- pulp. When I ran the search -- I haven't done a full literature search, but the pulp extract data was included because it came up when I was looking for olive, and it wasn't a whole lot of other data. So, I included it in my report. So, I would've come across, I'm sure, the other two if it was out there. So, a head's up. So, if you want to include those in the --

DR. BELSITO: Yeah, that's what my comment was, need more info on hydrolyzed because it hasn't yet been inserted.

MS. BURNETT: Okay.

DR. RETTIE: So, for the one that's in the table currently, we don't have method of manufacturing or any composition information. Although we have the composition and manufacturing for the actual fruit itself, the hydrolyzed part, presumably quite a bit different -- or could be. So I think we need that.

DR. SNYDER: Add it to the list.

DR. BELSITO: To reiterate what I have, fruit leaf and seed are safe as used. Discuss the olive fruit extract bleaching. Bud and flower manufacturing, 28-day dermal tox and positive other endpoints. Sensitization and irritation. And that seems to be a recurring theme for bark, branch wood, wood, husk, powder, sap extract. We also need manufacturing, 28-day dermal, if absorbed, other tox endpoints, sensitization and irritation.

So, actually, on everything other than the fruit leaf and seed, we need manufacturing, 28-day dermal tox, sensitization and irritation. And then we need more information, anymore that you can find on hydrolyzed that haven't been inserted yet.

DR. SNYDER: Well, hydrolyzed, we've got oral tox, we've got oral acute --

DR. BELSITO: At that point, she wasn't including those ingredients, so make sure that there was nothing that wasn't incorporated.

DR. SNYDER: Okay.

MS. BURNETT: I found that in the initial search and added it just because I thought it was helpful.

DR. SNYDER: Okay.

DR. BELSITO: Okay. Did I catch everything?

DR. SNYDER: You did.

MS. BURNETT: I think so.

Cohen Team – December 5, 2022

DR. COHEN: Okay, Olive. So, this is a draft report. It's the first time we're reviewing this and it's a safety assessment for 20 derived ingredients. They're used as a skin conditioning agent. The husk powder and seed powder are reportedly to function as abrasives. The leaf extract has the highest concentration of use in a leave on formulation of 2 percent. The highest concentration for a rinse off is 10 percent in a shaving cream. The leaf extract has the highest frequency of use at 182 formulations, and the fruit extract at 118.

As a reminder, the panel previously reviewed olive fruit oil and concluded this ingredient is safe for use in cosmetics. We also have a question to the panel whether we include hydrolyzed olive fruit, hydrolyzed olive fruit extract, and hydrolyzed olive leaf extract into this report.

So maybe before we dig in, should we just address that issue right now? Do we want to include that here?

DR. ROSS: Well, there is some data using those preps in the report. And actually, it's quite important data. So, I think it sounds reasonable. I'd like Bart's advice.

DR. SLAGA: Are we talking about adding the hydrolyzed?

DR. COHEN: Yes.

DR. SLAGA: Yeah.

DR. COHEN: Include it, right?

DR. SLAGA: Yes.

DR. BERGFELD: Could we ask Bart, he was involved in setting up these ingredient lists. Why wasn't it included at the beginning?

DR. HELDRETH: So, when we've been making priority groupings of late, we've been trying to keep the groupings rather small and concise and only looking at those ingredients with a significant frequency of use so that there would be some attraction to the safety assessment, whether by consumers or by industry themselves.

But to the point of adding these three, yeah, typically, if the panel has asked to add ingredients and there's data supporting it there, you're already doing the work, looking at the safety of these ingredients, it's really not much of a leap to count them as part of your assessment.

DR. ROSS: There are no uses of those?

MS. BURNETT: I'm not sure.

DR. HELDRETH: I'm not sure.

DR. COHEN: I don't --

MS. BURNETT: I'm not sure, yet, on that.

DR. ROSS: I got that somewhere.

DR. COHEN: Yeah. It says currently there are no uses for these three ingredients. I highlighted it in the report.

MS. BURNETT: We haven't asked for the survey on the concentration. That's what it is.

DR. COHEN: Ahh.

DR. ROSS: Ahh.

MS. BURNETT: But once you approve it, we'll ask Council to survey those three.

DR. ROSS: Okay.

DR. BERGFELD: Would that go to a draft tentative or do we do an IDA or just a quiet request?

MS. BURNETT: It would be requested -- we'll probably just wait a meeting in a time we'll get the data back. So, it'll be in the next route.

DR. BERGFELD: So, table?

DR. HELDRETH: No. I don't believe there's any need to table it. We'll just simply -- this won't come back in March, it'll come back in June, so that there's plenty of time for Carol to conduct and receive the results of a survey.

DR. COHEN: And the hydrolyzing process wouldn't change these products with any significance that we shouldn't put them together here. Like 15 years from now we're splitting them back out again. Because the current 20 right now are quite different. It's all the method of manufacturing of these items, but not so much a processing in the same way. Right?

MS. BURNETT: I mean, we separated hydrolyzed wheat protein from other things previously, but that's because there was data that became an issue. We don't have any data indicating there's an issue, so.

DR. COHEN: So, we could agree to put them in. And then if there's some contrary information that comes around, we could split it back out?

DR. HELDRETH: Okay. You can split it back out or you can simply have a split conclusion --

DR. COHEN: Yeah.

DR. HELDRETH: -- in the same report saying that we don't have the data to support the hydrolyzed version because of whatever reason.

DR. COHEN: But we'll give everyone enough time, right, because this is already gotten -- this started running because the horn ran up and everyone started to move.

DR. HELDRETH: That's right.

DR. COHEN: Okay. And then we can just go to the meat of this. I had a question, why weren't all the fruit components considered GRAS? Don't we eat a lot of --

MS. BURNETT: So --

DR. BERGFELD: Olive oil.

MS. BURNETT: So, the way -- well --

DR. COHEN: We eat the olives.

DR. BERGFELD: And olive oil.

MS. BURNETT: Anything that was recognized as a food before 1950 something, it just falls under it's safe.

DR. ROSS: Historical.

MS. BURNETT: There's no CFR designation for it, it's a food. Anything that's been eaten, it's still food.

DR. HELDRETH: That's right.

DR. COHEN: So, I could just start with what I have. We need a method of manufacturing for branch extract, bark extract, bud extract, flower extract, leaf, sap extract, seed and wood extract. Does that jive?

DR. HELDRETH: Everything but the fruit?

DR. COHEN: Huh?

DR. HELDRETH: Everything but the fruit?

DR. COHEN: Yeah. And impurities for branch extract, flower, water, husk powder, leaf water and seed powder. I mean, we can ask for those although it may change -- it doesn't necessarily connect with my conclusion.

DR. TILTON: Do we need to request, for the hydrolyzed extract, specifically, or is that already covered in the fact that we are going to add it?

DR. COHEN: It's not in the report, so it's not in the IDA for that. But can we physically just include it now and there's an IDA for it?

DR. HELDRETH: Yeah. I mean, if the panel agrees tomorrow to include these three ingredients, it's certainly reasonable to go ahead and ask for information there. Christina will go out and do a search and see what's available in the literature, but -- you know.

DR. BERGFELD: I mean, the question really is, are you going to make this as a report, an IDA for the hydrolyzed? Or you do it quietly and just make these other ingredients as an IDA?

DR. HELDRETH: Well, these three ingredients will be added to this report, assuming that the whole panel agrees tomorrow. And then the IDA can apply to the original ingredients and the three if needed.

DR. BERGFELD: Okay. I have a question about the abrasive use in the fruit, the husk and the seed and maybe even the bark. Not a lot on those. But it's an abrasive, it's a different kind of a use.

DR. COHEN: It's like an exfoliant.

DR. BERGFELD: Yeah.

DR. COHEN: Well, we've looked at abrasives before, right, exfoliants?

DR. BERGFELD: But you may not need all of the information if you don't receive it.

DR. COHEN: Yes, right, right.

DR. BERGFELD: Because of the use.

DR. COHEN: I completely get it.

DR. BERGFELD: Mm-hmm.

DR. ROSS: When we go out and ask for the information on the hydrolyzed, could we ask also on chemical composition so we can get some comparisons to the actual fruit extract? Because that, I think, would inform whatever conclusions we come to.

DR. COHEN: So, also, do we need dermal tox on bark, bud, branch, flower, sap and wood?

DR. ROSS: All the use -- I got it here.

DR. TILTON: Well, I had said that we need information on dermal penetration and absorption and, if absorbed, then yes we would need toxicity data.

MS. BURNETT: Is that possible with this being a botanical.

DR. HELDRETH: Yeah, typically with the botanicals since it's a mixture of components, we almost never get anything on the ADME side just because, how do you start the test when you don't know what's going on --

DR. COHEN: What are you looking for?

DR. HELDRETH: Yeah. To see what went through the skin. You know what I mean?

DR. COHEN: Okay.

DR. HELDRETH: So, I would jump right to the tox.

DR. TILTON: So then just the tox?

DR. HELDRETH: Yeah. If you have the composition. You probably want the composition.

DR. ROSS: So, David, I have also a couple of other things I wanted your input on here. The dermal leaf extract was okay for irritation and sensitization up to five percent, maybe even 20 percent for this one reported. Maximum use is 2 percent, so we're okay there, right? The fruit extract was only up to 0.0025 percent in studies. And the maximum use of the fruit extract here is 0.5 percent. So, do we need that?

DR. COHEN: Yeah, I noted that. The fruit extract -- just looking at the composition. It didn't strike me as something that I was/would be very worried about.

DR. ROSS: Yeah.

DR. COHEN: I guess I was trying to commi- -- so, actually, one of the comments I have is that the fruit extract appears to be different things to different manufacturers.

DR. ROSS: Yes.

DR. COHEN: Right. And that was one issue, right, so this is either going to be pressed fruit or through some other extraction process.

DR. ROSS: Though all these things are going to be phenols, polyphenols, flavonoids. You know.

DR. BERGFELD: Yeah, that makes sense.

DR. ROSS: They all have form.

DR. COHEN: Yeah.

DR. HELDRETH: Well, there will even be different concentrations and maybe even constituents between --

DR. COHEN: Based on process.

DR. HELDRETH: -- different process. Even if we're just talking about, you know, extra virgin olive oil, virgin olive oil. It depends on what stage you're pulling it from.

DR. COHEN: You know, when I was looking this over, I was channeling Don a little bit on this. People put lots of olive products on their skin all the time and we just don't run into major issues with it. Sometimes it's transiently burning and stinging.

But people use extra virgin olive oil, right on their skin out of the bottles, regular olive oil. And so, some of that was coming into my contemplation of this as not something that was as concerning to me, just based on the years of patient experience here.

But look, this is a draft report. We can ask for it and see what we get. So, we'd like irritation and sensitization.

DR. ROSS: Fruit extract.

DR. COHEN: For fruit extract at max use.

DR. ROSS: Well, you're not done yet. I had two more questions for you.

DR. COHEN: No, no. I didn't think I was.

DR. ROSS: Well the other one was we had the different product that you commented on in your introduction, which was the olive fruit unsaponifiables, and that's the one in shaving cream, I believe, at 10 percent. Do we need to do anything with them?

DR. COHEN: Yeah, I think probably the same thing. Let me just see what I have written here. Hmm, no.

DR. BERGFELD: It does say that the fruit extract is GRAS.

DR. COHEN: You're talking about sensitization.

DR. ROSS: Yeah, I was talking about sensitization not oral. I think the tox is fine.

DR. COHEN: Yeah. I looked at this as sort of olive oil. Is unsaponified fruit olive oil? Right, you would of saponify an oil, right, a fat?

DR. ROSS: "Unsaponifiables is the remaining fraction of olive fruit remaining after fractional distillation."

DR. COHEN: That's the problem.

DR. ROSS: I'm not sure it's oil.

MS. BURNETT: In the dictionary they're listed as separate ingredients, but I don't -- there's a fruit oil unsaponifiable and then there's fruit unsaponifiable. But as we saw, one supplier saying that their fruit extract is olive oil, but that's not necessarily all of them. I'm not sure.

DR. COHEN: Okay.

DR. ROSS: That was my second one.

DR. COHEN: Wait, there's more. Hold on. Let me put this one. The fruit extract at max use and the unsapon- -- but --

DR. ROSS: And I'm fine if we deem that it's -- yeah, that's okay.

DR. COHEN: Let me just go back to which item this was. Yeah, fruit unsaponified.

DR. ROSS: Yeah. So, it's a separate product category on the right side.

DR. COHEN: And we don't have composition and impurities on it, so we really don't exactly know.

DR. ROSS: Yeah.

DR. COHEN: Okay. Okay, what else? No, no, no, this is it. This is the draft, right? We want to get as much as we can in here.

DR. ROSS: Yeah, it's the draft. So, I did note that there were ocular usage of 3 and 11 with the fruit extract and the leaf extract, respectively. We have no concentrations in that document that we use for ocular. And I just wanted to ask my colleagues whether we needed some sort of ocular, molecular or in vitro test with these things once we get the concentrations? A pretty low number of uses, 3 and 11.

DR. COHEN: So, what's the ask? Ocular tox?

DR. ROSS: Some indication of ocular irritation. And that's my question for you, whether we ask for this with the relatively low number of uses.

DR. BERGFELD: One.

DR. ROSS: It says 3 and 11 here.

DR. BERGFELD: I have one in the Table. Okay.

DR. ROSS: Or maybe it's not worth it?

DR. COHEN: No, because you don- -- I don't like to make the assumption that these are the only products on the market, right?

DR. BERGFELD: Oh, you're right there's another one -- three.

MS. BURNETT: Leaf extract has 11 uses.

DR. COHEN: Mm-hmm.

DR. ROSS: Yeah, the leaf extracts got 11 it says in the eye area. That's from my old version of the table, immediately.

MS. BURNETT: This is a good example. This report's a good example of the two-use table when it's multiple ingredients.

DR. COHEN: They're used differently.

MS. BURNETT: Yes. So, which would be better?

DR. COHEN: So, David, do you want, we can ask.

DR. ROSS: I don't know.

DR. COHEN: Ocular irritation studies.

DR. ROSS: Consensus to see whether we'd prefer it or not.

DR. COHEN: No, no.

MS. BURNETT: If you want to ask for the concentration, too?

DR. ROSS: Well, we don't know the concentration so we can't really get the test if we don't know the concentrations.

DR. COHEN: Which constituent?

DR. ROSS: It was on the olive --

MS. BURNETT: The leaf extract has 11 uses.

DR. ROSS: The leaf extract and the fruit extract was three uses, but as Wilma said it's probably less than that.

DR. HELDRETH: Right.

DR. ROSS: So, I don't know if you need it on both, but --

DR. HELDRETH: I mean, we can certainly ask for the concentration. If you don't get it, remember that assuming that there's some sort of a safe conclusion the report will have a caveat in the conclusion that says for those ingredients that don't have a use reported, the expectation is they're used at the similar concentrations of use as others in the report. So, if you're trying to think of what concentration to evaluate it at, I would pick the maximum use concentration reported in the report for other ingredients.

DR. COHEN: But that's tricky, Bart.

DR. HELDRETH: Yes.

DR. COHEN: Like, when we look at pepper, you can say all right, so the fruit you'll use at 1 percent, and we have nothing on the seeds. Can you imagine 1 percent on the crushed seeds, right, that would be pretty intense, right?

DR. HELDRETH: Sure.

DR. COHEN: Okay, so, are we going out with safe as used for anything right now?

MS. BURNETT: It sound like --

DR. HELDRETH: Well, if you're doing an IDA you don't have to have any sort of conclusion.

DR. COHEN: Okay. Right. I guess, in our own heads. So can I just organize our needs, because I'm going to present this tomorrow.

DR. ROSS: Oh, so you're presenting this one?

DR. COHEN: Yes.

DR. ROSS: Okay.

DR. COHEN: The method of manufacturing for the constituents I mentioned earlier, which were numerous and you can see on the table. Impurities that we mentioned. We want dermal tox on bark, bud, branch, flower, sap, and wood. Is there anything? Susan?

DR. TILTON: Is that acute and repeated dose?

DR. COHEN: What would we want, just acute?

DR. ROSS: I think any indication that you can get on toxicity.

DR. TILTON: Okay.

DR. BERGFELD: You saw the definition of bud, which is a small flower.

DR. TILTON: There's also husk on there.

DR. COHEN: Yes. And it's interesting because I was, in my mind, putting husk with the fruit extract.

DR. BERGFELD: It's an abrasive though.

DR. COHEN: I know, but -- all right. And irritation/sensitization for fruit extract at max use and non-saponified fruit.

DR. ROSS: At max use, yeah.

DR. COHEN: Yeah, at max use.

DR. ROSS: Yeah.

DR. COHEN: And for leaf and fruit extract, we need concentration of use and ocular irritation. Does that summarize our needs?

DR. ROSS: I think so. Yeah.

DR. COHEN: I'm color coding everything so I know what to call out tomorrow.

DR. ROSS: There was no DART on the leaf extract, but there was no genotox either. So, I didn't have too much of a problem with that.

DR. BERGFELD: Can you go through the introduction page and just check off the ones you think have complete information, of those two columns at the top of the document?

DR. ROSS: I'm not sure there are.

DR. BERGFELD: Introduction review of the safety of --

DR. COHEN: Well, it looked like --

DR. BERGFELD: Like none of them?

DR. COHEN: -- leaf. No, leaf extract.

DR. BERGFELD: Yeah.

DR. COHEN: No, leaf extract we needed -- do we have concentration of use for leaf extract?

DR. ROSS: Yeah, we do. And you've got skin irritation and sensitization data.

DR. COHEN: So why did we say we needed concentration of use for leaf extract?

DR. ROSS: For ocular, I think.

DR. COHEN: Ah.

MS. BURNETT: The data we received was below maximum use concentration.

DR. TILTON: That was for fruit extract data.

DR. COHEN: That was for fruit extract and unsaponified fruit. For the leaf extract was the ocular tox. Are we just looking for ocular irritation for leaf extract and fruit extract? Where's the concentration issue?

DR. ROSS: Because it wasn't reported, the concentrations.

DR. COHEN: For which one because I want to be very specific.

DR. ROSS: For both. For both.

MS. BURNETT: There's no ocular concentrations.

DR. HELDRETH: That's right. The eye area says none reported for both.

DR. ROSS: For any of them, yeah.

DR. COHEN: Do we need the concentration or just the ocular tox on that, if we have max use?

DR. ROSS: But we don't.

DR. HELDRETH: We don't.

DR. COHEN: We don't have max use?

DR. ROSS: No.

DR. HELDRETH: Not for the eye area.

DR. ROSS: So, we need the max use for someone to do an ocular -- molecular test I would say rather than using more animals.

DR. COHEN: Okay, I clarified it. Okay.

MS. BURNETT: Did you want to comment on these tables in this report for comparison sake?

DR. COHEN: I think the vote might go very similarly to the other, but is there any comment about the Use tables? Tom, are you there?

DR. SLAGA: Yeah, I'm here. Sorry.

DR. COHEN: No, that's okay.

DR. SLAGA: Go ahead.

DR. COHEN: Any comments about the use table, the old verses the new?

DR. SLAGA: Well, I'll repeat what I said before, I could go with either table.

DR. COHEN: I like the new one. And you guys like the old one still?

DR. ROSS: I still like the old one, yeah.

DR. COHEN: Okay. And there's not an IDA for the hydrolyzed -- official IDA for the hydrolyzed components. We're just going to gather the information for it. Is that right, or are we going to call it an IDA?

DR. HELDRETH: I mean, Christina will go and do a literature search to see if it's out there between now and the next time you see it. But if you have specific concerns, we'll be asking Carol to do a concentration of use survey and we'll be pulling information from VCRP for frequency of use.

MS. BURNETT: I mean, with the hydrolyzed fruit extract, since that came up in the search and I didn't have other data, I went ahead and wherever I found that, incorporated it in the report.

DR. COHEN: You put it in.

MS. BURNETT: So, where you see it in the report, that's where the data came in because I was thinking it would be supporting data. Now if this hadn't been suggested to add these ingredients, the reverse question would've been, should we pull this data because it's not on these specific ingredients. But if we're adding that supporting data, we're good.

DR. HELDRETH: So then you'll likely have, already in front of you, what's available in the literature for the hydrolyzed.

MS. BURNETT: Fruit. Yeah.

DR. HELDRETH: So, if you feel that there's data gaps, then you may as well move forward, put them in the IDA.

DR. COHEN: Okay, so what do we need for the hydrolyzed material?

MS. BURNETT: Let me see. So, you have data on acute oral repeated dose, DART oral, in vitro and in vivo genotox. So, you don't have method of manufacture or composition.

DR. COHEN: And irritation and sensitization?

MS. BURNETT: Correct.

DR. COHEN: Okay, so let's go with that.

DR. ROSS: Yeah.

DR. COHEN: Okay.

DR. TILTON: So, for the other components that are data poor, we had requested acute toxicity but there is also no irritation or sensitization data for those.

DR. COHEN: For which?

DR. TILTON: The components that are not fruit or leaf. So, the bark, branch --

DR. BERGFELD: Sap.

DR. TILTON: Right. That group of them that are sort of data poor, we requested acute tox data. We could also request irritation/sensitization data if it's available.

DR. COHEN: Got it. Okay.

DR. BERGFELD: How much do we count on the old document on olives that we --

DR. COHEN: Olive oil?

MS. BURNETT: The vegetable oil?

DR. BERGFELD: Mm-hmm.

MS. BURNETT: I don't believe there was a lot of data there. I'm trying to remember.

DR. BERGFELD: The juice is contained in the vegetative parts -- or fruits, which is -- would that be vegetable oil in that description of generic plant parts? Juice, the liquid contained in the vegetative parts or fruits? So, if it's olive oil --

MS. BURNETT: That would be the fatty acid component.

DR. BERGFELD: But would it be from the juice or from the whole crushed plant, or the leaf and the fruit?

DR. HELDRETH: Crushed fruit.

MS. BURNETT: It was from the fruit.

DR. BERGFELD: Fruit.

MS. BURNETT: Crushed fruit.

DR. COHEN: But one of the suppliers just said that the fruit extract was olive oil.

DR. BERGFELD: Yeah. I know. I did see that we had incorporated some of that data information to this particular document under fruit then.

MS. BURNETT: I am not sure we wanted to just because that was just one suppliers reporting. It might not be the whole representation, but we can bring in the data. That would be helpful for reviewing the document.

DR. BERGFELD: Might be.

DR. COHEN: Have we ever folded an existing report into a new one? I mean, why wouldn't we take olive oil and just put it in this one and then reset?

DR. HELDRETH: Okay.

DR. COHEN: If it was safe as used, olive fruit extract, to me, sounds a lot like olive oil for some manufacturers.

MS. BURNETT: Right.

DR. COHEN: So why would we want to look at that one again in eight years from -- when was it was done?

MS. BURNETT: It was part of a 200-some ingredient report. It's just one ingredient because the title of the report is fatty acid plant oils.

DR. HELDRETH: Plant oils.

DR. COHEN: Plant oils.

MS. BURNETT: So, there were like 200 ingredients.

DR. COHEN: Oh my god.

MS. BURNETT: I mean, we could easily split out that data and bring it into the report.

DR. HELDRETH: Yeah, you can pull the one ingredient out of it and then --

DR. COHEN: Yeah, maybe we should do that as we go along if that happens.

MS. BURNETT: We might've done that when we were reviewed coconut fruits after we did -- because coconut oils has been reviewed several times. And I think we did bring that data in for a read across in summary form.

DR. COHEN: Okay, so one of the other things we'll ask is to incorporate the olive fruit oil report into this one as a permanent member of this report.

MS. BURNETT: Okay.

DR. COHEN: Do you agree? Just one less thing to --

DR. BERGFELD: Well, you might have a lot of information there that's useful.

DR. COHEN: Yeah. Right. That might surprise us.

MS. BURNETT: I'll have it ready and available for tomorrow. If you'd like me to send it to you in case you want to see it, I can do that, too.

DR. BERGFELD: That'd be nice.

DR. COHEN: Yeah, we could look at it. Okay. I think we've crushed the olive. Sorry.

DR. ROSS: You've been waiting to use that one.

DR. COHEN: I know. They don't come around.

DR. BERGFELD: Just to be specific, though, before we move on, the question I had was in the introductory page when you have those two columns of lists, have we covered everything? I mean, I would put the bud with the flower in the data information portion.

DR. COHEN: Right. I see what you're -- you don't want us to come back as a draft tentative and say we want more things.

DR. BERGFELD: Yeah.

DR. COHEN: Right. Bud extract.

DR. BERGFELD: I don't know how you line these up, just out of curiosity. But if I were lining them up just for clarity for myself, I'd put all the fruits together or the flowers, and that would include the bud. And then I would take all the abrasives and put them together, the husk, the bark. Even the seed power was an abrasive and the wood extract, I believe.

DR. COHEN: You know, the only thing that I got concerned about, is the definition of the item doesn't always match the method of manufacturing of the item.

DR. BERGFELD: Right.

DR. COHEN: So, I'm very leery of taking the definition and applying it. Yeah, you're right, the bud is a small flower, but we just don't have method of manufacturing on the bud extract, we don't know --

DR. BERGFELD: Well, I mean, you can ask for it.

DR. COHEN: Yeah, we did.

DR. BERGFELD: But I mean -- to say you could couple it. This is confusing to me to have all these listed like this and no sort of -- this is a group, flower that come in water and extracts, powders, whatever. And this is a group of the leaves that come in powder, water.

MS. BURNETT: I just have them listed alphabetically.

DR. COHEN: Yeah, but the alphabetical listing does group them by -- look like it's leaf, leaf, leaf, leaf, seed, seed. You want them by functional-- you mean, by functionality? Yeah.

DR. BERGFELD: I guess that's what I'm saying. Because then we could really pull out what we don't have.

DR. COHEN: These are a slog no matter how you slice these.

DR. BERGFELD: But I'm confused what we don't have now.

DR. COHEN: All right. So, any other comments on olives? We're okay to move on?

DR. BERGFELD: Who's presenting this tomorrow?

DR. COHEN: Me.

DR. BERGFELD: Oh, okay.

DR. COHEN: No, we're going to have a good time with it. What's the protocol for the live meeting and breaking and things like that?

DR. HELDRETH: It's up to you to call for a break whenever you'd like. And then we typically break at noon for lunch.

DR. COHEN: So, let's just try to --

DR. BERGFELD: 11:45, so you can do another one.

DR. COHEN: We have -- yeah, at least.

DR. ROSS: Easy ones.

DR. COHEN: I'd like to present only the easy ones, if I can make that request.

DR. HELDRETH: You have to go in order.

DR. COHEN: Bart's very fair.

Full Panel – December 6, 2022

DR. COHEN: Olive, this is a draft report and it's obviously the first time we're reviewing this. This assessment has 20 derived ingredients. Most are used as skin conditioning agents. And the Husk Powder and Seed Powder are reportedly functioning as abrasives.

The Leaf Extract has the highest concentration of use in a leave-on formulation of 2 percent, and the Olive Fruit Unsaponifiables at 10 percent in a shaving cream. The Leaf Extract has the highest frequency of use. And the Fruit Extract is also used quite a bit.

As for the question of Hydrolyzed Olive Oil, Hydrolyzed Olive Fruit Extract and Hydrolyzed Olive Leaf Extract, we suggested adding these three ingredients.

Our motion for the report is an insufficient data announcement with the following needs: method of manufacturing for the Olive Branch Extract, Bark Extract, Bud Extract, Flower Extract, Leaf Sap Extract, Seed and Wood Extract; impurities for Branch Extract Flower Water, Husk Powder, Leaf Water, Seed Powder, dermal tox on Bark, Bud, Branch, Flower, Sap and Wood, and irritation and sensitization for Fruit Extract at maximum use.

For the eye area for the Leaf Extract and Fruit Extract we'd like concentrations of use and ocular irritation. And, for the hydrolyzed materials, we have acute, oral, tox, DART, in vitro and in vivo genotox, so we'd like method of manufacturing, impurities, irritation and sensitization at max use.

And we had a suggestion to incorporate Olive Fruit Oil into this report, and keep it here instead of in that much larger report of fruit oils.

DR. BERGFELD: And that's a motion?

DR. COHEN: And that's a motion.

DR. BERGFELD: Dr. Belsito, discussion or seconded, or both?

DR. BELSITO: Their insufficiencies are much larger than ours. We felt the Fruit Leaf and Seed were safe as used. Otherwise, we pretty much agreed with their insufficient needs. So, at this point, since we're going insufficient, we're willing to go along with the additional requests.

DR. BERGFELD: So you're seconding the motion?

DR. BELSITO: Yeah, I would just point out that asking for concentrations of use, Carol's already done that. We're not going to get it. The assumption will be it could be used at the highest reported concentration.

DR. COHEN: Yeah, we're aware of that, and I think just reiterating the question over and over again may demonstrate some of our desires and needs.

DR. BELSITO: Okay.

MS. BURNETT: Could you repeat which ingredients you wanted sensitization and irritation data, and if you still want ocular data?

DR. COHEN: Okay. Irritation and sensitization for Fruit Extract at max use, and ocular irritation for Leaf Extract and Fruit Extract. Did we miss any that you had?

DR. BELSITO: We had sensitization and irritation on Bud, Flower, Bark, Branch Wood, Wood, Husk, Power and Sap Extract.

DR. COHEN: Yeah.

DR. BERGFELD: Is that similar?

DR. COHEN: Yeah, now that Don enumerated more and was better.

DR. BERGFELD: Any other questions? I'm going to call the question then, all those in favor of an insufficient data announcement? Unanimous, thank you very much.

DR. KLAASSEN: May I add somethings?

DR. BERGFELD: Yes, please, Curt.

DR. BELSITO: Yes.

DR. KLAASSEN: Okay, as many of you maybe know I'm also a corn and soybean farmer, and thus, I don't enter my comments on corn and soybean. Since we're talking about olives here, I have no connection with olives. But I had a Chinese postdoc that came over to my lab in the '90s with a suitcase full of Chinese herbal medicines. And, every time I wasn't looking he was trying to do an experiment to see if they had all these magical potions. And, finally I say, okay, you pick out six chemicals out of your suitcase, but it has to be a pure chemical not just some leaf.

So, we did that, and then we looked for hepatotoxicity after pretreatment with one of these chemicals, a very important chemical, at high concentrations in olives, and that is oleanolic acid. And if you give oleanolic acid to animals, and then the next day give them a hepatotoxicant, there won't be any liver injury. And we did that with 10 different hepatotoxicants. And it's almost like magic.

And, at first we couldn't figure it out in the '90s what was going on, but then a group in Japan discovered another receptor called nrf2. And nrf2 is important for increasing oxidative stress related protective enzymes, as well as Phase II drug metabolizing enzymes. And, so, I think it's a nice example of things in plants that might be doing some real good to us. And, anyhow, it was a kind of a fun study. That's all.

DR. BERGFELD: Okay, any other comments?

MS. BURNETT: One more question.

DR. BERGFELD: Yes?

MS. BURNETT: I just want to confirm, I will be bringing over the olive oil summary, yes or not?

DR. COHEN: Oh, yeah.

DR. BELSITO: I mean, why bring it out of another report?

DR. COHEN: I think, Don, if someone six month or a year from now wants to just look at Olive, right, in their product, it just houses everything in one place as opposed to having -- the oil has already been cleared. And it seems to make more sense for manufactures to have it all in the same place as opposed to hunting for it.

MS. BURNETT: I do want to advise the Panel, when we wrote that plant-derived fatty acid oil report, we did not include systemic toxicity because those were all known food products. And since we knew that the ingestion was going to be greater exposure than the dermal, we did not include that type of data. So, if I do bring that over there will be no systemic tox in that.

DR. COHEN: I think we'd be okay with that, though.

DR. BELSITO: I just think it belongs in the plant-derived oils. If people want to look up olive oil, well, if you Google an ingredient on the CIR website, it tells you which report to go to when you type it in. So it's not a lot of confusion there.

DR. COHEN: I think one of the things that -- when you look at the Fruit Extract in our report, one of them is olive oil, right? This is not the Fruit Extract. When you look in method of manufacturing, there's different preparations for it including one that says oil.

DR. BELSITO: Right.

DR. COHEN: So, why not have this as just a repository of all olive material? It was just for the future to make it --

DR. BELSITO: I'll leave that to Bart.

DR. COHEN: All right. We're not digging our heels in on this at all, though.

DR. BELSITO: Okay.

DR. BERGFELD: You have a comment, Bart?

DR. HELDRETH: It's the Panel's choice if we want to bring that information in, or bring that information in and bring the ingredient into the report. I mean, we can bring the information in and --

DR. COHEN: Not extract -- we could have them run in parallel, you mean?

DR. HELDRETH: Well, I mean --

DR. BELSITO: No, you bring the information on the oil, but the actual oil in the conclusion that it's safe as used is in the plant-derived oil doc.

DR. HELDRETH: That's correct. It's just simply using the olive oil information for inferences, too.

DR. SNYDER: Just reference it in the discussion.

DR. BELSITO: Right.

DR. SNYDER: It's been previously reviewed. Just put it in the discussion.

DR. RETTIE: Just for my clarification, are the fruit oils you're talking about a mixture of fruit oil and essential oils?

DR. HELDRETH: No, they're all fatty acid type oil, triglycerides.

DR. RETTIE: Okay.

DR. BELSITO: Plant-derived.

DR. HELDRETH: Not volatile type.

DR. RETTIE: Not volatile. Okay, thanks.

DR. HELDRETH: So, but for Dr. Snyder's point, we cannot just put it in the discussion and reference it there. We don't reference -- so the data itself would have to be put into the report. And then we can talk about it in the discussion.

DR. BELSITO: And the introduction could say that the oil was previously reviewed in the plant-derived oils.

DR. HELDRETH: That could work just fine.

DR. RETTIE: Yeah.

DR. BERGFELD: So, I think we've resolved this. Have we yet? We're going to reference it, sounds like?

DR. COHEN: Yeah.

DR. BELSITO: Yeah.

DR. BERGFELD: Than rather bring it over?

DR. COHEN: Yeah.

DR. BERGFELD: Yeah. And I believe that we've concluded then the Olive with an insufficient data. Is that correct?

DR. COHEN: Yes.

DR. BELSITO: Yes.

JUNE 2023 PANEL MEETING – DRAFT TENTATIVE REPORT

Belsito Team – June 12, 2023

DR. BELSITO: Okay. Here's another one. So, at the December 2022 meeting, we issued an insufficient data announcement. We're asking for method of manufacture for hydrolyzed olive fruit, hydrolyzed olive fruit extract, hydrolyzed olive leaf extract, olive bark extract, olive branch extract, olive bud extract, olive flower extract, olive husk powder, olive leaf, olive sap extract, olive seed powder and olive wood extract. The composition impurities for hydrolyzed olive fruit, olive fruit extract, hydrolyzed olive leaf extract, olive branch extract.

I mean, pretty much the same that we asked for. Method of manufacture. We asked for a 28-day dermal tox, again, on most of what were already mentioned if not all. And depending upon that, additional DART and genotox data, dermal irritation and sensitization on that whole group of olive ingredients that I've already mentioned, and ocular irritation data on olive fruit extract and olive leaf extract if available.

We did get data and we got this nice little handout that sort of helps us. I think that in terms of method of manufacture, what we're missing is the seed -- what we -- can we impute some of them from the definitions, like olive flower water, olive fruit extract and olive fruit unsaponifiables? I mean, this comes up all the time. Can we impute how it's manufactured from the definition? And Paul is shaking his head no.

DR. SNYDER: No, I'm just saying it's just the same old issue over and over with these botanicals.

DR. BELSITO: Right.

DR. SNYDER: And there's no uses for the seed.

DR. BELSITO: Right.

DR. SNYDER: No reported uses.

DR. BELSITO: Well, the seed we can go insuffi- --well we have a 28-day dermal tox for the seed.

DR. SNYDER: Is that page from Wave three that you have in your hand?

DR. BELSITO: I don't know what page this is from.

MS. BURNETT: Hold it up so I can see.

MS. FIUME: It follows the memo.

DR. BELSITO: It's in your memo and then I just check things out there.

MS. BURNETT: On PDF Page 4, to try to make it easier, what data we received and what we didn't, I made a little chart. So, the highlighted shows what we actually got. The Xs were all what you asked for. So, we actually only received data on the irritation --

DR. BELSITO: Fruit extract. Right.

MS. BURNETT: Yeah, and it was just the dermal irritation and ocular irritation.

DR. RETTIE: So, your summary table in the memo was really quite helpful. Once I go beyond the fact that X means something different from what we got.

MS. BURNETT: Oh, sorry. Yes. Should've put data not received.

DR. SNYDER: The leaf extract has the highest number of uses with the majority of them as leave-ons and the fruit extract has the second highest with most of those as leave-ons and the maximum concentration is 2 percent.

DR. BELSITO: There is a mention at some point about pigmentation.

MS. BURNETT: It's a reported function.

DR. BELSITO: Oh, yeah.

MS. BURNETT: There's no actual data.

DR. BELSITO: Yeah, that's just my point. There's no data on that.

MS. BURNETT: It's a reported function to be skin bleaching agent for the fruit extract and leaf extract. And we have the caveat sentence in the introduction about how it's not part of the panel's purview.

DR. BELSITO: Right. So where are we with these? First of all, in terms of manufacturing, can we impute from definition? In which case the only one we don't have is olive seed, but then we have a 28-day dermal on olive seed. Does that give us enough confidence that the seed is safe?

MS. FIUME: I'm sorry, Don, where is the 28-day dermal?

DR. SNYDER: Yeah. I don't think it's seed.

MS. FIUME: Is there any dermal -- long term dermal tox?

DR. BELSITO: It's X'ed here.

DR. RETTIE: That means we have it.

MS. FIUME: That meant that was needed data.

DR. SNYDER: That's needed data.

DR. BELSITO: Oh.

DR. SNYDER: That's needed data. We didn't get anything.

MS. BURNETT: Where it's highlighted in yellow is what you actually received. That was what you needed.

DR. SNYDER: All the rest was a need.

MS. BURNETT: Sorry.

DR. SNYDER: It's kind of backwards, yeah.

DR. RETTIE: Yeah.

MS. FIUME: We need to do a table like families, the different designations and then the X. Sorry about that.

MS. BURNETT: So, yeah.

DR. BELSITO: So, I read the report and then I just added where there weren't X's. Oh, lord. I did it backwards.

MS. BURNETT: Largely you did not receive --

DR. BELSITO: Anything. Yeah, I mean, we just got -- and the max concentration of use is 0.45 in a leave on for --

DR. SNYDER: For what?

DR. BELSITO: -- the fruit extract.

DR. SNYDER: Oh, for the fruit. Yeah.

DR. RETTIE: I felt the last time we felt we could do some of the imputing for fruit, leaf and seed. But we still needed root extract, bark extract, branch extract, sap extract and husk powder. That was, I think, where we left it last time and we got none of that --

DR. BELSITO: Right, we had --

DR. RETTIE: -- this time.

DR. BELSITO: Right.

DR. RETTIE: So, those needs are still there. And this is just our second look at it so we could stay with what we did last time.

DR. BELSITO: Well, but then it goes out as an IDA. I mean, this is just not a second look. I mean, it's already gone out as an IDA, this would be a tentative.

MS. FIUME: Yes, this would be a tentative report.

DR. SNYDER: This is a draft tentative.

MS. FIUME: Correct.

DR. BELSITO: I mean, this is the second time we're looking at it. So, since I looked at this completely backwards, I apologize. Where are we with these? Are we staying with all of our insufficiencies and basically -- I mean, if we're okay with the fruit extract, which we were, why are we having problems with hydrolyzed fruit extract?

DR. RETTIE: I didn't think we were.

DR. BELSITO: Well, we're asking for method of manufacturing. We're asking for composition and impurities. I mean, we have insufficiencies there.

MS. BURNETT: So, at the last meeting the hydrolyzed ingredients were not part of the report, and the panel added them since we already had data in there on them and since it was already going out as an insufficiency. It was just added to the -- we're already asking for stuff, so let's go ahead and ask for more on these new three additions.

DR. SNYDER: The tox data is very clean on the leaf and fruit extract. I mean, we've got 90-day NOELs in rats up to a 1000 milligrams per kilogram, so.

DR. BELSITO: So basically, what you're saying is the leaves and the fruits are fine.

DR. SNYDER: And the seed.

DR. RETTIE: Correct.

DR. BELSITO: And seed.

DR. SNYDER: Let's see what we got, it's --

DR. BELSITO: Seed, we have method of manufacture, we have composition and impurities, we have dermal irritation/sensitization. If I'm reading the table right now.

MS. BURNETT: You can also go to the data profile page. That will show -- on PDF Page 6, that shows what you actually have.

DR. KLAASSEN: Yeah. You know, we don't have that great of data for the seed but --

DR. BELSITO: Well, X means we're missing the data.

MS. BURNETT: On PDF Page 6 it means you have it.

DR. KLAASSEN: You have the data.

DR. BELSITO: Okay.

MS. BURNETT: Sorry.

DR. SNYDER: And there's no uses for the seed.

MS. FIUME: Seed powder has use.

DR. SNYDER: Oh, does it?

MS. FIUME: I believe so.

MS. BURNETT: They both have an X.

MS. FIUME: They both have an X, so they must have some type of use.

DR. BELSITO: They're used as an abrasive, aren't they?

DR. SNYDER: I felt the data was pretty good for the fruit and the leaf for sure.

DR. KLAASSEN: Yes.

DR. SNYDER: There's good tox data, good genotox data, developmental data and everything's off the charts.

MS. BURNETT: So, the- --

DR. KLAASSEN: And we eat it.

MS. FIUME: Yeah.

DR. RETTIE: Fruit, leaf, and seed.

DR. SNYDER: Well, the seed -- I guess I had seed, but now we're questioning the seed. How much data do we have on the seed?

MS. BURNETT: Apparently, I didn't update the one table, but there are no uses reported for the seed, but there is for the seed powder. The seed powder is used in cleansing agents, body and hand products and other skin products.

DR. BELSITO: So, for the seed we have a reported use, and we have composition and impurities. And for the seed powder we have a reported use, we have method of manufacturing, we have human irritation and human sensitization for the seed powder.

DR. SNYDER: And what's the maximum concentration of that seed powder use?

MS. BURNETT: No reported.

DR. SNYDER: None.

MS. BURNETT: Not reported.

DR. SNYDER: All right. I mean, the max for the leave on is two percent, so if we say safe as used we would be applying up to 2 percent, so.

DR. BELSITO: So, are you proposing that we go with all the fruit components, all the leaf components and the seed components safe as used?

DR. SNYDER: I'm fine with that.

DR. KLAASSEN: Me too.

DR. RETTIE: I can live with that.

DR. BELSITO: Okay. And then the bark, branch, flower, wood, we basically need --

DR. RETTIE: And sap.

DR. BELSITO: -- and sap.

DR. SNYDER: Still insufficient for all those previous needs.

DR. BELSITO: Insufficient for all the previous needs.

DR. RETTIE: Did you mention husk?

DR. SNYDER: All remaining components are insufficient for the previous needs. Keep it simple. Does that seem reasonable, Christina?

MS. BURNETT: Yep. Any additional topics for Discussion or is that okay?

DR. SNYDER: I don't think I had any.

DR. BELSITO: Let me get to the Discussion.

DR. SNYDER: You got the pesticides, the heavy metals, all that other stuff's in there, so.

DR. BELSITO: I think the Discussion is okay.

DR. SNYDER: The airbrush thing is that last paragraph there, if you want to read that there.

MS. FIUME: So is the skin lightening paragraph staying in the Discussion --

DR. BELSITO: No.

MS. FIUME: -- or it's coming out?

DR. BELSITO: Well, wait a minute. It is listed as a function in the cosmetic dictionary. Perhaps it should be mentioned that there was no data provided that showed that there was a skin lightening effect, but the usual caveat of the --

DR. SNYDER: Drug effect.

DR. BELSITO: -- that this would be a drug effect and not at our purview. So, I mean, it's not like we have any data and I don't know who threw that in and why. But I think probably just so there's no confusion, that we're saying safe as used and there's skin lightening. That there is no evidence that there is skin lightening, but if there were.

MS. FIUME: I think we have some standard wording for that that we can switch it to.

DR. KLAASSEN: Right.

DR. BELSITO: Okay. Anything else? So, what is the skin lightening? Is it in the discussion at all at this point?

MS. BURNETT: Yes. It's the second full paragraph. It starts with, "data included in this report indicated that extracts of the fruit and leaves..." It goes on to --

DR. BELSITO: Okay. I would say that according to the dictionary extracts are reported to function as skin lightening, however there is no data in this report to support that claim. And furthermore, and then our boilerplate sentence about a biological effect should not occur with a cosmetic.

MS. BURNETT: We'll update that.

DR. BELSITO: Okay. Anything else?

DR. KLAASSEN: Nope.

DR. BELSITO: Okay.

Cohen Team – June 12, 2023

DR. COHEN: Okay, we're rounding the bend. Olive. So at the December meeting, we issued an IDA of the 23 ingredients. So, we had method of manufacturing for many of them, composition and impurities for many of them, 28-day dermal tox on

many of them and, if positive, additional data needed. Dermal irritation and sensitization for Olive Fruit, Olive Fruit Extract, Hydrolyzed Olive Leaf, ocular data for Olive Fruit, olive leaf extract if available.

And Christina put together a table that made things a lot easier.

MS. BURNETT: I hope.

DR. COHEN: Well, the question was, what did the Xs mean?

MS. BURNETT: The other group had the same Problem. The Xs meant that's what you asked for. The highlighted data is what you got.

DR. COHEN: Yes. I did have to stare at this for a while.

MS. BURNETT: Yeah. Unfortunately the other team misunderstood it, so.

DR. ROSS: Oh, I think I misunderstood it. See, I got that big question mark. Christina, it's not in this Use Table.

MS. BURNETT: Right.

DR. COHEN: So the Xs is what we asked for?

MS. BURNETT: The X's are what you asked for, and the highlighted is what you got.

DR. ROSS: Ah.

DR. COHEN: I figured it out by just looking at the first one and then looking down the list and it matched.

MS. BURNETT: Yeah.

DR. ROSS: You're just smarter than I am. What can I say.

DR. COHEN: No, it was pure desperation.

MS. BURNETT: It was a valiant attempt to make it easier and missed the target. Sorry.

DR. COHEN: I had, thank you for the table, it made life much easier, in my note.

MS. BURNETT: Okay.

DR. COHEN: And I will submit that to the group.

DR. ROSS: Good. Now I understand. So now I have a list of what I need.

DR. COHEN: So I can open it up and then we can come to a conclusion on what we can clear. Okay. Fruit, leaf and seed, and maybe husk.

DR. TILTON: I had safe in use for fruit, leaf and seed.

DR. COHEN: I wanted us to look at husk. To add it in. So, you had the same ones.

DR. ROSS: Why did you go with leaf and seed?

DR. COHEN: I'll have to go back now.

DR. ROSS: Because fruit, I can understand, obviously, we have skin irritation and sensitization at max. We've got ocular at max. So fruit extract I think is safe as used. Leaf extract, for example, we had no ocular data -- now I understand this table. And we've got eight uses, three in eye lotions. So, I felt that we needed some ocular data with leaf extract. But if you look at the Use Tables, we don't have a concentration.

DR. COHEN: Wait, I'm just going back to try to answer your question.

DR. ROSS: So, with respect to leaf extract and the seed, I wondered why you were going with those? Because Seed we got no new data, right?

DR. TILTON: No.

MS. BURNETT: Correct. And I, inadvertently, on the data profile, have it checked that there is a use and there is not a reported use for the seed.

DR. COHEN: We have leaf extract for irritation at 100 percent for human irritation. We have sensitization of leaf extract at 5 percent. We have seed powder, 25 percent, HRIPT.

DR. ROSS: That doesn't show up in the summary table right?

DR. COHEN: Go -- yeah.

DR. ROSS: Yes, it does. Yes, it does.

DR. COHEN: Yeah. So, I thought that was okay.

DR. TILTON: Yeah, that's what I had noted. And it was just that there was no irritation or sensitization.

DR. COHEN: Tom, thoughts on what items you had down to clear for olive? And then we'll swing back around, David.

DR. SLAGA: I have all that are eaten are safe. From the fruit to the leaves are eaten in different forms.

DR. COHEN: What did you have for seed?

DR. SLAGA: And the rest of them are insufficient.

DR. COHEN: What about seed?

DR. BERGFELD: Powder. The seed powder.

DR. SLAGA: The what?

DR. BERGFELD: Are you talking seed powder?

DR. COHEN: Seed powder, yeah.

DR. ROSS: Six uses.

DR. BERGFELD: But you've got human and you've got irritation and sensitization.

DR. TILTON: I think we had -- we previously discussed the overlap between fruit and seed.

DR. ROSS: Or was it fruit and leaf?

DR. COHEN: But fruit and seed makes more sense.

DR. TILTON: In terms of. We have a lot of data for leaf, so it has its own dataset.

DR. COHEN: That's right.

DR. ROSS: Apart from ocular, yeah.

DR. TILTON: Yes. But there's not a lot of -- there's no evidence for dermal irritation or sensitization, so I wasn't that concerned about ocular. But we previously had the discussion, yeah, about the overlap between consumption of fruit and seed.

DR. COHEN: (Inaudible) uses?

MS. BURNETT: Of the husk, I don't believe so.

DR. COHEN: So I mean, method of manufacturing for husk is, according to the dictionaries, obtained from drying and grinding the husks. Isn't the husk the fruit and the seed ground together after they press it out for oil? I thought that was from the fruit.

MS. BURNETT: So, the generic definition of what a husk is, is the dry outer covering of a fruit or seed.

DR. COHEN: Yeah.

DR. BERGFELD: Covering.

DR. COHEN: Yeah, it's the olive skin.

DR. ANSELL: Yes. It doesn't have a nut, right?

DR. COHEN: It's a fruit with nut in the center, so the husk is just -- is the skin around it. So I thought, technically, it would be covered. Like, you can't clear the fruit because they don't skin the fruit. And you eat the fruit with the skin on it. And the husk, I thought was after they sort of process it for other items.

MS. BURNETT: So the husk could either envelop both the seed and the fruit together. Or it is the layer between the fruit and the seed. But I don't know what this case is.

DR. COHEN: Either way it's the fruit. Either way it's still the -- you can't have the fruit without the husk.

MS. BURNETT: Okay. It's different for these botanicals because I'm thinking of like a tomatillo. You've got the dry skin husk over the fruit, and then the seeds are inside.

DR. COHEN: Right. Or coconut or something.

MS. BURNETT: You know, olives, I've seen olives on a tray before. The fruit is exposed. It doesn't have a husk because it's skin. So, where is that husk, I have no idea.

DR. TILTON: It's not defined in here.

MS. BURNETT: Right. It's very generic, have no clue. In my interpretation, it was the covering around the seed. But that's is my --

DR. COHEN: Even if it is. Even if it is, it's still covered. But I might be a hero for nothing because there's no uses that we would find, right.

MS. BURNETT: Right.

DR. COHEN: So, I guess the olive husk manufacturers will --

DR. BERGFELD: I wrote down no constituents either.

DR. COHEN: Huh?

MS. BURNETT: No impurities or constituents.

DR. COHEN: Okay. So are we going to -- so we'll stick with fruit, leaf and seed?

DR. ROSS: Seed powder, right?

DR. BERGFELD: Seed powder.

DR. COHEN: Right. Let me just go back and make sure I'm clear.

DR. TILTON: Leaf extract, fruit extract, seed powder.

DR. COHEN: Give me that again.

DR. ROSS: Fruit extract. And we're still -- I was still talking about leaf extract, but Susan is okay with that one and then seed powder. Correct?

DR. TILTON: Um-hmm.

DR. COHEN: Wait, so are all the fruit items cleared? All the fruit items are cleared, right?

DR. ROSS: I think so. We had ocular of the skin, irritation, sensitization.

DR. COHEN: And then for leaf, leaf extract, powder and water, I thought we were going to clear all of those. Hold on.

DR. TILTON: I was thinking it'd be grouped.

DR. COHEN: If you look at the method of manufacturing, it seems like those can be grouped. I want to get as many as I could grouped together from -- that's where I brought the husk in. Because I thought method of manufacturing would allow us to draw those in.

MS. BURNETT: So seed should technically be covered too.

DR. COHEN: Yeah.

MS. BURNETT: And the powder since you're just grinding up the seed.

DR. COHEN: Right. The powder is from the seed.

DR. ROSS: So if you are grouping, that includes -- that covers the hydrolyzed versions, too, correct? If you're doing all the fruits and all the leaves.

DR. COHEN: Yeah. Team, any reason not to do that?

DR. ROSS: So the seed is covered with the fruit.

DR. COHEN: Say that -- yeah.

DR. ROSS: The seed is covered with the fruit.

DR. BERGFELD: Unless we have the seed powder. It has the studies, and you grind up the seed to get the powder?

DR. COHEN: Right. And we have sensitization and irritation on seed powder. Because this has got the seed and the fruit has the seed in it too.

DR. ROSS: You're not eating the seed. You're not eating the seed.

DR. COHEN: No.

DR. ROSS: Unless you make a mistake.

DR. COHEN: That happens every now and again.

DR. ROSS: But that was my only hangup with the seed. It's not as opposed to fruit. It's not something you are regularly chewing on.

DR. COHEN: And that's because you don't have tox on it?

DR. ROSS: Well, there's nothing.

DR. COHEN: We have irritation and sensitization, but we don't have --

DR. ROSS: Yeah, that was my sense of it.

DR. COHEN: Tom, do you have any comments on the seed, seed powder?

DR. SLAGA: On the seed?

DR. COHEN: Yes.

DR. SLAGA: There's very little data, so I have it as insufficient.

DR. ROSS: I'd agree. I mean, if you were eating it like the fruit, it would be just fine. But we're not.

DR. COHEN: Yes. I guess -- we don't have dermal tox on it.

DR. ROSS: I mean, the seed powder you've got additional human data, so I think that's good.

DR. COHEN: You're talking about irritation and sensitization?

DR. ROSS: Yeah.

DR. COHEN: Well the seed powder is derived from the seed.

DR. ROSS: The seed. Yeah.

DR. COHEN: Right. So, what are you caught up on? Are you caught up on the fact that we have no other toxicology about what's in that seed?

DR. ROSS: Correct.

DR. COHEN: So we're saying no to seed? Let's just make sure we're good.

DR. ROSS: Yeah, let's read it again.

DR. COHEN: Because it's --

DR. ROSS: Yeah, olive seed, methanol and ethanol water extracts, cinnamids, flavonoids, fatty acids and terpenes, which is -- it's what you predicted.

DR. COHEN: And it's a hydroxytyrosol. It says it's the main bioactive ingredient, right?

DR. ROSS: Hydroxytyrosol. Yeah.

DR. COHEN: And the seed.

DR. ROSS: Yeah.

DR. COHEN: Which is in the oil, too, right? Because I could see you could buy it as a supplement.

MS. BURNETT: It's in the leaf extract.

DR. COHEN: Susan, you didn't get caught up in it before, right. with the seed?

DR. TILTON: in the prior discussion you mean?

DR. COHEN: In your conclusion before. What are you thinking?

DR. ROSS: Well, as Tom said, there's very little data on the seed. However seed powder, you've got the human data. It did say correctly that seed powder is derived from the seed. It's one of these process things. But you've got very little toxicology data. It's not eaten as a food. Not that I know anyway.

DR. TILTON: Yeah, I had grouped it with the fruit and that may not be correct. Because as we said, we wouldn't be consuming it with the fruit.

DR. BERGFELD: Are we considering all the extracts of hydrolyzed of the leaf and the fruit?

DR. COHEN: Yes.

DR. BERGFELD: Because there's a bunch of those. So, the things that we don't really have good data on, a bark, and branch, and bud and husk --

DR. COHEN: Right.

DR. BERGFELD: -- and the seed and wood.

DR. COHEN: Those are not going through.

DR. BERGFELD: Those are not going through?

DR. COHEN: It's the seed.

DR. TILTON: Bark, branch, bud, flower, husk, sap and wood.

DR. COHEN: The husk.

DR. TILTON: And maybe husk.

DR. COHEN: Do we have seed powder use? No concentration of use. I guess the question is, how reliable do we lean on the composition and impurities if we have -- because if you look at that composition and impurities of the seed, there's nothing in there that really makes you worry too much. But we haven't leaned on that for other chemicals. It's like, oh, we know what's in there so it's okay.

DR. ROSS: Yeah, but the absolute amounts.

DR. COHEN: But there have been times when we've looked at -- what was that? I don't remember what sea creatures they were. But it was basically we looked at the composition and impurities and said there's nothing in here that's sensitizing, even though we had no sensitization data.

DR. HELDRETH: Typically, we look at botanicals and we say, okay, we have or don't have tox data on the whole mixture to support the safety there. And then we only look at constituents for things of concern. Is there too much linalool in there? Is there too much of some other sensitizer or something in there?

And that's when we usually go after, does anything here in the constituents give us pause? Instead of the other way of we have safety confirmation on all of the components, and does it add up to a safe botanical.

DR. COHEN: In those cases, though, we're using this formulated to be non-sensitizing as our escape valve, right, for that?

DR. HELDRETH: Only if there is a constituent concern.

DR. COHEN: Right.

DR. HELDRETH: You know, we have botanicals that don't have the caveat.

DR. COHEN: But this one we have sensitization data on -- and irritation data. But the question that David brings up, that I think is reasonable, is there any other toxicology issue with the seed other than sensitization and irritation? Is that fair?

DR. ROSS: Well, it just doesn't seem to be covered. Like, we don't seem to have that data, and it's not eaten as a food.

DR. COHEN: Yeah. That's right, it's not -- there's the beginning and the end and nothing in the middle.

DR. ROSS: It's a British (inaudible).

MS. BURNETT: So, back to the olive husk issue. Just a quick Google search says the olive husk is the solid residual obtained after olive oil extraction. So, it's like the skin and the seeds and whatever fragments --

DR. COHEN: So, the waste?

MS. BURNETT: Yes. And in this case it's the powder so they dried it out.

DR. COHEN: That's why I want it included because it's covered.

DR. ROSS: So give me that again, your definition.

MS. BURNETT: The husk, when they produce olive oil and they smash the olives and get all the oil out. It's leftover skin, pulp, seed, seed fragments. That's what the olive husk is -- according to Google. I'm looking at a --

DR. COHEN: What is that?

MS. BURNETT: Oh, this is a paper.

DR. COHEN: Is that a peer reviewed?

MS. BURNETT: It's from a journal, yeah. Journal of Critical Reviews. I have not heard of that one before.

DR. COHEN: I actually heard of that.

MS. BURNETT: It's by some Algerian scientist. But other returns on Google showed it's called -- the alternative name is olive pomace.

DR. BERGFELD: But we don't have oil to look at.

MS. BURNETT: Right. We've already reviewed olive oil, so --

DR. BERGFELD: So, it's okay?

MS. BURNETT: Yeah.

DR. BERGFELD: Okay.

MS. BURNETT: That was under the fatty acid plant derived.

DR. BERGFELD: Thank you.

MS. BURNETT: So you've already reviewed olive oil, and that was safe as used.

DR. ROSS: I think this is the only remaining issue. You cleared the leaf extract on ocular based on its --

DR. COHEN: Irritation and sensation. High concentration.

DR. ROSS: High concentration, that's okay. So this is the only thing that worries me.

DR. COHEN: So, we can have this as part of the discussion tomorrow, right? I can introduce -- I think this is mine -- fruit, leaf and husk, and then indicate that we'd like to have a conversation about the seed.

It's not a boxing match, right? I mean, we want their input on it.

DR. ROSS: And I mean you do have -- you have an irritation and sensitization data.

DR. COHEN: We have skin stuff on this. We just don't have other tox stuff on this.

DR. ROSS: And maybe you don't need it.

DR. COHEN: Is it okay to do it that way.

DR. HELDRETH: Sure. So, we have local effects, we just don't have systemic.

DR. COHEN: Right. Okay.

DR. BERGFELD: Are you considering flower and bud together?

DR. COHEN: Flower and bud, we didn't clear that, right?

DR. BERGFELD: No. But you're putting it in the insufficient area?

DR. COHEN: So, what I'm going to present tomorrow for brevity, is what we've approved. And maintain the insufficiencies from before that aren't those that are cleared. Is that okay?

DR. TILTON: Yes, I agree with that.

DR. COHEN: Because we can't spend the kind time on --

DR. BERGFELD: Are you clearing a fruit, husk and leaf with a description of husk?

DR. COHEN: Fruit, leaf and husk? We'll talk about husk. And then I'll ask the Belsito team that we'd like to go with that motion. And then, we'd like to have a discussion about seed, which I can amend my motion afterwards if there's a good discussion.

DR. TILTON: I mean, husk include seed, too.

MS. BURNETT: It's all the fragments. So I assume when they make olive oil, they run through a big press, the whole fruit.

DR. COHEN: So we'll come out with fruit and leaf and then we'll talk about seed and husk. That's a good point.

DR. ROSS: And if one includes the other then bingo. Yes. You've got the way forward.

DR. BERGFELD: Well you still have -- you've got the bark, and the branch, and the wood, and the sap.

DR. COHEN: We're leaving that behind.

DR. BERGFELD: I know.

MS. BURNETT: Flowers.

DR. COHEN: And the flowers. Yeah, I'm just going to talk about the pertinent positives that we passed and keep the remainder in the insufficiencies as it is. Otherwise, we'll spend three or four minutes just reading off these things. And you feel comfortable with it?

DR. TILTON: Oh, yeah. They were already listed as insufficiencies before.

DR. COHEN: Yeah, we're maintaining the insufficiencies.

MS. BURNETT: And there were no other discussion points for the report?

DR. BERGFELD: Well, it's going to be a discussion for the husk and what it contains.

MS. BURNETT: Right.

DR. BERGFELD: And maybe the olive oil document that's been included just before.

DR. ROSS: A few weeks ago I just used an olive press in Greece and I didn't think to define the constituents.

DR. COHEN: Did you crack any of the seeds?

DR. ROSS: I don't recall. I just press it down.

DR. COHEN: Because the seeds do get in there and get cracked up.

Full Panel Meeting – June 13, 2023

DR. COHEN: This is a draft tentative report on the safety of Olive. At the December meeting, the Panel issued an IDA with data needs including method of manufacturing, composition and impurities, 28-day dermal tox on a number of the constituents, dermal irritation and sensitization for the Olive Fruit, Fruit Extract and Olive Leaf and several others in ocular irritation. Christina provided a table for us that made it easier to adjudicate what we had received.

Our motion, and then I'd like to have further discussion, is for safe as used for the fruit and leaf-derived ingredients. I'll stop there for that motion, and then we can have a discussion about seed and husk.

DR. BERGFELD: Is there a second on that?

DR. BELSITO: We're okay with fruit and leaf. And since you asked about seed, we're also okay with seed.

DR. COHEN: Can we go into a discussion about it?

DR. BERGFELD: Yes.

DR. COHEN: So, you know, we have irritation and sensitization on the seed. I don't think we have any other tox data on the seed. We have composition, but nothing else really. So, we were going back and forth on this. We had it originally in, and then we kind of pulled it down. So, can you just walk us through that?

DR. BELSITO: Because the composition data didn't raise any flags.

DR. COHEN: What about husk?

DR. BELSITO: Husk, we didn't.

DR. COHEN: Why? I mean, husk is sort of the --

DR. BELSITO: Skin.

DR. COHEN: The skin, and we found a reference it's sort of the remainder of the flesh and the seed after the oil is extracted. It seem like if we were going to clear seed, then we could clear husk.

DR. BELSITO: Paul, I think you were the one who -- are you okay with husk?

DR. SNYDER: I'm looking at the composition data here, so --

DR. COHEN: And method of manufacturing, it might help.

DR. SNYDER: Yeah, I'm fine with it.

DR. BELSITO: And I was fine with it, but other members of our -- Curt, Allan, you're okay with husk?

DR. KLAASSEN: Yes, I am.

DR. COHEN: So, our team -- I just wanted to go through that again with our concern about the seed.

DR. ROSS: Support your tox, Curt, the seed, you thought that was okay on the oral tox and the rest of the tox? Because, I mean, it's not something we normally eat, right?

DR. COHEN: We don't have that tox, right?

DR. SNYDER: I didn't ping it, so I'm going to go back and look. So my notes, I don't have it pinged as issue for tox, so.

DR. ROSS: We went backwards and forward on this.

DR. COHEN: Yeah. I don't think there was any oral tox data.

DR. TILTON: There isn't, but we had originally included it, or I had, again, because of the composition and just not having very many concerns about it.

DR. COHEN: Right. We both had that.

DR. TILTON: Which seems to be the same conclusion that they came to.

DR. COHEN: Right. But we just really wanted to have a full group discussion about that, because we don't eat the seed and we're relying on simply composition and impurities on that.

DR. SNYDER: What's the max concentration of the Powder and Seed Powder?

DR. BELSITO: It's not used.

MS. BURNETT: Unknown. There was no reported use concentration for the Seed Powder. It has six uses, but the survey didn't provide a concentration piece.

DR. COHEN: We have two leave-ons, four wash offs, possible inhalation.

DR. BELSITO: And we felt that between the composition and impurities there was nothing that raised a flag for us that would necessitate additional data.

DR. BERGFELD: That could put in the discussion?

DR. SLAGA: We thought the absorption probably would be minimal also.

DR. ROSS: We got irritation and sensitization.

DR. COHEN: We have it.

DR. BELSITO: Yeah.

DR. COHEN: Yeah, we have that.

DR. SLAGA: Yeah, there is a little dermal irritation data in humans.

DR. SNYDER: Yeah, I still thought the seed is fine.

DR. COHEN: David?

DR. ROSS: Yeah, I mean, we can probably go with that.

DR. COHEN: Okay.

DR. BERGFELD: So, right now you got fruit, and you have seed, and you have leaf --

DR. COHEN: Fruit.

DR. BERGFELD: -- and husk.

DR. COHEN: Fruit -- yeah. Yeah.

DR. BELSITO: And husk, yeah.

DR. SNYDER: Fruit, leaf, seed and husk.

DR. COHEN: Fruit, leaf, seed, and husk.

DR. BELSITO: Everything else is insufficient for the original request.

DR. COHEN: Exactly.

DR. BERGFELD: This was Dr. Cohen's motion, and it's been seconded by Dr. Belsito's team. So we have four of the various fruit parts that have been approved as safe. And the remainder not, with the same needs that have been reiterated in the earlier insufficient document.

All right, I'm going to call the question; there's no further discussion. All those in favor of safe for different parts of the plant? Anyone disapproving? I didn't see what Tom did, did he approve? Unanimous then.

Okay. All right. Very nice discussion.

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

Status: Draft Final Report for Panel Review
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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., and the Senior Director is Monice Fiume. This safety assessment was prepared by Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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
EPA = Environmental Protection Agency
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
IC₅₀ = half-maximal inhibitory concentration
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*

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 23 *Olea europaea* (olive)-derived ingredients, most of which are reported to function as skin-conditioning agents in cosmetic products. Industry should minimize impurities that could be present in cosmetic formulations, such as heavy metals and pesticide residues, according to limits set by the US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA). The Panel reviewed all relevant data and concluded that 16 *Olea europaea* (olive)-derived ingredients (i.e., the fruit-, leaf-, husk-, and seed-derived ingredients) are safe in cosmetics in the present practices of use and concentration described in this safety assessment. Additionally, the Panel also concluded that the available data are insufficient to make a determination of safety for the remaining 7 *Olea europaea* (olive)-derived ingredients under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This assessment reviews the safety of the following 23 *Olea europaea* (olive)-derived ingredients as used in cosmetic formulations:

Hydrolyzed Olive Fruit	Olea Europaea (Olive) Fruit Unsaponifiables
Hydrolyzed Olive Fruit Extract	Olea Europaea (Olive) Fruit Water
Hydrolyzed Olive Leaf Extract	Olea Europaea (Olive) Husk Powder
Olea Europaea (Olive) Bark Extract	Olea Europaea (Olive) Leaf
Olea Europaea (Olive) Branch Extract	Olea Europaea (Olive) Leaf Extract
Olea Europaea (Olive) Bud Extract	Olea Europaea (Olive) Leaf Powder
Olea Europaea (Olive) Flower Extract	Olea Europaea (Olive) Leaf Water
Olea Europaea (Olive) Flower Water	Olea Europaea (Olive) Sap Extract
Olea Europaea (Olive) Fruit	Olea Europaea (Olive) Seed
Olea Europaea (Olive) Fruit Extract	Olea Europaea (Olive) Seed Powder
Olea Europaea (Olive) Fruit Juice	Olea Europaea (Olive) Wood Extract
Olea Europaea (Olive) Fruit Juice 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 considered a drug effect in the United States (US) and, therefore, is not addressed in this assessment as it 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 extensive search of the world's literature, last performed April 2023. 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 25° 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. For the general methodologies of processing *Olea europaea* (olive)-derived ingredients described below, it is unknown if these methodologies apply to cosmetic ingredient manufacturing. In several cases, the definition of the ingredients, as given in the *Dictionary*, provides insight as to the method of manufacture.

Olea Europaea (Olive) Flower Water

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

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

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

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

Olive husk may also be called olive pomace or olive cake.¹³ Olive husk is the solid residue obtained after olive oil extraction. It consists of the crushed hull, the skin, and the pulp of the olive, as well as some oil and water.

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 glycol solution.¹⁴ 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.¹⁵

Another supplier reported that *Olea Europaea* (Olive) Leaf Extract is produced by extracting dried raw olive leaves with 50 vol% ethanol solution and concentrating.¹⁴ The resulting material is then dissolved in 50 vol% 1,3-butylene glycol 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.¹⁶ The resulting material was then microwaved with distilled water, vacuum-filtered, and lyophilized.

Olea Europaea (Olive) Leaf Powder

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).¹⁷

Olea Europaea (Olive) Leaf Water

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.¹⁵

Olea Europaea (Olive) Seed Powder

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.^{18,19} Composition may also vary with use of fresh versus dried raw materials.²⁰ Oleuropein is the main phenolic component of the unprocessed fruit and leaves of *Olea europaea* L.¹⁸ 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.²¹

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 ppm copper, 0.03 ppm lead, and below the threshold of detection for zinc.²² From phytochemical analysis, the primary constituents of the powdered bark were reported as 36.01% total proteins, 0.82% total lipids, and 43.68% total carbohydrates. The yield of secondary constituents, 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.²³ 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.²⁴ 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.²⁵ 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.²⁶ 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.²⁷ 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 ripens.²⁸ 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.²⁹

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).³⁰ 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 5.³¹ 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.³² 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.³³

Ethanol:water extracts (80:20) of olive fruit were analyzed for hydroxycinnamic acids and flavonoids.³⁴ Measured values of hydroxycinnamic acids included trace amounts of ferulic acid and *p*-coumaric acid, trace to 1.0 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.³⁵ 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) Husk Powder

Raw olive husk contains the crushed hull of the fruit, skin, pulp, water (~25%) and residual oil (4.5 - 9%).¹³ *Cis*-Oleic acid is the most abundant fatty acid. Olive husk contains small amounts of nitrogen (crude protein) and a high proportion of fiber, consisting of 10% hemicellulose, 15% cellulose, and 27% lignin. Additional constituents include soluble phenols, calcium, magnesium, potassium, sodium, and iron. Lead, cadmium, chromium, and mercury content is reported to be below 1 mg/kg.

Olea Europaea (Olive) Juice Extract

A supplier reported that *Olea Europaea* (Olive) Juice Extract is comprised of saccharides and tannin.¹⁴ 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.²⁸

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.^{32,36} 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,³² while the oleuropein content from a microwave assisted aqueous extract was 11.59 mg/g (dry base),¹⁶ and an ultrasound-assisted extraction of olive leaves produced 13.39 mg/g oleuropein.³⁷

Constituent levels in olive leaves by extract type, cultivar, and production area are described in Table 6.^{3,38} 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.³⁹

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.⁴⁰ 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.⁴¹

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.³⁵ 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%.³³

An aqueous extract of olive leaves was determined to have the following soluble carbohydrates: myo-inositol, mannitol, galactose, glucose, fructose, sucrose, raffinose, and stachyose.⁴² 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.¹⁴ 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.¹⁷ No further details provided.

Olea Europaea (Olive) Sap Extract

Constituents of olive sap include terpenoids, phytohormones, alkaloids, sterols/steroids, retinols/retinoids, tocopherols, and carotenoids.¹⁹

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.⁴³ The main bioactive component of olive seeds has been identified as hydroxytyrosol.⁴⁴

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.⁴⁵ 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).⁴⁶

USE **Cosmetic**

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US 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 2023 VCRP survey data, *Olea Europaea* (Olive) Leaf Extract has the highest frequency of use; it is reported to be used in 170 formulations, with a majority of uses in leave-on skin care preparations (Table 7).⁴⁷ *Olea Europaea* (Olive) Fruit Extract is reported to be used in 124 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 surveys conducted by the Council in 2020 and 2023 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.^{48,49} 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. The 14 ingredients not in use, according to the VCRP and industry survey, are listed in Table 8.⁴⁷⁻⁴⁹

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%).^{47,48} 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 at 0.0002% in aerosol deodorant and *Olea Europaea* (Olive) Fruit Extract is used in face powders (no concentration reported).^{47,48} 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. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. 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.⁵⁰

Non-Cosmetic

Different parts of the olive tree have been used for centuries for nutritional properties and protective health effects.⁴³ 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.^{18,51,52} Leaves, fruit, and their constituents have been studied for health benefits such as antioxidant,^{18,27,36,53} antimicrobial,^{36,54-56} (including anti-malarial),⁵⁷ anti-inflammatory,^{18,27,35,58,59} antiviral (including anti-HIV activity),⁶⁰ cardioprotective,^{18,61} hepatoprotective,⁶² neuroprotective^{18,63,64}, and anti-cancer effects^{18,65} Olive leaves, extracts, and constituents have also been studied as potential treatments for diabetes (types 1 and 2),⁶⁶⁻⁶⁸ hypertension,^{69,70} and for protective effects against oxidative stress on kidneys and liver.⁷¹ Additional therapeutic uses for olive leaf and olive fruit have been studied for the treatment of wounds,⁷² intestinal morphological injuries,²⁷ and multiple sclerosis and other neurodegenerative diseases.³⁶ Olive drupes (fruit, pit and seed) have been studied for treating gastric disturbances,⁴⁴ reducing blood sugar, cholesterol, and uric acid,⁴³ and for protective effects on the tissues and functions of the liver, kidneys, and heart.^{43,73} Olive pits (including the seed) have been used in folk medicine to treat gastric disturbances.⁴⁴ Olive bark and wood have been studied for antioxidant,^{23,74} antidiabetic and anticancer activity,²² as well as antimicrobial activity^{23,24} (including anti-malarial).⁷⁵

Olive leaves and fruit extracts have been studied for use in natural food preservation and packaging.^{16,33,76,77} 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.⁷⁸

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 9. In mouse studies of olive stem bark extract, an aqueous hydrolyzed olive pulp (fruit) extract, and olive leaf extracts, the LD₅₀ was greater than 2000 mg/kg, which was the maximum dose tested for each ingredient.^{14,57,75,79} In rat studies, an aqueous hydrolyzed olive pulp (fruit) extract had an LD₅₀ greater than 5000 mg/kg, and olive leaf extract had an LD₅₀ greater than 2000 mg/kg.^{79,80}

Short-Term and Subchronic Toxicity Studies

Repeated-dose oral toxicity studies on *Olea europaea* (olive)-derived ingredients are summarized in Table 10. 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.^{79,81} 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 (0, 360, 600, 1000, 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.⁸² 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.⁸⁰ In a 42-d rat study with dietary concentrations of 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 dose of 1000 mg/kg bw/d for a proprietary olive leaf extract.⁸²

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

DART studies on *Olea europaea* (olive)-derived ingredients are summarized in Table 11. 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).⁸³ Hydrolyzed olive pulp (fruit) extract (aqueous; up to 2000 mg/kg/d) produced no treatment-related mortalities in F₀ mature male and female rats (treated 14 d before cohabitation until day before necropsy) or F₁ rat pups (including 2 pups/sex/litter that received treatment for 1 wk post-weaning), and produced no adverse effects in fertility or reproduction.⁷⁹ 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.^{11,79}

GENOTOXICITY STUDIES

In vitro and in vivo genotoxicity studies on *Olea europaea* (olive)-derived ingredients are summarized in Table 12. 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.⁷⁹ 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.⁸² 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.⁸⁴ A proprietary olive leaf extract was not genotoxic in an in vivo micronucleus assay (tested up to 200 mg/ml) in mice.⁸²

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.⁸⁵ 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).³⁶ 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 STUDIES

Dermal irritation and sensitization data for the *Olea europaea* (olive)-derived ingredients are summarized in Table 13. *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.¹⁴ An aqueous solution composed of 2.2% *Olea Europaea* (Olive) Fruit Extract was not irritating to rabbits when tested neat.⁸⁶ In further studies in rabbits, *Olea Europaea* (Olive) Leaf Extract was not a dermal irritant in primary or cumulative skin irritation tests when tested at up to 100%.¹⁴ 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.^{87,88} No irritation was observed in human dermal irritation studies of formulations containing 0.047% (n = 52)⁸⁹ or 1% *Olea Europaea* (Olive) Leaf Extract (n = 20; 22),^{90,91} or in a study with 100% *Olea Europaea* (Olive) Leaf Extract (n = 46).¹⁴ 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.⁹² 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.⁹³

An aqueous solution composed of 2.2% *Olea Europaea* (Olive) Fruit Extract was not sensitizing in a guinea maximization study when tested neat.⁸⁶ In another 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.¹⁴ In a human repeated-insult patch test (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.⁹⁴ 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).^{14,95,96} In an HRIPT with semi-occlusive patches, a product containing 25% *Olea Europaea* (Olive) Seed Powder was not a dermal sensitizer in 54 subjects.⁹⁷ 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.^{98,99}

OCULAR IRRITATION STUDIES**In Vitro****Olea Europaea (Olive) Fruit Extract**

In a neutral red release assay, an aqueous solution composed of 2.2% *Olea Europaea* (Olive) Fruit Extract was diluted in 0.9% sodium chloride to obtain the test concentrations of the solution of 5, 15, 25, 35, and 50% (i.e., test concentrations of the extract were 0.11, 0.33, 0.55, 0.77, and 1.1%, respectively).⁸⁶ The test concentrations of the solution were then analyzed through direct application on a monolayer of rabbit cornea fibroblasts. The half-maximal inhibitory concentration (IC₅₀) of the test material was higher than 50%. The percent mortality observed at the dilution of 50% was 10%. The cytotoxicity of the test material was thus negligible. No further details were provided.

Animal

Olea Europaea (Olive) Fruit Extract

The ocular irritation potential of an aqueous solution composed of 2.2% *Olea Europaea* (Olive) Fruit Extract was assessed in an acute eye irritation/corrosion test in rabbits in accordance with OECD TG 405.⁸⁶ A dose of 0.1 ml of the test material was applied neat. The test material was not irritating to rabbit eyes. No further details were provided.

CLINICAL STUDIES

Case Reports

Anaphylaxis was reported in a 21-yr-old woman with a history of allergic rhinitis and asthma following consumption of olives on 3 separate occasions.¹⁰⁰ 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 mm² 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.

In another case report of anaphylaxis, a 19-yr-old woman with a history of childhood atopic dermatitis, persistent mild rhinoconjunctivitis, and intermittent asthma presented with oral itching, generalized urticaria, lip and eyelid edema, dyspnea, sweating, and dizziness with emetic episode 30 min following ingestion of an olive in brine.¹⁰¹ The patient tolerated spices, garlic, olive oil, and there were no associated co-factors such as medication, alcohol, or exercise. Skin prick tests with an allergen battery were positive for dust mites, cat and dog dander, *Olea europaea* pollen, and grass pollen. Prick-by-prick tests with spices and garlic were negative, but were positive for olive fruit, both fresh and in brine (9 and 8 mm wheals, respectively). An open oral challenge with olive oil had negative results. IgE binding analysis detected reactive proteins (a thaumatin-like protein (Ole e 13) and a storage protein (conarchin-like protein)) as the probable allergens.

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.¹⁰² 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.¹⁰³ Two groups received commercial olive leaf extract as a liquid (5 ml) or as a capsule. Concentrations 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-blind. 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'-deoxyguanosine. 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.¹⁰⁴ 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 were 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 a cosmetic function in the US and, therefore, is not addressed in this assessment.

Olea europaea L. is an evergreen tree or shrub native to the Mediterranean region 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 2023 VCRP survey data, *Olea Europaea* (Olive) Leaf Extract is reported to be used in 170 formulations, with a majority of uses in leave-on skin care preparations. *Olea Europaea* (Olive) Fruit Extract is reported to be used in 124 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. Fourteen 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 LD₅₀ 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 LD₅₀ greater than 5000 mg/kg, and olive leaf extract had an LD₅₀ 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 F₀ mature male and female rats (treated 14 d before cohabitation until day before necropsy) or F₁ rat pups (including 2 pups/sex/litter that received treatment for 1 wk post-weaning), 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. An aqueous solution composed of 2.2% *Olea Europaea* (Olive) Fruit Extract was not irritating to rabbits when tested neat. In further 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 formulations containing 0.047% (n = 52) or 1% *Olea Europaea* (Olive) Leaf Extract (n = 20; 22), or in a study with 100% *Olea Europaea* (Olive) Leaf Extract (n = 46). 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 a 1-wk clinical use test of a bar soap containing 1% *Olea Europaea* (Olive) Seed Powder. An aqueous solution composed of 2.2% *Olea Europaea* (Olive) Fruit Extract was not

sensitizing in a guinea maximization study when tested neat. In another 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 an 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 no 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.

An aqueous solution composed of 2.2% *Olea Europaea* (Olive) Fruit Extract was diluted in 0.9% sodium chloride to obtain test concentrations (of the solution) of up to 50% for use in an in vitro ocular neutral red release assay. The IC_{50} of the test material was higher than 50%. The aqueous solution composed of 2.2% *Olea Europaea* (Olive) Fruit Extract was also not irritating to rabbit eyes when tested neat.

Anaphylaxis has been reported in patients 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 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

The Panel reviewed the safety of 23 ingredients derived from *Olea europaea* (olive), most of which are reported to function as skin conditioning agents in cosmetic products. The Panel concluded that the available data are sufficient for determining the safety of 16 ingredients, i.e., those derived from the fruit, husk, leaf, and seed, for use in cosmetic products. The Panel noted that the fruit and leaves are consumed as foods and health supplements; composition and other data on the husk and seed denote similarities to both the fruit and the leaf. This information, and the likelihood that these ingredients do not readily absorb, obviate the need for additional toxicological data.

The *Dictionary* indicates that skin bleaching agent is a reported function of extracts of the fruit and leaves of *Olea europaea*; however, no data have been discovered that support or disprove this potential effect. The Panel noted that skin lightening is considered a drug effect in the US, and should not occur during the use of cosmetic products.

The Panel also expressed concern about heavy metals, pesticide residues, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to minimize impurities in cosmetic formulations according to limits set by the US FDA and EPA.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., *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)). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <https://www.cir-safety.org/cir-findings>.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

The Panel also concluded that the data are insufficient for determining safety of the remaining 7 *Olea europaea* (olive)-derived ingredients. For these ingredients, the Panel felt that there may be differences in the methods of manufacturing, composition and impurities, and other data points, as compared to the ingredients that had sufficient data; thus, it was unclear if inferences from the fruit, leaf, husk, and seed could be applied to the bark, branch, bud, flower, sap, and wood ingredients. Accordingly, the additional data needed to determine the safety of these ingredients in cosmetics are:

- Method of manufacture for *Olea Europaea* (Olive) Bark Extract, *Olea Europaea* (Olive) Branch Extract, *Olea Europaea* (Olive) Bud Extract, *Olea Europaea* (Olive) Flower Extract, *Olea Europaea* (Olive) Sap Extract, and *Olea Europaea* (Olive) Wood Extract

- Composition and impurities data for *Olea Europaea* (Olive) Branch Extract and *Olea Europaea* (Olive) Flower Water
- 28-day dermal toxicity data for *Olea Europaea* (Olive) Bark Extract, *Olea Europaea* (Olive) Branch Extract, *Olea Europaea* (Olive) Bud Extract, *Olea Europaea* (Olive) Flower Extract, *Olea Europaea* (Olive) Sap Extract, and *Olea Europaea* (Olive) Wood Extract
 - If positive, additional data (e.g., DART and genotoxicity data) may be needed
- Dermal irritation and sensitization data for *Olea Europaea* (Olive) Bark Extract, *Olea Europaea* (Olive) Branch Extract, *Olea Europaea* (Olive) Bud Extract, *Olea Europaea* (Olive) Flower Extract, *Olea Europaea* (Olive) Sap Extract, and *Olea Europaea* (Olive) Wood Extract

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 16 *Olea europaea* (olive)-derived ingredients are safe in cosmetics in the present practice of use and concentration described in this safety assessment:

Hydrolyzed Olive Fruit*	<i>Olea Europaea</i> (Olive) Fruit Water*
Hydrolyzed Olive Fruit Extract*	<i>Olea Europaea</i> (Olive) Husk Powder*
Hydrolyzed Olive Leaf Extract*	<i>Olea Europaea</i> (Olive) Leaf*
<i>Olea Europaea</i> (Olive) Fruit	<i>Olea Europaea</i> (Olive) Leaf Extract
<i>Olea Europaea</i> (Olive) Fruit Extract	<i>Olea Europaea</i> (Olive) Leaf Powder
<i>Olea Europaea</i> (Olive) Fruit Juice*	<i>Olea Europaea</i> (Olive) Leaf Water
<i>Olea Europaea</i> (Olive) Fruit Juice Extract*	<i>Olea Europaea</i> (Olive) Seed*
<i>Olea Europaea</i> (Olive) Fruit Unsaponifiables	<i>Olea Europaea</i> (Olive) Seed Powder

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

Additionally, the Panel also concluded that the available data are insufficient to make a determination of safety for the following 7 *Olea europaea* (olive)-derived ingredients under the intended conditions of use in cosmetic formulations:

<i>Olea Europaea</i> (Olive) Bark Extract**	<i>Olea Europaea</i> (Olive) Flower Water**
<i>Olea Europaea</i> (Olive) Branch Extract**	<i>Olea Europaea</i> (Olive) Sap Extract
<i>Olea Europaea</i> (Olive) Bud Extract	<i>Olea Europaea</i> (Olive) Wood Extract**
<i>Olea Europaea</i> (Olive) Flower Extract**	

***There are currently no uses reported for these ingredients.*

TABLES**Table 1. Definitions and reported functions of the ingredients in this safety assessment.¹**

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

Table 2. Generic plant part definitions as they apply to *Olea europaea* (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 For olives, the husk may refer to the solid residue obtained after olive oil extraction ¹³
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 °C)	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 °C)	1.00 (range 0.99 - 1.01)	10
Water Solubility	Soluble in any proportion of water	10

Table 4. Secondary constituents for powdered olive bark (mg/g).²²

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).³¹

Cultivar	total polyphenol content*	total tannin content**	<i>p</i> -hydroxy-benzoic acid	vanillic acid	caffeic acid	syringic acid	<i>p</i> -coumaric acid	ferulic acid	sinapic acid	tyrosol	hydroxy-tyrosol	verbascoside	oleuropein	luteolin	chrysoeriol
<i>Italian cultivars</i>															
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
<i>Algerian cultivars</i>															
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- <i>O</i> -glucoside	2-methoxy oleuropein	oleuropein	luteolin	verbascoside	tyrosol	4-hydroxybenzoic acid	rutin	apigenin
<i>Ethanol extracts of Italian olive cultivars³⁸</i>											
Apollo	21.31	8.17*	39.78	10.51	24.28	2.66	0.16	NR	NR	NR	NR
Ascolanaterena	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
Moraiole	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
<i>Methanolic extracts of Tunisian olive cultivars³</i>											
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 (2023) and concentration (2020/2023) of use according to likely duration and exposure and by product category⁴⁷⁻⁴⁹

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Olea Europaea (Olive) Bud Extract		Olea Europaea (Olive) Fruit		Olea Europaea (Olive) Fruit Extract ^d	
Totals*	1	NR	14	0.6	124	0.0002-0.5
summarized by likely duration and exposure**						
Duration of Use						
<i>Leave-On</i>	1	NR	9	0.6	96	0.00025-0.45
<i>Rinse-Off</i>	NR	NR	5	NR	28	0.0002-0.5
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	3	NR
Incidental Ingestion	NR	NR	NR	NR	16	0.24
Incidental Inhalation-Spray	1 ^a	NR	5 ^b	NR	2; 30 ^a ; 29 ^b	0.0008
Incidental Inhalation-Powder	NR	NR	5 ^b ; 4 ^c	NR	3; 29 ^b	0.23-0.45 ^c
Dermal Contact	1	NR	12	0.6	95	0.00025-0.5
Deodorant (underarm)	NR	NR	NR	NR	NR	0.0008-0.005
Hair - Non-Coloring	NR	NR	2	NR	13	0.0002-0.069
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	3	NR	223	0.00025-0.24
Baby Products	NR	NR	NR	NR	NR	NR
as reported by product category						
Baby Products						
Baby Shampoos						
Baby Lotions/Oils/Powders/Creams						
Other Baby Products						
Eye Makeup Preparations						
Eye Lotion					1	NR
Other Eye Makeup Preparations					2	NR
Fragrance Preparations						
Cologne and Toilet Water					1	NR
Other Fragrance Preparation					1	NR
Hair Preparations (non-coloring)						
Hair Conditioner					6	0.0002
Hair Spray (aerosol fixatives)						
Rinses (non-coloring)						
Shampoos (non-coloring)			1	NR	4	0.0098
Tonics, Dressings, and Other Hair Grooming Aids			1	NR	NR	0.069 (not spray)
Other Hair Preparations					3	NR
Makeup Preparations						
Face Powders					3	NR
Foundations						
Lipstick					16	0.24
Makeup Bases					1	NR
Other Makeup Preparations					1	NR
Manicuring Preparations (Nail)						
Other Manicuring Preparations						
Personal Cleanliness Products						
Bath Soaps and Detergents			3	NR	2	0.00025-0.11
Deodorants (underarm)					NR	0.005 (not spray) 0.0008 (aerosol)
Feminine Deodorants					1	NR
Other Personal Cleanliness Products					4	NR
Shaving Preparations						
Beard Softeners						
Shaving Cream					NR	0.5
Skin Care Preparations						
Cleansing			1	NR	11	0.01
Depilatories						
Face and Neck (exc shave)			2	NR	14	0.4-0.45 (not spray)
Body and Hand (exc shave)			2	NR	14	0.23 (not spray)
Moisturizing			4	0.6 (not spray)	28	0.00025 (not spray)
Night	1	NR			2	0.00025 (not spray)
Paste Masks (mud packs)					1	NR
Other Skin Care Preparations					8	0.01
Suntan Preparations						
Suntan Gels, Creams, and Liquids						

Table 7. Frequency (2023) and concentration (2020/2023) of use according to likely duration and exposure and by product category⁴⁷⁻⁴⁹

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Olea Europaea (Olive) Fruit Unsaponifiables		Olea Europaea (Olive) Leaf Extract		Olea Europaea (Olive) Leaf Powder	
Totals*	10	10	170	0.0002-2	1	0.1
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	10	NR	125	0.0002-2	1	0.1
Rinse-Off	NR	10	45	0.0002-0.3	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	8	NR	NR	NR
Incidental Ingestion	NR	NR	1	0.002	NR	NR
Incidental Inhalation-Spray	2 ^a ; 7 ^b	NR	42 ^a ; 53 ^b	0.018	1 ^a	NR
Incidental Inhalation-Powder	7 ^b	NR	1; 53 ^b	0.0014-0.4 ^c	NR	0.1 ^c
Dermal Contact	10	10	157	0.0002-2	1	0.1
Deodorant (underarm)	NR	NR	NR	0.095 (not spray) 0.0002 (spray)	NR	NR
Hair - Non-Coloring	NR	NR	11	0.0005-0.018	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	NR
Mucous Membrane	NR	NR	28	0.0003-0.002	NR	NR
Baby Products	NR	NR	2	0.002-0.013	NR	NR
as reported by product category						
Baby Products						
Baby Shampoos			2	0.0065		
Baby Lotions/Oils/Powders/Creams			NR	0.013		
Other Baby Products			NR	0.002		
Eye Makeup Preparations						
Eye Lotion			3	NR		
Other Eye Makeup Preparations			5	NR		
Fragrance Preparations						
Cologne and Toilet Water						
Other Fragrance Preparation						
Hair Preparations (non-coloring)						
Hair Conditioner			2	0.003-0.018		
Hair Spray (aerosol fixatives)			NR	0.018 (pump spray)		
Rinses (non-coloring)			NR	0.0005		
Shampoos (non-coloring)			3	0.001-0.018		
Tonics, Dressings, and Other Hair Grooming Aids						
Other Hair Preparations			4	NR		
Makeup Preparations						
Face Powders			1	NR		
Foundations			NR	0.1		
Lipstick			1	0.002		
Makeup Bases						
Other Makeup Preparations			1	NR		
Manicuring Preparations (Nail)						
Other Manicuring Preparations			1	NR		
Personal Cleanliness Products						
Bath Soaps and Detergents			24	0.0003		
Deodorants (underarm)			NR	0.095 (not spray) 0.0002 (aerosol)		
Feminine Deodorants						
Other Personal Cleanliness Products			3	NR		
Shaving Preparations						
Beard Softeners						
Shaving Cream	NR	10	1	NR		
Skin Care Preparations						
Cleansing			7	0.0002-0.3		
Depilatories			1	NR		
Face and Neck (exc shave)	6	NR	30	0.0014-0.4 (not spray)		
Body and Hand (exc shave)	1	NR	23	NR	NR	0.1 (not spray)
Moisturizing	2	NR	41	0.0065 (not spray)	1	NR
Night			1	0.4 (not spray)		
Paste Masks (mud packs)			3	NR		
Other Skin Care Preparations	1	NR	13	0.002		
Suntan Preparations						
Suntan Gels, Creams, and Liquids			NR	2 (not spray)		

Table 7. Frequency (2023) and concentration (2020/2023) of use according to likely duration and exposure and by product category⁴⁷⁻⁴⁹

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Olea Europaea (Olive) Leaf Water		Olea Europaea (Olive) Sap Extract		Olea Europaea (Olive) Seed Powder	
Totals*	1	NR	NR	0.005	6	NR
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	1	NR	NR	0.005	2	NR
Rinse-Off	NR	NR	NR	0.005	4	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	1 ^b	NR	NR	NR	1 ^b	NR
Incidental Inhalation-Powder	1 ^b	NR	NR	NR	1 ^b	NR
Dermal Contact	1	NR	NR	NR	6	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.005	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
as reported by product category						
Baby Products						
Baby Shampoos						
Baby Lotions/Oils/Powders/Creams						
Other Baby Products						
Eye Makeup Preparations						
Eye Lotion						
Other Eye Makeup Preparations						
Fragrance Preparations						
Cologne and Toilet Water						
Other Fragrance Preparation						
Hair Preparations (non-coloring)						
Hair Conditioner			NR	0.005		
Hair Spray (aerosol fixatives)						
Rinses (non-coloring)						
Shampoos (non-coloring)			NR	0.005		
Tonics, Dressings, and Other Hair Grooming Aids						
Other Hair Preparations			NR	0.005		
Makeup Preparations						
Face Powders						
Foundations						
Lipstick						
Makeup Bases						
Other Makeup Preparations						
Manicuring Preparations (Nail)						
Other Manicuring Preparations						
Personal Cleanliness Products						
Bath Soaps and Detergents						
Deodorants (underarm)						
Feminine Deodorants						
Other Personal Cleanliness Products						
Shaving Preparations						
Beard Softeners						
Shaving Cream						
Skin Care Preparations						
Cleansing					4	NR
Depilatories						
Face and Neck (exc shave)	1	NR				
Body and Hand (exc shave)					1	NR
Moisturizing						
Night						
Paste Masks (mud packs)						
Other Skin Care Preparations					1	NR
Suntan Preparations						
Suntan Gels, Creams, and Liquids						

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.

**Likely duration and exposure are derived based on product category (see Use Categorization <https://www.cir-safety.org/cir-findings>)^a It is possible these products are sprays, but it is not specified whether the reported uses are sprays.^b Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.^c It is possible these products are powders, but it is not specified whether the reported uses are powders.^d Includes 2 uses described as Olive Extract in the VCRP.

Table 8. Ingredients not reported to be in use, according to VCRP and Council data.⁴⁷⁻⁴⁹

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

Table 9. 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	75
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	79
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	79
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	57
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	14
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	80

Table 10. 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; no toxicologically-relevant treatment-related lesions were observed in histopathological exams	81
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; gross necropsy observations and histopathology of selected tissues (no further description) performed at study end	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	79
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, 360, 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	82
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	80

Table 10. 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	82

Table 11. 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; one control group received no test material or vehicle, another received vehicle alone; body weights 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 when compared to control groups; 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 when compared to the control groups; no significant effects observed in body, prostate, or epididymis weights or in estradiol hormone levels	83
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 recorded; 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	79
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	11,79

Table 12. 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	<i>Salmonella typhimurium</i> TA97a, TA98, TA100, TA1335 or <i>Escherichia coli</i> 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	79
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	79
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	<i>S. typhimurium</i> TA98, TA100, TA1335, TA1537 or <i>E. coli</i> 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	82
4 different olive leaf extracts from different regions of Tunisia	Up to 5000 µg/ml	Aqueous, no further details	2 <i>S. typhimurium</i> TA 104 constructs	Bacterial Vitotox™ test, with and without S9 metabolic activation	Negative in 3 extracts, with or without metabolic activation; 4 th extract had borderline genotoxicity with metabolic activation; antigenotoxic properties were not observed	84
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 4 th extract that had borderline genotoxicity in the bacterial study described above	84
olive leaf extract; proprietary product with a standardized olive polyphenol content of 40%	<u>3 h exposure</u> Without S9: 250, 500, 750, 1000, or 1250 µg/ml With S9: 250, 500, 750, or 1000 µg/ml <u>20 h exposure</u> 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 an increase in the 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	82

Table 12. 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 CrI: 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	⁷⁹
Olive leaf extract; proprietary product with a standardized olive polyphenol content of 40%	50, 100, or 200 mg/ml in dose volume of 10 ml/kg bw	sterile water	Groups of male SPF CrI: 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	⁸²

Table 13. 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	14
ANIMAL						
Aqueous solution composed of 2.2% Olea Europaea (Olive) Fruit Extract	not reported	Neat; 0.5 ml dose	rabbits; no further details provided	Acute dermal irritation/corrosion test in accordance with OECD TG 404; no further details provided	Unclassified among the chemicals irritating to skin; no further details provided	86
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	14
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	14
HUMAN						
Face cream containing 0.0005% Olea Europaea (Olive) Fruit Extract	none	As supplied	19 subjects	SIOPT	No irritation; primary irritation index = 0.0	88
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	87
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	89
Liquid lip color containing 1% Olea Europaea (Olive) Leaf Extract	none	As supplied	20 subjects	SIOPT	No irritation; primary irritation index = 0.0	90
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	91
Olea Europaea (Olive) Leaf Extract	none	100%	46 subjects	Irritation study; occlusive patch; no further details provided	No irritation; no further details provided	14
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	92
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	93
SENSITIZATION						
ANIMAL						
Aqueous solution composed of 2.2% Olea Europaea (Olive) Fruit Extract	not reported	As supplied	guinea pigs; no further details provided	Guinea pig maximization study with intradermal injection and topical application in accordance with OECD TG 406; challenge patch was applied neat; no further details provided	Not a sensitizer; no further details provided	86
Olea Europaea (Olive) Leaf Extract	not reported	25% for 1 st induction; 100% for 2 nd 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	14
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	94

Table 13. 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	⁹⁵
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	¹⁴
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	⁹⁶
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	⁹⁷
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	⁹⁸
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	⁹⁹

REFERENCES

1. Nikitakis J, Kowcz A. Web-Based International Cosmetic Ingredient Dictionary and Handbook. <https://incipedia.personalcarecouncil.org/winci/>. Washington, DC: Personal Care Products Council. Accessed 05/01/2023.
2. Burnett CL, Fiume MM, Bergfeld WF, et al. Safety Assessment of Plant-Derived Fatty Acid Oils. *Int J Toxicol*. 2017;36(Suppl):51S-129S.
3. Edziri H, Jaziri R, Chehab H, et al. A comparative study on chemical composition, antibiofilm and biological activities of leaves extracts of four Tunisian olive cultivars. *Heliyon*. 2019;5(5):e01604.
4. Omer SA, Elobeid MA, Elamin MH, et al. Toxicity of olive leaves (*Olea europaea* L.) in Wistar albino rats. *Asian J Anim Vet Adv*. 2012;7(11):1175-1182.
5. Liphshitz N, Gophna R, Hartman M, Biger G. The beginning of olive (*Olea europaea*) cultivation in the Old World: A reassessment. *J Archaeol Sci*. 1991;18(4):441-453.
6. Bracci T, Busconi M, Fogher C, Sebastiani L. Molecular studies in olive (*Olea europaea* L.): Overview on DNA markers applications and recent advances in genome analysis. *Plant Cell Rep*. 2011;30(4):449-462.
7. Hashmi MA, Khan A, Hanif M, Farooq U, Perveen S. Traditional uses, phytochemistry, and pharmacology of *Olea europaea* (olive). *Evid Based Complement Alternat Med*. 2015;2015:541591.
8. D'Angeli S, Falasca G, Matteucci M, Altamura MM. Cold perception and gene expression differ in *Olea europaea* seed coat and embryo during drupe cold acclimation. *New Phytol*. 2013;197(1):123-138.
9. Anonymous. 2022. Olea Europaea (Olive) Fruit Extract - Summary information. Unpublished data submitted by the Personal Care Products Council on September 1, 2022.
10. Anonymous. 2022. Olea Europaea (Olive) Leaf Extract - Summary information. Unpublished data submitted by the Personal Care Products Council on September 1, 2022.
11. Soni MG, Burdock GA, Christian MS, Bitler CM, Crea R. Safety assessment of aqueous olive pulp extract as an antioxidant or antimicrobial agent in foods. *Food Chem Toxicol*. 2006;44(7):903-915.
12. The Innovation Company. 2022. Olea Europaea (Olive) Fruit Extract Method of Manufacture. Unpublished data submitted by the Personal Care Products Council on August 15, 2022.
13. Medouni-Haroune L, Zaidi F, Medouni-Adrar S, Kecha M. Olive pomace: From an olive mill waste to a resource, an overview of the new treatments. *J Crit Rev*. 2018;5(6):1-6.
14. Anonymous. 2022. Summary information Olea Europaea (Olive) Fruit Juice Extract and Olea Europaea (Olive) Leaf Extract. Unpublished data submitted by the Personal Care Products Council on October 11, 2022.
15. Anonymous. 2022. Method of Manufacture - Olea Europaea (Olive) Leaf Extract and Olea Europaea (Olive) Leaf Water. Unpublished data submitted by the Personal Care Products Council on August 9, 2022.
16. Martiny TR, Raghavan V, de Moraes CC, da Rosa GS, GL D. Bio-based active packaging: Carrageenan film with olive leaf extract for lamb meat preservation. *Foods*. 2020;9(12):1759.
17. Anonymous. 2022. Method of Manufacture - Olea Europaea (Olive) Leaf Powder. Unpublished data submitted by the Personal Care Products Council on August 9, 2022.
18. Nediani C, Ruzzolini J, Romani A, Calorini L. Oleuropein, a bioactive compound from *Olea europaea* L., as a potential preventive and therapeutic agent in non-communicable diseases. *Antioxidants (Basel)*. 2019;8(12):578.
19. Sofo A, Fausto C, Mininni AN, Dichio B, Lucini L. Soil management type differentially modulates the metabolomic profile of olive xylem sap. *Plant Physiol Biochem*. 2019;139:707-714.

20. Breakspear I, Guillaume C. A quantitative phytochemical comparison of olive leaf extracts on the Australian market. *Molecules*. 2020;25(18):4099.
21. Goldsmith CD, Vuong QV, Sadeqzadeh E, Stathopoulos CE, Roach PD, Scarlett CJ. Phytochemical properties and anti-proliferative activity of *Olea europaea* L. leaf extracts against pancreatic cancer cells. *Molecules*. 2015;20(7):12992-13004.
22. Liaqat S, Islam M, Saeed H, Iqtedar M, Mehmood A. Investigation of *Olea ferruginea* Roylebark extracts for potential in vitro antidiabetic and anticancer effects. *Turk J Chem*. 2021;45(1):92-103.
23. Mehmood A, Murtaza G. Phenolic contents, antimicrobial and antioxidant activity of *Olea ferruginea* Royle (Oleaceae). *BMC Complement Altern Med*. 2018;18(1):173.
24. Cheryot KR, Olila D, Kateregga J. In-vitro antibacterial activity of selected medicinal plants from Longisa region of Bomet district, Kenya. *Afr Health Sci*. 2009;9(S1):42-46.
25. Taamalli A, Abaza L, Roman DA, et al. Characterisation of phenolic compounds by HPLC-TO/IT/MS in buds and open flowers of "Chemlali" olive cultivar. *Phytochem Anal*. 2013;24(5):504-512.
26. Rhouma HE, Trabelsi N, Chimento A, et al. *Olea europaea* L. flowers as a new promising anticancer natural product: Phenolic composition, antiproliferative activity and apoptosis induction. *Nat Prod Res*. 2021;35(11):1836-1839.
27. Mahdavi FS, Mardi P, Mahdavi SS, et al. Therapeutic and preventive effects of *Olea europaea* extract on indomethacin-induced small intestinal injury model in rats. *Evid Based Complement Alternat Med*. 2020;2020:6669813.
28. Guinda A, Rada M, Delgado T, Gutierrez-Adanez P, Castellano JM. Pentacyclic triterpenoids from olive fruit and leaf. *J Agric Food Chem*. 2010;58(17):9685-9691.
29. Drakou M, Birmpa A, Koutelidakis AE, Komaitis M, Panagou EZ, Kapsokefalou M. Total antioxidant capacity, total phenolic content and iron and zinc dialyzability in selected Greek varieties of table olives, tomatoes and legumes from conventional and organic farming. *Int J Food Sci Nutr*. 2015;66(2):197-202.
30. Beltran G, Bejaoui MA, Jimenez A, Sanchez-Ortiz A. Ethanol in olive fruit. Changes during ripening. *J Agric Food Chem*. 2015;63(22):5309-5312.
31. Dekdouk N, Malafronte N, Russo D, et al. Phenolic compounds from *Olea europaea* L. possess antioxidant activity and inhibit carbohydrate metabolizing enzymes in vitro. *Evid Based Complement Alternat Med*. 2015;2015:684925.
32. Kritikou E, Kalogiouri NP, Kolyvira L, Thomaidis NS. Target and suspect HRMS metabolomics for the determination of functional ingredients in 13 varieties of olive leaves and drupes from Greece. *Molecules*. 2020;25(21):4889.
33. Martinez L, Castillo J, Ros G, Nieto G. Antioxidant and antimicrobial activity of rosemary, pomegranate and olive extracts in fish patties. *Antioxidants (Basel)*. 2019;8(4):86.
34. Tamasi G, Baratto MC, Bonechi C, et al. Chemical characterization and antioxidant properties of products and by-products from *Olea europaea* L. *Food Sci Nutr*. 2019;7(9):2907-2920.
35. Omar SH, Kerr PG, Scott CJ, Hamlin AS, Obied HK. Olive (*Olea europaea* L.) biophenols: A nutraceutical against oxidative stress in SH-SY5Y cells. *Molecules*. 2017;22(11):1858.
36. Qabaha K, Al-Rimawi F, Qasem A, Naser SA. Oleuropein is responsible for the major anti-inflammatory effects of olive leaf extract. *J Med Food*. 2018;21(3):302-305.
37. Giacometti J, Zauhar G, Zuvic M. Optimization of ultrasonic-assisted extraction of major phenolic compounds from olive leaves (*Olea europaea* L.) using response surface methodology. *Foods*. 2018;7(9):149.
38. Nicoli F, Negro C, Vergine M, et al. Evaluation of phytochemical and antioxidant properties of 15 Italian *Olea europaea* L. cultivar leaves. *Molecules*. 2019;24(10):1998.

39. Zairi A, Nour S, Zarrouk A, Haddad H, Khelifa A, Achour L. Phytochemical profile, cytotoxic, antioxidant, and allelopathic potentials of aqueous leaf extracts of *Olea europaea*. *Food Sci Nutr*. 2020;8:4805-4813.
40. Sarikurkcü C, Locatelli M, Tartaglia A, et al. Enzyme and biological activities of the water extracts from the plants *Aesculus hippocastanum*, *Olea europaea* and *Hypericum perforatum* that are used as folk remedies in Turkey. *Molecules*. 2020;25(5):1202.
41. Yu M, Gouvinhas I, Rocha J, Barros AIRNA. Phytochemical and antioxidant analysis of medicinal and food plants towards bioactive food and pharmaceutical resources. *Sci Rep*. 2021;11(1):10041.
42. Cataldi TRI, Margiotta G, Iasi L, Di Chio B, Xiloyannis C, Bufo SA. Determination of sugar compounds in olive plant extract by anion-exchange chromatography with pulsed amperometric detection. *Anal Chem*. 2000;72(16):3902-3907.
43. Saad AB, Tiss M, Keskes H, et al. Antihyperlipidemic, antihyperglycemic, and liver function protection of *Olea europaea* var. Meski stone and seed extracts: LC-ESI-HRMS-based composition analysis. *J Diabetes Res*. 2021;2021:6659415.
44. Reis R, Sipahi H, Zeybekoglu G, et al. Hydroxytyrosol: The phytochemical responsible for bioactivity of traditionally used olive pits. *Euroasian J Hepatogastroenterol*. 2018;8(2):126-132.
45. Perez-Bonilla M, Salido S, van Beek TA, et al. Isolation and identification of radical scavengers in olive tree (*Olea europaea*) wood. *J Chromat A*. 2006;1112(1-2):311-318.
46. Perez-Bonilla M, Salido S, van Beek TA, et al. Isolation of antioxidative secoiridoids from olive wood (*Olea europaea* L.) guided by on-line HPLC-DAD-radical scavenging detection. *Food Chem*. 2011;124(1):36-41.
47. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD. 2023. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2023; received February 2, 2023.)
48. Personal Care Products Council. 2020. Concentration of Use Information by FDA Product Category: Olive-Derived Ingredients. Unpublished data submitted by the Personal Care Products Council on February 28, 2020.
49. Personal Care Products Council. 2023. Concentration of Use by FDA Product Category: Hydrolyzed Olive Fruit, Hydrolyzed Olive Fruit Extract, and Hydrolyzed Olive Leaf Extract. Unpublished data submitted by the Personal Care Products Council on February 22, 2023.
50. EUR-Lex. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1223-20221217&qid=1681317694221>. Accessed 04/28/2023. .
51. Flemmig J, Kuchta K, Arnhold J, Rauwald HW. *Olea europaea* leaf (Ph.Eur.) extract as well as several of its isolated phenolics inhibit the gout-related enzyme xanthine oxidase. *Phytomedicine*. 2010;18(7):561-566.
52. Bouzabata A. Traditional treatment of high blood pressure and diabetes in Souk Ahras District. *J Pharmacogn Phytotherapy*. 2013;5(1):12-20.
53. Mehraein F, Sarbishegi M, Golipoor Z. Different effects of olive leaf extract on antioxidant enzyme activities in midbrain and dopaminergic neurons of Substantia Nigra in young and old rats. *Histol Histopathol*. 2016;31(4):425-431.
54. Karygianni L, Cecere M, Skaltsounis AL, et al. High-level antimicrobial efficacy of representative Mediterranean natural plant extracts against oral microorganisms. *Biomed Res Int*. 2014;2014:839019.
55. Markin D, Duek L, Berdicevsky I. In vitro antimicrobial activity of olive leaves. *Mycoses*. 2003;46(3-4):132-136.
56. Ali NH, Faizi S, Kazmi SU. Antibacterial activity in spices and local medicinal plants against clinical isolates of Karachi, Pakistan. *Pharm Biol*. 2011;49(8):833-839.

57. Misganaw D, Engidawork E, Nedi T. Evaluation of the anti-malarial activity of crude extract and solvent fractions of the leaves of *Olea europaea* (*Oleaceae*) in mice. *BMC Complement Altern Med*. 2019;19(1):171.
58. De Cicco P, Maisto M, Tenore GC, Ianaro A. Olive leaf extract, from *Olea europaea* L., reduces palmitate-induced inflammation via regulation of murine macrophages polarization. *Nutrients*. 2020;12(12):3663.
59. Fukumitsu S, Villareal MO, Aida K, et al. Maslnic acid in olive fruit alleviates mild knee joint pain and improves quality of life by promoting weight loss in the elderly. *J Clin Biochem Nutr*. 2016;59(3):220-225.
60. Lee-Huang S, Zhang L, Huang PL, Chang Y-T, Huang PL. Anti-HIV activity of olive leaf extract (OLE) and modulation of host cell gene expression by HIV-1 infection and OLE treatment. *Biochem Biophys Res Commun*. 2003;307(4):1029-1037.
61. Pais P, Villar A, Rull S. Impact of a proprietary standardized olive fruit extract (SOFE) on Cardio-Ankle Vascular Index, visual analog scale and C-reactive protein assessments in subjects with arterial stiffness risk. *Drugs R D*. 2016;16(4):355-368.
62. Jemai H, Mahmoudi A, Feryeni A, et al. Hepatoprotective effect of oleuropein-rich extract from olive leaves against cadmium-induced toxicity in mice. *Biomed Res Int*. 2020;2020(4398924):1-9.
63. Mohagheghi F, Bigdeli MR, Rasoulia B, Hashemi P, Pour MR. The neuroprotective effect of olive leaf extract is related to improved blood-brain barrier permeability and brain edema in rat with experimental focal cerebral ischemia. *Phytomedicine*. 2011;18(2-3):170-175.
64. Rabiei Z, Bigdeli MR, Rasoulia B, Ghassempour A, Mirzajani F. The neuroprotection effect of pretreatment with olive leaf extract on brain lipidomics in rat stroke model. *Phytomedicine*. 2012;19(10):940-946.
65. Benot-Dominguez R, Tupone MG, Castelli V, et al. Olive leaf extract impairs mitochondria by pro-oxidant activity in MDA-MB-231 and OVCAR-3 cancer cells. *Biomed Pharmacother*. 2021;134:111139.
66. Skalli S, Hassikou R, Arahou M. An ethnobotanical survey of medicinal plants used for diabetes treatment in Rabat, Morocco. *Heliyon*. 2019;5(3):e01421.
67. Cumaoglu A, Rackova L, Stefek M, Kartal M, Maechler P, Karasu C. Effects of olive leaf polyphenols against H₂O₂ toxicity in insulin secreting β -cells. *Acta Biochim Pol*. 2011;58(1):45-50.
68. Wainstein J, Ganz T, Boaz M, et al. Olive leaf extract as a hypoglycemic agent in both human diabetic subjects and in rats. *J Med Food*. 2012;15(7):1-6.
69. Elkafrawy N, Younes K, Naguib A, et al. Antihypertensive efficacy and safety of a standardized herbal medicinal product of *Hibiscus sabdariffa* and *Olea europaea* extracts (NW Roselle): A phase-II, randomized, double-blind, captopril-controlled clinical trial. *Phytother Res*. 2020;34(12):3379-3387.
70. Ismail MA, Norhayati MN, Mohamad N. Olive leaf extract effect on cardiometabolic profile among adults with prehypertension and hypertension: A systematic review and meta-analysis. *PeerJ*. 2021;9:e11173.
71. Abugomaa A, Elbadawy M. Olive leaf extract modulates glycerol-induced kidney and liver damage in rats. *Environ Sci Pollut Res Int*. 2020;27(17):22100-22111.
72. Koca U, Suntar I, Akkol EK, Yilmazer D, Alper M. Wound repair potential of *Olea europaea* L. leaf extracts revealed by in vivo experimental models and comparative evaluation of the extracts' antioxidant activity. *J Med Food*. 2011;24(1-2):140-146.
73. Kang H, Koppula S. *Olea europaea* Linn. fruit pulp extract protects against carbon tetrachloride-induced hepatic damage in mice. *Indian J Pharm Sci*. 2014;76(4):274-280.
74. Altarejos J, Salido S, Perez-Bonilla M, et al. Preliminary assay on the radical scavenging activity of olive wood extracts. *Fitoterapia*. 2005;76(3-4):348-351.

75. Hailesilase GG, Rajeshwar Y, Hailu GS, Sibhat GG, Bitew H. In vivo antimalarial evaluation of crude extract, solvent fractions, and TLC-isolated compounds from *Olea europaea* Linn Subsp. *cuspidata* (Oleaceae). *Evid Based Complement Alternat Med.* 2020;2020:12.
76. Garcia AV, Alvarez-Perez OB, Rojas R, Aguilar CN, Garrigos MC. Impact of olive extract addition on corn starch-based active edible films properties for food packaging applications. *Foods.* 2020;9(9):1339.
77. Thielmann J, Kohnen S, Hauser C. Antimicrobial activity of *Olea europaea* Linne extracts and their applicability as natural food preservative agents. *Int J Food Microbiol.* 2017;251:48-66.
78. Cohen SM, Flikushima S, Gooderham NJ, et al. GRAS 27 Flavoring Substances. *Food Technol.* 2015;69(1):41-59.
79. Christian MS, Sharper VA, Hoberman AM, et al. The toxicity profile of hydrolyzed aqueous olive pulp extract. *Drug Chem Toxicol.* 2004;27(4):309-330.
80. Gaube Guex C, Reginato FZ, Figuerdeo KC, et al. Safety assessment of ethanolic extract of *Olea europaea* L. leaves after acute and subacute administration to Wistar rats. *Regul Toxicol Pharmacol.* 2018;95:395-399.
81. Heilman J, Anyangwe N, Tran N, Edwards J, Beilstein P, Lopez J. Toxicological evaluation of an olive extract, H35: Subchronic toxicity in the rat. *Food Chem Toxicol.* 2015;84:18-28.
82. Clewell AE, Beres E, Vertesi A, et al. A comprehensive toxicological safety assessment of an extract of *Olea europaea* L. leaves (Bonolive™). *Int J Toxicol.* 2016;35(2):208-221.
83. Najafizadeh P, Dehghani F, Shahin MP, Taj SH. The effect of a hydro-alcoholic extract of olive fruit on reproductive argons in male Sprague-Dalwy rat. *Iran J Reprod Med.* 2013;11(4):293-300.
84. Verschaeve L, Edziri H, Anthonissen R, et al. In vitro toxicity and genotoxic activity of aqueous leaf extracts from four varieties of *Olea europea* (L.). *Pharmacogn Mag.* 2017;13(Suppl 1):S63-S68.
85. Juan ME, Wenzel U, Ruiz-Gutierrez V, Daniel H, Planas JM. Olive fruit extracts inhibit proliferation and induce apoptosis in HT-29 human colon cancer cells. *J Nutr.* 2006;136(10):2553-2557.
86. Anonymous. 2023. Olea Europaea (Olive) Fruit Extract - Summary Information. Unpublished data submitted by the Personal Care Products Council on March 8, 2023.
87. Anonymous. 2013. 4-Day face use test (face cream contains 0.0005% Olea Europaea (Olive) Fruit Extract). Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
88. Anonymous. 2013. Human patch test (face cream contains 0.0005% Olea Europaea (Olive) Fruit Extract). Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
89. Anonymous. 2002. Clinical safety in use test - moisturizer containing 0.047% Olea Europaea (Olive) Leaf Extract. Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
90. Anonymous. 2008. Human patch test - liquid lip color containing 1% Olea Europaea (Olive) Leaf Extract. Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
91. Anonymous. 2008. 5-Day use test (lips) - product containing 1% Olea Europaea (Olive) Leaf Extract. Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
92. Anonymous. 2013. Human patch test (scrub contains 0.025% Olea Europaea (Olive) Seed Powder). Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
93. Anonymous. 2013. 1-Week home use test of a bar soap containing 1% Olea Europaea (Olive) Seed Powder. Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
94. Anonymous. 2014. Repeated insult patch test (product contains 0.0025% Olea Europaea (Olive) Fruit Extract and 0.035% Olea Europaea (Olive) Seed Powder). Unpublished data submitted by the Personal Care Products Council on August 16, 2022.

95. 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). Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
96. 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). Unpublished data submitted by the Personal Care Products Council on August 17, 2022.
97. Anonymous. 2007. Human repeat insult patch test with challenge (product contains 25% Olea Europaea (Olive) Seed Powder). Unpublished data submitted by the Personal Care Products Council on August 17, 2022.
98. 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). Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
99. 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). Unpublished data submitted by the Personal Care Products Council on August 16, 2022.
100. Alvarez-Eire MG, Pineda de la Losa F, Varela Losada S, Gonzalez de la Cuesta C, Ricard Palacios R. Anaphylaxis to olive fruit due to lipoprotein sensitization. *Allergol Immunopathol (Madr)*. 2011;40(3):198-200.
101. Prados-Castaño M, Reguero-Capilla M, Bartolome B, Ochando Diez-Canseco M, Quiralte J. Allergens responsible of olive fruit ingestion anaphylaxis. *J Investig Allergol Clin Immunol*. 2022;33(5):8 pages.
102. Theoharides TC, Stewart JM, Tsilioni I. Tolerability and benefit of a tetramethoxyluteolin-containing skin lotion. *Int J Immunopathol Pharmacol*. 2017;30(2):146-151.
103. Kendall M, Batterham M, Obied H, Prenzler P, Ryan D, Robards K. Zero effect of multiple dosage of olive leaf supplements on urinary biomarkers of oxidative stress in healthy humans. *Nutrition*. 2009;25(3):270-280.
104. Wanitphakdeedecha R, Ng JNC, Junsuwan N, et al. Efficacy of olive leaf extract-containing cream for facial rejuvenation: A pilot study. *J Cosmet Dermatol*. 2020;19(7):1662-1666.