Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: May 23, 2022
Panel Meeting Date: June 16-17, 2022

This safety assessment was prepared by Preethi S. Raj, Senior Scientific Analyst/ Writer, CIR.

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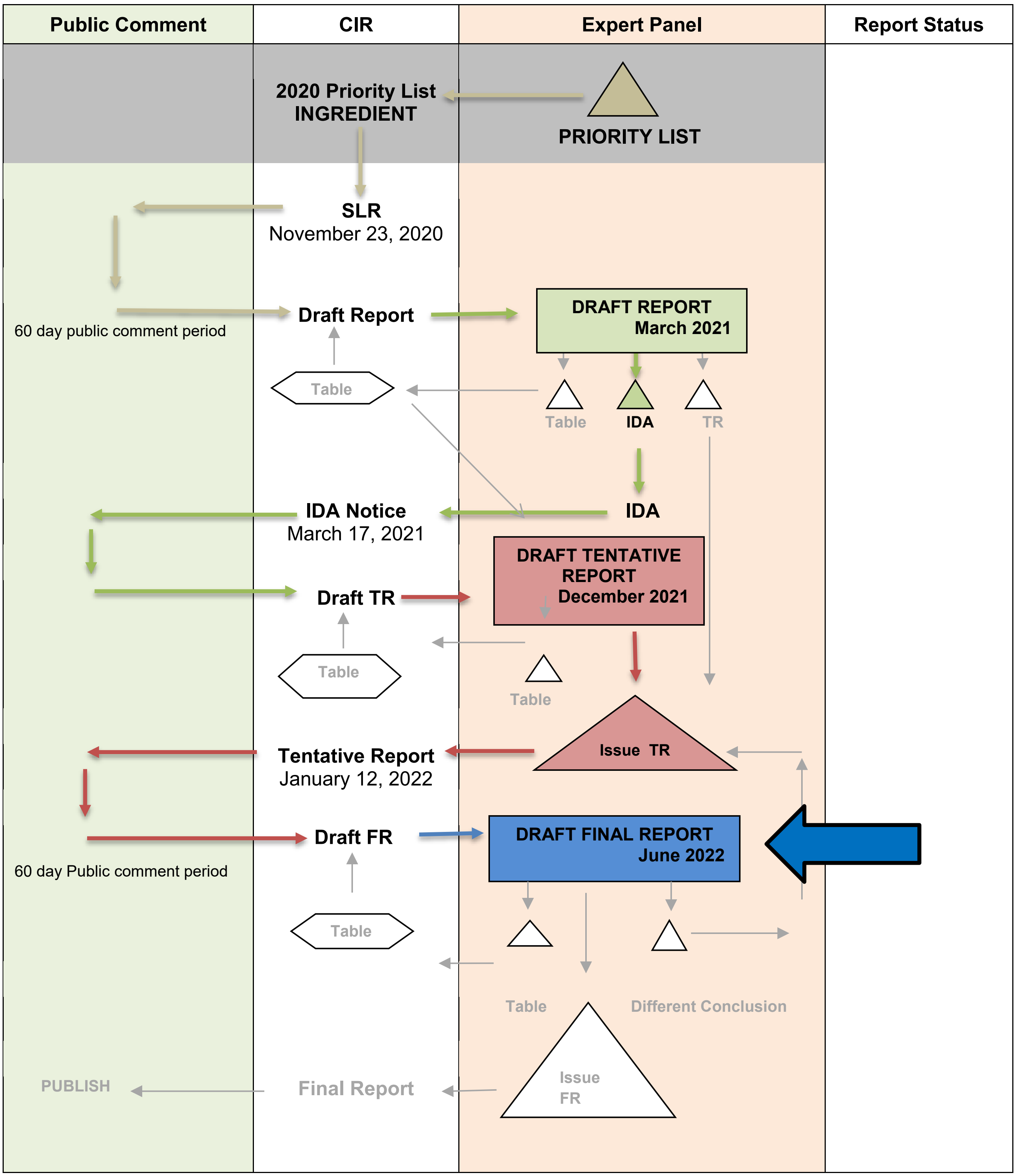
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Salvia officinalis* (Sage)-Derived Ingredients

MEETING June 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

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

Date: May 23, 2022

Subject: Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics (*identified as report_Sage_062022 in the pdf*). This is the third time the Panel is seeing a safety assessment of these 12 cosmetic ingredients. At the December 2021 Panel meeting, the Panel issued a Tentative Report for public comment with the split conclusion that the following 6 leaf and oil ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Salvia Officinalis (Sage) Leaf
Salvia Officinalis (Sage) Leaf Extract
Salvia Officinalis (Sage) Leaf Oil
Salvia Officinalis (Sage) Leaf Powder
Salvia Officinalis (Sage) Leaf Water
Salvia Officinalis (Sage) Oil

However, the Panel also concluded that the available data are insufficient to make a determination that the remaining 6 *Salvia officinalis* (Sage)-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Salvia Officinalis (Sage) Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice
Salvia Officinalis (Sage) Flower/Leaf/Stem Water
Salvia Officinalis (Sage) Root Extract
Salvia Officinalis (Sage) Water

The data requested to satisfy the insufficiency are:

- 28-day dermal toxicity study for the Salvia Officinalis (Sage) Flower/Leaf/Stem Extract, Salvia Officinalis (Sage) Root Extract, or for the whole plant
    - depending on the results of the requested dermal study, additional toxicity data may be needed

No data were received in response to this request.

Updated VCRP data were received and have been incorporated (*VCRP_Sage_062022*). Reported use categories and number of uses did not change significantly. Changes reflecting updated VCRP data are highlighted in yellow. Also, changes to the language involving the inhalation exposure boilerplate and use in airbrush delivery systems have been highlighted to aid the Panel's review.

Comments on the Tentative Report that were received from the Council (*PCPCcomments_Sage_062022*) have been addressed. A comments response checklist is included (*response-PCPCcomments_Sage_062022*).
Also included in this package, for your review, are a flow chart (*flow_Sage_062022*), minutes from the previous meeting (*transcripts_Sage_062022*), literature search strategy (*search_Sage_062022*), ingredient data profile (*dataprofile_Sage_062022*), and ingredient history (*history_Sage_062022*).

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

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Memorandum

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

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

DATE: January 27, 2022

SUBJECT: Tentative Report: Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics (release date January 12, 2022)

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

Key Issue
Cosmetic Use – When describing the IFRA restriction for thujone, the statement "can therefore be restricted if found at higher levels in these ingredients" is not correct. Under the table of natural substances containing thujone, the IFRA standard states: "The natural contribution of Thujone is determined by the sum of the natural contributions of each of its isomers.

This is a non-exhaustive indicative list of typical natural presence for Thujone and is intended to be used in the absence of own analytical data. If analysis has shown that the level of the restricted ingredient in a natural complex substance is different from what is provided in this Annex I, then the analytically determined level should be used in place of the indicative level.

It should further be noted that natural complex substances themselves can be restricted by an IFRA Standard. For a detailed list of natural contributions, please refer to the Annex I of IFRA Standards, publicly available on the IFRA website (www.ifrafragrance.org)." (Currently there is not a specific restriction for sage-derived ingredients).

It would also be helpful to note that the IFRA limits for thujone are based on neurotoxicity.

Additional Considerations
Abstract; Discussion – As the ingredients considered safe when formulated to be non-sensitizing are the essential oil, and those derived from leaves, it is not clear why the word "mainly" is needed. It is likely that the ingredients derived from Flower/Leaf/Stem are also "mainly" derived from leaves.

Introduction – When discussing RIFM's role, it would be helpful to mention the 1978 monograph (reference 34). Although sage ingredients may not be on the current agenda, it is misleading to state that they have not been reviewed. RIFM has sponsored some studies on sage-derived ingredients, and these studies are summarized in the 1978 monograph.

Chemical Properties – It is not clear why the chemical properties on Salvia Officinalis (Sage) Leaf Extract from reference 9 are stated in the text, while the properties on the Leaf Extract from reference 11 are presented in Table 2. All the information should be presented in Table 2, with a summary of the information in the text.

Method of Manufacture – The ingredient definitions do not need to be presented in this section if they do not provide any information about the method of manufacture (the definitions of Salvia Officinalis (Sage) Leaf Oil, Salvia Officinalis (Sage) Leaf Powder and Salvia Officinalis (Sage) Root Extract can be deleted from this section).

Composition and Impurities, Salvia Officinalis (Sage) Oil – In this report, it would be helpful to use one name for a component or indicate a common name after the name given in the original reference. For example, the ECHA dossier (reference 3) used some chemical names for components. The names used in the ECHA dossier are other names for components mentioned elsewhere in this report. See the attached table for some suggestions of other names for the names of the components as stated in the ECHA dossier.

Non-Cosmetic Use – Please correct: “excessing sweating” to “excessive sweating”

Genotoxicity – Units of mg/ml should be called concentration rather than dose.

Genotoxicity; Summary – Please add the word “it” to “however, was not considered genotoxic”

Skin Irritation – It would be helpful to note that TG 431 is a skin corrosion test, while TG 439 is a skin irritation test.

Summary – The case report section states that the subject (reference 50) only reacted to *Salvia officinalis* extract (implying no reaction to polygonum). In contrast the Summary states: that the subject had positive reactions to both *Salvia officinalis* extract and polygonum. Which section is correct?

Table 2 – If available, please indicate the solvent used for the leaf extract from reference 11. In this table, three different names are being used for a similar property: Specific Gravity, Density, and Relative Density. Specific gravity and relative density are the same – please use one name. The order in which the properties are presented should also be consistent – Density or Specific Gravity should be presented either before or after Refractive Index, not both before and after Refractive Index.

Table 3 – Although concentrations are not presented in the ECHA dossier (reference 3), it would be helpful to add the main components of Salvia Officinalis Oil according to ECHA to this table to show that it is consistent with the other references.

Major Sage Oil Components

Component As stated in ECHA Dossier	Other Identified Names	Other Names in CIR report
1-isopropyl-4-methylbicyclo[3.1.0]hexan-3-one	3-Thujanone; Chrysanthone; Thujone (alpha and beta); CAS No. 1125-12-8 (1)	Alpha- and beta-thujone
DLbornan-2-one	Camphor; CAS No. 76-22-2 (1)	Camphor
cineole	Eucalyptol; 1,8-Cineole; CAS No. 470-82-6 (1)	1,8-Cineole
(1S, 4S, 5R)-4-methyl-1-(1-methylethyl)bicyclo[3.1.0]hexan-3-one	CAS No. 471-15-8; beta-Thujone; Isothujone; 3-Thujanone (2)	Beta-Thujone
camphene	CAS No. 79-92-5 (1)	Camphene
humulene	CAS No. 6573-98-6; alpha-Humulene; alpha-Caryophyllene (1)	Alpha-Humlene
pin-2(3)-ene	CAS No. 80-56-8; alpha-Pinene; 2-Pinene (1)	Alpha-Pinene
caryophyllene	CAS No. 87-44-5; beta-Caryophyllene (1)	Beta-Caryophyllene
(1S-endo)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol	CAS No. 464-45-9: Borneol (1)	Borneol
pin-2(10)-ene	CAS No. 127-91-3; beta-Pinene (1)	Beta-Pinene
p-mentha-1,4-diene	CAS No. 99-85-4; gamma-Terpinine; Crithmene; Moslene; Alpha-Terpinine (1)	Alpha-Terpinene; gamma-Terpinene
Dipentene	CAS No. 138-86-3; Limonene (1)	Limonene
L-born-2-yl acetate	CAS No. 5655-61-8; Bornyl Acetate (1)	Bornyl Acetate
7-methyl-3-methyleneocta-1,6-diene	CAS No. 125-35-3; Myrcene; beta-Myrcene (1)	Myrcene; beta-Myrcene

(1) PubChem; (2) NIST Chemistry Webbook

Salvia officinalis-derived Ingredients - June 16-17, 2022 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: January 27, 2022 (Comments on TR from December 2021 meeting)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Key Issue: Cosmetic Use -incorrect to say that thujone "can be restricted if found at higher levels in these ingredients" -IFRA standard states "The natural contribution of Thujone is determined by the sum of the natural contributions of each of its isomers." - if analytical data suggests - natural complex substances themselves can be restricted by IFRA standards (Annex I) – although, currently there is no specific restriction for sage-derived ingredients - note that IFRA limits for thujone are based on neurotoxicity	Have placed naturally occurring thujone levels under Composition Have placed thujone level 'restrictions' in finished products in the Cosmetic Use section	
2	Abstract; Discussion – it likely that ingredients derived from the Flower/Leaf/Steam are also mainly derived from the leaves – so, do not need to point this out only for the oil ingredient and leaf-derived ingredients only	Deleted 'mainly'	
3	Introduction – when discussing RIFM's role it would be helpful to mention the 1978 monograph. RIFM has sponsored some studies on sage-derived ingredients in this monograph.	Have revised and cited RIFM monograph	
4	Chemical properties – All the chemistry info should be presented in Table 2, with a summary of the info in the text. Currently, the properties for Leaf Extract (ref 9) are stated in the text, and properties for the Leaf Extract (ref 11) are in Table 2	Have included Leaf Extract info (in trade mixture) in Table 2	
5	Method of manufacture – don't need to include wINCI definitions if they don't actually describe how the ingredients are made. Can delete the definitions listed for Leaf Oil, Leaf Powder, and Root Extract	Have deleted definitions which do not include details describing the process	
6	Composition and Impurities, Oil – in this report, it would be helpful to use one (the same) name for a component, or indicate a common name after the name given in the original ref. Pls refer to attached Table.		
7	Non-Cosmetic Use – change "excessing sweating" to "excessive sweating"	revised	
8	Genotoxicity – units of mg/ml should be called concentration, rather than dose	revised	
9	Genotoxicity, Summary – add 'it' to "however, was not considered genotoxic"	added	
10	Skin Irritation – Note that TG 431 is the skin corrosion test, and TG 439 is a skin irritation test	Noted	
11	Summary – clarify if the subject in the case report had a positive reaction to both polygonium and the extract ingredient, or only one (differences in text and Summary)	Revised summary	
12	Table 2 – please indicate the solvent used for the leaf extract from ref 11	Mentioned (aqueous)	
13	Table 3 – although concentrations are not presented in the ECHA dossier (ref 3), it would be helpful to add the main components of the Oil ingredient to this table to show consistency with other references.		

CIR History of:

Salvia officinalis-derived Ingredients

January 2020

-FDA frequency of use data obtained

February and October 2020

-Concentration of use data submitted by Council for most ingredients (Feb) and the Leaf Oil (Oct)

November 2020

- SLR posted on the CIR website

Data received (Salvia Officinalis (Sage) Leaf Extract):

- December 10, 2020: Salvia Officinalis (Sage) Leaf Extract (method of manufacture, impurities and specifications)

- January 5, 2021: Summary Information for Salvia Officinalis (Sage) Leaf Extract. (method of manufacture, composition, impurities, and summary acute toxicity, genotoxicity, and dermal irritation)

January 2021

New VCRP data were received

March 2021

A Draft Report was presented to the Panel at the March meeting. An IDA was issued for the following data needs:
For all ingredients:
• Composition and impurities data, and dermal irritation and sensitization data, at the maximum concentration of use

For the Salvia Officinalis (Sage) Leaf Extract:
• 28-d dermal toxicity data (if absorbed, other toxicological & genotoxicity endpoints for systemic toxicity)

For the Salvia Officinalis (Sage) Root Extract:
• Method of manufacture and 28-d dermal toxicity data (if absorbed, other toxicological & genotoxicity endpoints for systemic toxicity)

Data received (Salvia Officinalis (Sage) Leaf Extract, Leaf Water, and Oil):

- April 1, 2021: Specifications for Salvia Officinalis (Sage) Leaf Extract and Salvia Officinalis (Sage) Leaf Water

- April 29, 2021: HRIPTs for products containing 0.03% Salvia Officinalis (Sage) Oil and 0.005% Salvia Officinalis (Sage) Leaf Extract

December 2021

A Draft Tentative Report was presented to the Panel at the December meeting. The Panel issued a Tentative Report for public comment with the split conclusion that the following 6 (of 12) Salvia officinalis (sage)-

derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Salvia Officinalis (Sage) Leaf
Salvia Officinalis (Sage) Leaf Extract
Salvia Officinalis (Sage) Leaf Oil
Salvia Officinalis (Sage) Leaf Powder
Salvia Officinalis (Sage) Leaf Water
Salvia Officinalis (Sage) Oil

The Panel discussed that most of these ingredients are derived from the leaf, and subsequently have GRAS status, mitigating systemic toxicity concerns. The Panel acknowledged that constituents with the highest potential for sensitization are found in the leaf and oil ingredients, and accordingly, identified the need for manufacturers and cosmetic formulators to avoid reaching levels of plant constituents that may cause sensitization or adverse aggregate exposures. However, the Panel also concluded that the available data are insufficient to make a determination that the following 6 Salvia officinalis (sage)-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Salvia Officinalis (Sage) Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice
Salvia Officinalis (Sage) Flower/Leaf/Stem Water
Salvia Officinalis (Sage) Root Extract
Salvia Officinalis (Sage) Water

The additional data needed to determine safety for these cosmetic ingredients comprise:

• 28-day dermal toxicity data for the Salvia Officinalis (Sage) Flower/Leaf/Stem Extract, Salvia Officinalis (Sage) Root Extract, or for the whole plant

 o depending on the results of the study, additional toxicity data may be needed

June 2022

A Draft Final Report is being presented for Panel review.

Salvia officinalis-derived Ingredients Data Profile* – June 16-17th, 2022 – Writer, Preethi Raj

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Salvia Officinalis (Sage) Extract	X	X						X						X															X
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract		X						X						X															
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice		X																											
Salvia Officinalis (Sage) Flower/Leaf/Stem Water		X																											
Salvia Officinalis (Sage) Leaf	X	X																											
Salvia Officinalis (Sage) Leaf Extract	X	X	X				X								X					X				X					
Salvia Officinalis (Sage) Leaf Oil	X						X	X			X									X	X			X					
Salvia Officinalis (Sage) Leaf Powder																													
Salvia Officinalis (Sage) Leaf Water	X	X																											
Salvia Officinalis (Sage) Oil	X	X					X	X			X			X	X				X	X	X			X		X			X
Salvia Officinalis (Sage) Root Extract																													
Salvia Officinalis (Sage) Water	X	X																											

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

Salvia officinalis – derived ingredients (12 ingredients- June 16-17, 2022 Panel Meeting)

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Salvia Officinalis (Sage) Leaf Extract	84082-79-1	✓	✓	✓	✓	✓*	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Salvia Officinalis (Sage) Extract	84082-79-1	✓	✓	✓	✓	✓*	✓	✓*	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract	84082-79-1	✓	✓	✓	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice	84082-79-1	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Salvia Officinalis (Sage) Flower/Leaf/Stem Water	84082-79-1	✓	NR	✓	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Salvia Officinalis (Sage) Leaf	84082-79-1	✓	✓	✓	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Salvia Officinalis (Sage) Leaf Oil	8022-56-8 84776-73-8	✓	✓	✓	NR	✓*	✓*	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	
Salvia Officinalis (Sage) Leaf Powder	84082-79-1	✓	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Salvia Officinalis (Sage) Leaf Water	84082-79-1	✓	NR	✓	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Salvia Officinalis (Sage) Oil	8022-56-8	✓	✓	✓	✓	✓*	✓*	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	
Salvia Officinalis (Sage) Root Extract	84082-79-1	✓	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Salvia Officinalis (Sage) Water	84082-79-1	✓	NR	✓	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
Salvia Officinalis (Sage) Leaf Extract	84082-79-1	✓	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Extract	84082-79-1	✓	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract	84082-79-1	✓	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice	84082-79-1	NR	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Flower/Leaf/Stem Water	84082-79-1	NR	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Leaf	84082-79-1	✓	NR	#32950	NR	NR	NR
Salvia Officinalis (Sage) Leaf Oil	8022-56-8 84776-73-8	✓	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Leaf Powder	84082-79-1	NR	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Leaf Water	84082-79-1	NR	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Oil	8022-56-8	✓	NR	NR	✓	NR	NR
Salvia Officinalis (Sage) Root Extract	84082-79-1	✓	NR	NR	NR	NR	NR
Salvia Officinalis (Sage) Water	84082-79-1	NR	NR	NR	NR	NR	NR

✓- found in database, or, data was available
✓*- found in database, but data was either irrelevant or not accessible
NR – not reported

Search Strategy

[*document search strategy used for PubMed and/or Toxnet]:* - [*total # of hits/ #hits that were useful*]
Salvia officinalis – 779
(((((salvia officinalis) OR (sage)) OR (84082-79-1)) OR (8022-56-8)) OR (84776-73-8)) AND (toxicity) – 4900/308
(salvia officinalis) OR (sage) OR (8022-56-8) OR (salvia officinalis leaf extract) OR (salvia officinalis extract) OR (salvia officinalis flower extract) OR (salvia officinalis leaf extract) OR (salvia officinalis stem extract) OR (salvia officinalis flower juice) OR (salvia officinalis leaf juice) OR (salvia officinalis stem juice) OR (salvia officinalis flower water) OR (salvia officinalis leaf water) OR (salvia officinalis stem water) OR (salvia officinalis leaf) OR (salvia officinalis leaf powder) OR (salvia officinalis leaf water) OR (salvia officinalis leaf oil) OR (salvia officinalis oil) OR (salvia officinalis root extract) OR (salvia officinalis water):
AND (method of manufacture) – 43/1
AND (impurities) – 5/0; salvia officinalis pesticide – 240/0
AND (dermal penetration) – 1/1
AND (toxicokinetics; pharmacokinetics) – 184/0
AND (acute toxicity) – 34/2
AND (subacute toxicity) – 3/0
AND (chronic toxicity) – 22/0
AND (inhalation toxicity) – 4/0
AND (dermal toxicity) - 1/0
AND (oral toxicity) – 30/0
AND (reproductive toxicity) – 4/1
AND (teratogenicity)- 8/1
AND (genotoxicity) – 21/3
AND (carcinogenicity) – 50/2
AND (mutagenicity)- 54/4
AND (endocrine effects)- 47/1
AND (pigmentation) – 51/0
AND (dermal irritation and sensitization) – 0/0
AND (ocular irritation) – 0/0
AND (mucous membrane irritation) – 0/0
AND (clinical trials) – 485/5
Salvia officinalis leaf extract – 100/3; Salvia officinalis extract- 414/10 ;Salvia officinalis flower extract – 13/2; Salvia officinalis stem extract – 8/0; Salvia officinalis flower juice- 0/0; Salvia officinalis flower/leaf/stem juice – 0/0; Salvia officinalis flower/leaf/stem water- 35/12; Salvia offiicinalis leaf -161/20' Salvia officinalis leaf powder – 2/0; Salvia officinalis leaf oil – 41/12; Salvia officinalis oil - 172/25 ; Salvia officinalis root extract- 22/3; Salvia officinalis water – 23/105

General Web Search

Pharmacokinetics sage salvia officinalis – 41,300/30

Updated search on 5/10/2022:
((((((((((((((((((((((((((((((((((salvia officinalis extract) OR (sage extract)) OR (salvia extract)) OR (84082-79-1)) OR (salvia officinalis flower extract)) OR (sage flower extract)) OR (salvia officinalis leaf extract)) OR (sage leaf extract)) OR (salvia officinalis stem extract)) OR (sage stem extract)) OR (salvia officinalis flower juice)) OR (sage flower juice))) OR (salvia officinalis leaf juice)) OR (sage leaf juice)) OR (salvia officinalis stem juice)) OR (sage stem juice)) OR (salvia officinalis flower water)) OR (sage flower water)) OR (salvia officinalis leaf water)) OR (sage leaf water)) OR (salvia officinalis stem water)) OR (sage stem water)) OR (salvia officinalis leaf)) OR (sage leaf)) OR (salvia officinalis leaf powder)) OR (sage leaf powder)) OR (salvia officinalis oil)) OR (sage oil)) OR (8022-56-8)) OR (salvia officinalis root extract)) OR (sage root extract)) OR (sage root)) OR (salvia officinalis water)) OR (sage water)) OR (salvia officinalis leaf oil)) OR (sage leaf oil)) AND (toxicity)– 345/0

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Connected Papers (www.connectedpapers.com)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org

- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- 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
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
- 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/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- 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
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.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
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- 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) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

MARCH 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – March 11, 2021

DR. BELSITO: Okay. Great. Okay. So now sage. This is the first time we're looking at it. We got quite a bit of data, so let's see how that crunches out. So yeah, the first question I have, Preethi, is under "Chemical Properties," and I think Council also brought this up for the flower/leaf/stem water. You say that essential oil obtained from leaves, flowers, and stalks by steam distillation is a light yellow, dah, dah, dah, dah. And that to me is not leaf water. Water and oil don't mix. I think they maybe get that water during the same distillation process, but the two ingredients are quite different.

MS. RAJ: Yes. Thank you, Dr. Belsito. There was a bit of confusion as to how to classify this ingredient because a lot of this data was taken from an ECHA dossier in which the definition that they had given -- they called it an extractive, which is kind of blanket term for various things. It could be a tincture. It could be an essential oil. It could be -- a ton of these. But then it also kind of -- the way that definition was written it seemed to match closest to the INCI definition for the flower, leaf, and stem water.

So in the Cohen team, we were discussing how definitely the panel would need more clarification on the method of manufacture for these ingredients, which plant parts they're taken from and how they're exactly made because it seems like the water and the oil, which are byproducts of the steam distillation process, could be also derived from a water, as weird as that sounds. So yeah, definitely I think the panel will need more clarification on the method of manufacture.

DR. BELSITO: Yes. Yeah. I think we need, certainly, the method of manufacture for the leaf oil.

DR. LIEBLER: Yeah. I had insufficient for the root and for the flower ingredients for method of manufacture, and composition and impurities for the root, and for comp and impurities for the flower ingredients.

DR. BELSITO: For composition and impurities, I had flower/leaf/stem extract, juice and water, leaf, leaf powder and water, and root extract and water.

MS. RAJ: I'm going to have to get all these again from you, but I do want to also ask the panel Council mentioned reclassifying whatever we had called the flower/leaf/stem water ingredients as the oil ingredients, which there are two. There's a leaf oil, and then there's just an oil ingredient. How does the panel feel about that?

DR. LIEBLER: Well, do you mean renaming them?

MS. RAJ: Yeah. More like correctly classifying them under the oil ingredients as opposed to how it is right now. It says flower/leaf/stem water ingredient. But as you just pointed out, Dr. Belsito, that distinction is not very clear.

DR. LIEBLER: Yeah. I think, Preethi, the names are the names. We're stuck with them. And any imprecision in what the name conveys about the nature of the substance is what we need to resolve. So I agree there could be, from the description that you mentioned, chemical properties -- what says it's a water sounds like an oil. And so we simply need method of manufacture, which I think would be key for that.

And that's why I said the flower ingredients, meaning the flower/leaf/stem, the whatever other has flower in it. Those are all insufficient for composition and impurities. We could just say method of manufacture, composition and impurities and then readdress it next time. And then the root, of course, we got pretty much nothing. I think we're probably okay on the leaf and then the sage extract, which I believe is the whole plant or the leaves.

MS. RAJ: Yeah.

DR. LIEBLER: Don, you mentioned leaf as being a problem, but it looks like we've got pretty good method of manufacture on leaf-containing things. And then composition and impurities, that's our strong suite on the leaf, either the oils and the leaf extract.

DR. BELSITO: No. For manufacture, I just said sage leaf oil. But are you fine with the idea of we have sage oil? We --

DR. LIEBLER: Yeah. That's what I was looking to, Don. The sage oil, it's going to be mainly leaves.

DR. BELSITO: Okay. So, then we don't need that for method of manufacture. And for impurities, I had the flower/leaf/stem extract, juice, and water from those parts. And for leaf, I had leaf powder and leaf water. And for root, I had root extract and root water. But you don't think we need them except for root? You're happy with --

DR. LIEBLER: Yeah. Because I think leaf extract and leaf oil kind of covers the basis for -- and the sage oil kind of covers the basis for the leaf-containing ingredients.

DR. BELSITO: Okay. And covers the basis for the flower/leaf/stem ingredients?

DR. LIEBLER: No. Anything with flower in it is still insufficient for composition and impurities.

DR. BELSITO: And root.

DR. LIEBLER: And the root, correct.

DR. BELSITO: Okay.

DR. LIEBLER: I think we're probably pretty close to where the Cohen team is as well, sounds like.

DR. BELSITO: So, the reason for not asking for all components, the leaf, leaf powder, and water is what, Dan?

DR. LIEBLER: Well, I think we've actually pretty good descriptions of the leaf extract and leaf oil. And then the sage oil, sage being the whole extract and plant, sage extract would be -- I'm presuming whole plant which is mainly leaves.

DR. BELSITO: Okay. So, do we need it for the flower/leaf/stem extract?

DR. LIEBLER: Yeah. Anything with flower in it I came to the conclusion was inadequate.

DR. BELSITO: Okay. So, we need composition/impurities for flower/leaf/stem extract, flower/leaf/stem juice, flower/leaf/stem water, root extract, and root water. Is that what you're saying?

DR. LIEBLER: Yeah. The hitch could come in whether or not the extracts are covered by the oils because we do have Table 2 which has a lot of data on two different leaf oils -- has the two different sage oils, essentially.

DR. BELSITO: Uh-huh.

DR. LIEBLER: And, so, Table 2 is pretty good. And I think the only question is whether the other team feels that we can cover the extract with the oil data. And it really depends on how the extract is prepared.

DR. BELSITO: Okay. But we have information on the leaf extract.

DR. LIEBLER: Right.

DR. BELSITO: Right. Okay.

DR. LIEBLER: Go back up to this method of manufacture for the -- let's see -- the leaf extract, yeah, these are hydroalcoholic extracts.

DR. BELSITO: We have it for the flower/leaf/stem extract.

DR. SNYDER: Dan, can you look on PDF page 12 at the top, the sage oil? It says it was prepared by drying and grinding aerial parts of the plant. So, would that not include everything other than the root?

DR. LIEBLER: Yeah. It would include everything, right. And in fact, the table with the definitions indicates it's the whole plant.

DR. SNYDER: Because we have an eight-week tox study where the NOAEL was 250 milligrams per kilogram per day. So, there's nothing really can be going on in there with anything that's above ground, right?

DR. LIEBLER: Yeah. I think we're reasonably covered with whole plant and leaf for method of manufacture, composition, and impurities.

DR. BELSITO: Okay. But we have good, really detailed manufacturing for the extract. So, I guess you'd be concerned about residual methanol?

DR. LIEBLER: No.

DR. BELSITO: Then what are we looking for in terms of an impurity?

DR. LIEBLER: Right. Method of manufacture, we've got. Impurities --

DR. SNYDER: I think we were okay for everything but the root.

DR. LIEBLER: Yeah. The flower is okay for method of manufacture, but we really don't have anything on composition and impurities for the flower -- for the flower-related ingredients. So, PDF 12 under "Composition/Impurities," you got the sage extract, sage leaf extract, sage leaf oil, sage oil, nothing flower related, nothing root related.

DR. SNYDER: But according to the method of manufacture of the sage oil, that would include the flower, right?

DR. LIEBLER: Well, most of the sage isn't flower, most of it is leaf. So, there might be a little flower in it.

DR. BELSITO: Okay.

DR. LIEBLER: You know what I'm saying, Paul?

DR. SNYDER: Yeah. I do, yeah.

DR. LIEBLER: Okay.

DR. BELSITO: So, we need composition and impurities for the flower/leaf/stem extract, juice and water, and the root extract and water.

DR. LIEBLER: Right.

DR. BELSITO: That's where we're at?

DR. LIEBLER: Right.

DR. BELSITO: Okay.

DR. LIEBLER: Right. Now if somebody could provide us the -- well, no. I won't complicate it any further. Yes. That's right. We need those.

DR. BELSITO: So, then we don't have any absorption data and metabolism distribution, and we have very little DART data. But obviously, the levels are quite high. They are suggesting some effects. So, do we need either a 28-day dermal on those that aren't GRAS -- because several of these are GRAS, right? We just don't really know what parts. I would presume it's the leaf?

DR. LIEBLER: Right.

MS. EISENMANN: Perhaps -- I mean, this is a sage that you use for Thanksgiving.

DR. LIEBLER: Right.

DR. BELSITO: Right. That's what I'm saying. But --

MS. EISENMANN: It's food.

DR. BELSITO: -- that it's derived from the leaf.

DR. SNYDER: Well, it's stem, too.

DR. LIEBLER: Right.

DR. BELSITO: Okay.

DR. LIEBLER: And, Carol, that means it's only a once-a-year exposure.

MS. EISENMANN: No. I use it a lot more than that.

DR. LIEBLER: Sausage.

DR. BELSITO: Okay. So then do we need -- what I'm saying is do we need absorption data for the root? Do we need it for the flower?

DR. LIEBLER: Absorption doesn't really tell us anything with botanicals.

DR. BELSITO: Okay. So, a 28-day dermal?

DR. LIEBLER: Yeah. We could do a 28-day dermal.

DR. BELSITO: At the highest concentration of use?

DR. LIEBLER: Yeah.

DR. SNYDER: Yeah. I had the safe as used other than the root because I figured it was GRAS. We got a 250 milligram per kilogram per day, NOAEL for the sage oil, which is everything above ground. So that's kind of where I was at. But I'll go with the flow.

DR. BELSITO: Okay. So, then we just would need a 28-day dermal for the root?

DR. SNYDER: Yep.

DR. BELSITO: Or the root water?

MS. RAJ: For both the root extract and the water ingredient, Dr. Belsito?

DR. BELSITO: That's what I'm asking.

DR. SNYDER: In the absence of absorption data.

DR. LIEBLER: No. The root extract only. There's just one root ingredient, right?

DR. SNYDER: Yes.

DR. LIEBLER: That's all we need it for, just the root.

MS. RAJ: Okay. Thank you.

DR. BELSITO: You need 28-day dermal for the root extract or absorption. No. You said not absorption.

DR. LIEBLER: Right. 28 day --

DR. BELSITO: 28 day dermal if absorbed --

DR. LIEBLER: Just go right to the dermal because there's no absorption data that we could get that we would find useful because it's a botanical. It's so complex.

DR. SNYDER: Right.

DR. BELSITO: Right. So, we need a 28-day dermal for the root extract and if positive?

DR. SNYDER: Yeah. If absorbed, then systemic toxicity, yeah -- other endpoints.

DR. BELSITO: Okay. Other data may be necessary or other endpoints?

DR. SNYDER: May be necessary, yes.

DR. LIEBLER: The 28-day dermal is just a toxicity study, right?

DR. SNYDER: Correct.

DR. LIEBLER: Yeah. So, if that's negative, then we're done with that.

DR. SNYDER: Probably not going to get it because it's not used.

DR. LIEBLER: Right. Of course.

DR. BELSITO: Okay.

DR. SNYDER: And we did get some comments, Don. Did we need to talk about those or not?

MS. RAJ: I do have a question. Also, there was no data for the leaf powder ingredient, but -- oh. I guess that comes under the leaf ingredients. So, I guess that's fine?

DR. BELSITO: Okay. So that in terms of the DART data, Paul, we just get rid of that by the very high doses, okay? Is that right?

DR. SNYDER: Yes. Again, it's not really a DART study, anyway. It was the developed mammary gland over the estrous cycle.

DR. BELSITO: Okay. What about the genotox? We're okay with that except, again, like that would be another endpoint for the root. Is that correct? I would also point out that we don't have any mammalian for flower/leaf/stem water and the flower and the leaf extract.

DR. SNYDER: I wasn't concerned with it being GRAS but --

DR. BELSITO: Okay. I mean, is --

DR. SNYDER: Yep. I understand.

DR. BELSITO: So, we're just going with saying nothing about genotox just -- at this point?

DR. SNYDER: Yeah.

DR. BELSITO: Okay. So, the only one that --

DR. SNYDER: We're only talking 0.38 percent is the maximum for the -- I don't remember which one it was. Yeah. The leaf extract was 0.38 percent. That was the maximum concentration of use.

DR. BELSITO: Okay. So, you're comfortable with the information we have on genotox for all of them except the root, and that will then depend on the 28-day dermal. Irritation, we have it only for the leaf extract. And I don't know --

DR. SNYDER: We got it for the -- the oil --

DR. BELSITO: But we don't --

DR. SNYDER: -- is 8 percent oil or leaf oil? One of them.

DR. BELSITO: Yeah. We don't know.

DR. SNYDER: Yeah.

DR. BELSITO: So, where are we? We are --

DR. SNYDER: Well, we got two new HRIPTs in Wave 2.

MS. RAJ: Much lower than the maximum reported concentration of use, though.

DR. SNYDER: Correct. Right, 0.01 and 0.015.

DR. BELSITO: Yeah. I had we need all except for the leaf oil for sensitization. And then the question, could the oil be used to read across from the leaf oil? Oh, we didn't know. Well --

DR. SNYDER: Right. We don't know which it is.

DR. BELSITO: -- I guess, my question was, wherever this oil is extracted from, can it substitute for sage or sage leaf oil? Because I don't think there's going to be a lot of oil in the root -- or in the stem, rather -- but maybe I'm wrong. Aren't you going to find most of the oil in a leaf? What do you think, Dan?

DR. LIEBLER: Yeah. I think so.

DR. SNYDER: If you look on page 19 and go down to composition of the leaf oil versus the oil, is there anything there that would concern you for sensitization?

DR. LIEBLER: I'm scrolling.

DR. BELSITO: Yeah. Well, you got that huge gap in thujone, not as sensitizer, but it has its own toxicity. But it'll be very low by the final formulation. Camphor, not really much of a sensitizer. Borneol, not really much of a sensitizer. And, again, the concentrations are going to end up being very low. Caryophylene, no. I think the -- I mean, not really, Paul.

DR. SNYDER: Yeah. I didn't think so either. And so irrespective, we have an 8 percent whatever oil it is. With 25 it was negative. And then we got those lower ones.

DR. BELSITO: Yeah. But I guess the question I have is can the oil -- so the oil -- I think the oil can cover the leaf. But I don't know if it can cover other parts. And then the question is can it cover a leaf extract? But it's not likely that they would contain more sensitizers than the oil.

DR. LIEBLER: The oil is going to sort of supreme in concentration of sensitizers because it's mostly those terpenes.

DR. BELSITO: So, what do we need in terms of sensitization? And what do we need in terms of irritation? Really, the only information that we have about composition is on the oil, correct? And the sensitization data that we have -- I don't know why it's not going back to the page.

DR. LIEBLER: My take is that the oil is going to have the highest concentrations of substances of concern for sensitization, the terpenes.

DR. BELSITO: Okay.

DR. LIEBLER: And so sage oil or sage leaf oil should suffice for that purpose if you're going to prioritize what to do sensitization on because you clearly -- you got this maximization test on 25 subjects. I don't know how satisfactory that is. It's up to you and David to -- and we'll want to talk about -- but if you're going to prioritize something for sensitization data, I would think it's the oil, either the sage oil or the leaf oil or both.

DR. BELSITO: I would agree. So, we got a human max 8 percent in petrolatum, no sensitization. A small number of subjects, but it's supported by the lack of --

DR. LIEBLER: Composition issues.

DR. BELSITO: -- well, and also the lack of clinical studies. You're talking about a botanical. You're talking about a plant that people handle. It's been ground up if they're cooking and rubbing sage onto whatever. And we've got two reports, one of a sage extract and one of a sage oil. So, I think the oil would have the highest component of sensitizers, and the lack of clinical data suggests that sensitization is not an issue in cosmetic products. Is that fair?

DR. SNYDER: Yeah.

DR. LIEBLER: Yeah.

DR. BELSITO: And irritation? I mean, we have an in vitro.

DR. SNYDER: I didn't think it has an irritant.

DR. BELSITO: Yeah. I certainly didn't see anything in the oil that looked irritating, but that's all we have composition on. And I'm just looking. The highest leave-on use 0.38 for the leaf extract? Is that right? Then we have irritation data (audio skip) on the leaf extract undiluted at 10 percent --

MS. RAJ: Sorry, excuse me. If we were to reclassify the flower, leaf, and stem water as an oil ingredient, that would leave us with irritation and, I guess, sensitization data only on the oil ingredients.

DR. BELSITO: No. I think we're not --

DR. SNYDER: No. I think we're good on those.

DR. BELSITO: We're not reclassifying the water as an oil.

DR. LIEBLER: Yeah.

DR. BELSITO: We think that steam distillation -- they take one fraction which has gone up in the steam, and that's the water extract. And then what's left is the oil extract.

DR. LIEBLER: I think what happens, for what it's worth, is that the steam contains aqueous and oil-like components. Once they're condensed and they collect in a little vial or a bottle, the aqueous goes to the bottom and the oil comes to the top. I remember literally seeing that, Don, when we took the tour --

DR. BELSITO: Oh, yeah. That's right, in GRAS.

DR. LIEBLER: Yeah. When they were doing the iris root, remember that?

DR. BELSITO: Yeah. And then they skim it, and then they further purify it.

DR. LIEBLER: Right. But I think the Council memo makes the point very well about the difference between a water and an essential oil. And I think calling it an essential oil is probably a misnomer, even if somebody else used that term. And unless we have a better description that makes it clearer what's the aqueous component, what's the oil component, we should stick with the water being more like a water and not an oil.

DR. EISENMANN: Yeah. But we're talking about all the studies that came from the ECHA dossier were on an oil. And I think they are not -- they're in the report as water. So, I looked at the dossier, and the way they describe the material that they're supporting is as an oil. (Audio skip) call it sage oil. So, all those studies should be as an oil, not as the water.

DR. LIEBLER: Yeah. But Carol, can't --

DR. EISENMANN: So, yes, there's a difference, but the studies from the dossier are on an oil. And I think that's the main material of commerce anyway.

DR. LIEBLER: Carol, can we associate what's in the ECHA document with a high degree of confidence with a cosmetic ingredient?

DR. EISENMANN: I would assume so because they're providing that material that they have to be doing what's in commerce.

DR. LIEBLER: Right.

DR. EISENMANN: I have to look again and see if any of the suppliers are the same as what we have listed.

DR. LIEBLER: Let me rephrase my question. Which cosmetic ingredient in our list could the ECHA data be associated with?

DR. EISENMANN: That is the issue. I'm not sure if it's the oil, which would be like the whole plant or the above-ground oil or just the leaf.

DR. LIEBLER: Okay. That's what we need to know.

DR. EISENMANN: I can't tell that. But I believe it's an oil and not a water --

DR. LIEBLER: Yeah.

DR. EISENMANN: -- based on what I read.

DR. BELSITO: Okay. But for the leaf -- so first of all, flower/leaf/stem, a major component would be leaf, right?

DR. LIEBLER: I think so.

DR. BELSITO: Right. And the oil would be largely derived from the leaf. And, so, if the oil is safe, then (audio skip). And given the highest concentration of use at 0.57, I'm not sure why we're having problems with the other above-ground components. I agree with the root but --

DR. LIEBLER: I'm not sure either.

DR. BELSITO: Paul, Curt?

DR. SNYDER: I didn't have an issue.

DR. KLAASSEN: Yeah. I'm not concerned.

DR. BELSITO: Okay. So, we're going insufficient for the root components for a 28-day dermal and (audio skip) necessary and safe as used for all the others?

DR. SNYDER: That's what I have.

DR. BELSITO: Okay. And in the discussion, Preethi, we obviously need the usual plant and inhalation boilerplate and the fact that the sage leaf and presumably stem are GRAS components and would be the major component of the flower/leaf/stem extract, juice and water -- the leaves would contribute the greatest amount to those. And, so, we felt that the -- and that the oil would contain the major sensitizers and that mitigated the need for sensitization data on the other ingredients except for the root.

DR. SNYDER: We don't have a maximum concentration of use for the root because it's not used.

DR. BELSITO: So, we probably won't get it, and then we'll just go insufficient, right?

DR. SNYDER: Yeah.

MS. RAJ: So, thank you, Dr. Belsito and everyone. I just want to clarify. Is it a split conclusion, where you are asking for the composition and impurities for all the flower ingredients -- ingredients which contain flower in them, you're asking for composition and impurities? And, also, for the -- is it the extract, the juice, the root extract, and the water ingredient you also want the composition and impurities?

DR. BELSITO: I thought we just said that those were all safe as used.

DR. SNYDER: Yeah. I think we came back around, Preethi.

MS. RAJ: I see. Okay.

DR. SNYDER: So, they're safe as used.

DR. BELSITO: So, basically, the leaf is going to be the major driver for all tox endpoints for the other parts of the plant except the root.

MS. RAJ: Okay. So, you no longer need the method of manufacture and composition/impurities for the flower ingredients because the leaf will drive that. Is that right?

DR. LIEBLER: Right. Correct.

MS. RAJ: Okay. But you still want method of manufacture, composition and impurities for the root extract and a 28-day dermal tox for the root extract?

DR. BELSITO: Right.

DR. SNYDER: And sensitization.

MS. RAJ: And sensitization. And no need for irritation, right, just sensitization?

DR. BELSITO: For root? Yeah.

MS. RAJ: Yeah.

DR. BELSITO: We need sensitization and irritation.

DR. KLAASSEN: Which we'll never get.

MS. RAJ: And, I guess, then it's a split conclusion then because you're going insufficient for the root extract, but then you're safe for all the other things?

MR. HELDRETH: No, Preethi, there's no conclusion. It's a draft report with insufficiencies, so the only thing coming out of this meeting is an IDA.

MS. RAJ: Okay.

MR. HELDRETH: For the root.

MS. RAJ: Yeah. Sorry.

DR. SNYDER: We're sorry. We were very confusing.

DR. LIEBLER: Yeah.

MS. RAJ: Yeah. I'm still trying to get a handle on botanicals, so excuse me.

DR. LIEBLER: Well, I hope you weren't hoping for good sage wisdom from us.

MS. RAJ: That's okay. I think I got a good share of that.

DR. LIEBLER: Yeah. You have another one: papaya.

DR. BELSITO: Yeah. So basically, yeah. So, all of them except the root-derived components are safe as used. And for the root we need manufacture, impurities, 28-day dermal, and, if absorbed, other systemic endpoints and sensitization and irritation at concentration of use.

DR. SNYDER: Well, I think we could say at the max for -- because we'll say it's used as others, and the max is 0.38.

MS. RAJ: Thank you.

DR. BELSITO: Okay. Anything else on this?

MS. RAJ: I think that's it.

Cohen Team – March 11, 2021

DR. COHEN: Okay. The next item for this very sage teem is sage. I'm sorry, I couldn't help myself. This is Preethi's. It's a draft report. This is the first time we're reviewing it.

This safety assessment is for 12 items. It's used as a skin conditioning agent and a fragrance. The leaf extract has the greatest frequency of use. The leaf extract also has the highest reported concentration of use at 0.38 percent. There are formulations that will expose the mucus membranes in bath soaps and detergents and the use of the sage oil at 0.02 percent.

MS. RAJ: Dr. Cohen --

DR. COHEN: Yes.

MS. RAJ: I'm so sorry to interrupt you, but I just realized I wanted to ask the panel one last thing about the levulinic report.

DR. COHEN: Yes, of course.

MS. RAJ: Because we got a comment from Council suggesting that they wanted the outcome of the RIFM assessment to be included as a separate section in a risk assessment part of the report. So, I just wanted to know the panel's thought on that, and what exactly needs to be included in this.

DR. SHANK: We haven't seen that RIFM statement, have we?

MS. RAJ: So, it's an Api (phonetic) et al. report that has been included in the report. But I guess Council thought that there needs to be a separate risk assessment section in that report. And the outcome of that assessment needs to be included in there. But to me, that seemed a little vague. I wasn't really sure what they wanted in there.

DR. SHANK: Maybe Alex could explain that to us.

DR. BERGFELD: Or Jay.

DR. SHANK: Jay.

DR. ANSELL: Yeah. We just thought that the RIFM analysis included tox data endpoints which were relevant to this discussion. But since we feel that in aggregate the tox questions are addressed, I think just making sure that it's identified in the discussion would be sufficient.

MS. RAJ: So sorry, Jay, am I hearing we wouldn't need a separate risk assessment section then? You just want it to be mentioned in the discussion?

DR. ANSELL: We want to make sure that people are aware of the data that RIFM identified that would be relevant. It's a food additive use and human studies.

MS. RAJ: Okay.

DR. COHEN: So, this would appear in the discussion, and since this is a tentative report, we'll see it before we finally approve it, right?

DR. ANSELL: Yes.

MS. RAJ: Okay. Thank you.

DR. COHEN: Okay. Back to sage. We have the information on leaf extract using pump and aerosol sprays at up to 0.002, and the leaf oil is in suntan formulations. And the flower leaf stem water and sage water are reported to function only as a fragrance, so I'll need your help how we adjudicate that. So, can we cluster all these in here? Can we include all of them and read-across?

DR. SLAGA: I have one question. It was unclear to me that sage extract -- if it's the whole plant, or there's one sentence where it mentions how it's made, that it's related -- it's the leaf. We already have a leaf extract. It doesn't make sense to me. If it's the whole plant then, you know, that gives us more read-across potential. So, does anyone know for sure if it is the whole plant?

DR. COHEN: Well, when you read that, it looks like it's a tiny batch of just leaves. I hardly --

DR. SLAGA: Yeah. That's what it sounds like to me --

DR. COHEN: -- (inaudible) a commercial application with method of manufacturing.

MS. RAJ: Can anyone from wINCI comment?

DR. SHANK: I have another question, Preethi. All of the data, at least the toxicology data for these ingredients --

MS. RAJ: Yes.

DR. SHANK: -- are in italics, which means they're not necessarily cosmetic ingredients. Is that correct? So, we really don't have any toxicology information on --

MS. RAJ: That's correct.

DR. SHANK: -- sage ingredients that we know that they're cosmetic ingredients?

MS. RAJ: Yes. We only received the two HRIPTs that are known cosmetic ingredients. Yes.

DR. SHANK: Right. But the tox data are all sort of generic, I guess.

MS. RAJ: Yes.

DR. SHANK: I'm really not too sure how to handle that. I would like to have some information to help me extrapolate from the data that's in the report, at least the tox data, and how that applies to cosmetic ingredients. So, I guess this is a question for the chemists.

DR. SLAGA: I had the same concern as you, Ron, also, and I didn't know how to deal with that. There's a lot of data, so to speak, in there.

DR. SHANK: Yes. Correct. Now, this is a food or an herb. Yes, an herb.

MS. RAJ: Yeah. Which would make the consumption very less.

DR. PETERSON: Much -- yeah. Very low.

DR. SHANK: Yeah. So, I guess we could rely on that. Yeah. If it's a food, we don't need very much tox data.

DR. SLAGA: Yeah. Also, the sage is put on meats as a flavoring. And, so to say -- the leaf extract, so actually, we have a lot of safety relationships there too, that it's eaten.

DR. ANSELL: The approach we followed in the past, and that we support, is that materials which are food items with a long history of use can use that to resolve the systemic issues that -- because of the processing in a water or an oil, there would be a need to look at topical effects. But the food use would address the systemic issues.

DR. SLAGA: Right. I agree.

DR. SHANK: Okay. I agree also.

DR. COHEN: Well, we had a memo --

DR. PETERSON: So --

DR. COHEN: Oh, go ahead. Go ahead.

DR. PETERSON: The only thing we don't have much information on is the root extract, and I don't --

DR. BERGFELD: Not there.

DR. PETERSON: And I think the --

MS. RAJ: Yeah. It doesn't --

DR. PETERSON: -- the root would be --

DR. SLAGA: Don't have any on the root I don't think.

MS. RAJ: Hmm-mmm.

DR. COHEN: Right. And I have the same thing. We have nothing on the root.

MS. RAJ: And excuse me, I don't know if this is the right moment to bring this up, but Council did also bring up that a lot of this data is coming from an ECHA dossier in which we felt the definition aligned the most with the wINCI definition for salvia officinalis flower, leaf, and stem water. But they, you know, brought to our attention that, you know, there's a difference between the water and the oil. They felt that whatever was described in the ECHA dossier was more relevant or pertinent to the oil ingredients, which would be the leaf oil and the, you know, oil. So, I guess, how does the panel feel about that?

MS. FIUME: And just to add a little bit to that. So, the ECHA dossiers, especially when it comes to botanicals, often they're hard to discern. It'll describe the test product as an extractive, which could be a number of items. It did say a steam distillate. We were basing the fact that the water was a steam distillate.

And, Jay, you can clarify further that the steam distillation could produce a water or an oil. I believe the CAS number may correspond to the oils, so it may be appropriate to put it under the oil for the whole plant. Between Council and the panel's preference or expertise, we will move the data wherever you feel it is most appropriate. But, Jay, if you want to go on a little further about how those are processed and then classified as to the ingredient.

DR. ANSELL: Yeah. I think this is the first round, and so we're going to be quite open to resolve some of these questions. But yeah. I mean, the water and the oil -- the oil is typically made through steam distillation. And, so, we do think that's the most relevant. But we'll take that under advisement and come back with, you know, more detail as we go forward.

MS. FIUME: And this is a point of clarification for the panel then. In instances where in the report currently, there are data for the flower, leaf, steam, water, that will no longer be true. It would most likely be placed under the oil of the whole plant, which would mean, then, there's no tox data for that water ingredient.

DR. COHEN: That's kind of how I read into it, particularly after Bart's memo. It's that we have a lot of data on the oil, but I don't know what that water fraction, you know, may have in it and what data we have on that by trying to extrapolate back. And we already pointed out the method of manufacturing for the sage extract just looks like it's coming from leaves.

MS. FIUME: That may be a placement issue. Reading it again, I wonder if that should be placed under the leaf extract, being that it looks like it's a tea made out of sage leaves, and we can move that. So being that this is the first time, we would have -- I think asking for that in an IDA, and even clarification as to what is in all those plant parts, wouldn't be a bad thing to help the panel really figure out what's what in this report.

DR. COHEN: Yes.

DR. ANSELL: No, I was just also going to point out concerning discussions of roots, we would not extend the food use to plant parts which are not in fact, you know, food items.

DR. SHANK: Right.

DR. SLAGA: Right.

DR. ANSELL: So, focusing typically in these analyses on fruits or stem, fruit, leaf combinations.

DR. COHEN: So, could you guys help me articulate what we're going to ask for tomorrow in our IDA? Do we want impurities and method of manufacturing for root?

DR. PETERSON: Yes.

DR. SLAGA: Yes.

DR. PETERSON: Yeah.

DR. COHEN: And what about relevant tox data since it's --

DR. SLAGA: Irritations, sensitization, and genotox.

MS. RAJ: Preferably at the maximum use of concentration or higher?

DR. SLAGA: Right.

DR. SHANK: We have genotox on the oil.

DR. SLAGA: But not the root.

DR. SHANK: Oh, you were talking just the root.

DR. SLAGA: We're on the root.

DR. COHEN: We're on root now.

DR. SLAGA: Yeah. We're down under the ground.

DR. SHANK: Sorry.

DR. COHEN: We're working our way up. Anything else on root that we want right now?

DR. PETERSON: Did you put composition? So, we have method of manufacturing, composition, and impurities.

DR. COHEN: Yes.

MS. RAJ: So, am I hearing right that you want all this information only for the root ingredient?

DR. PETERSON: We're not --

DR. COHEN: Well, no. We're just on root now.

MS. RAJ: Oh.

DR. SLAGA: Yeah.

MS. RAJ: Okay.

DR. COHEN: We're working our way up to the aerial parts of the plant.

MS. RAJ: Okay.

DR. COHEN: And Wilma, thank you for pointing that out in the introduction how challenging these can be. I felt you were speaking to me.

DR. BERGFELD: Speaking to myself. Oh, my god, wait until you get to red algae.

DR. COHEN: Okay. So now, what about the aerial parts of the plant, and how do we adjudicate the aqueous versus the oil parts? What do we feel we have, and what do we need?

DR. PETERSON: Well, I have gotten all confused now by what is oil and what is water because of the conversation we've just had. But I think we have a lot of information on what's an oil.

DR. SLAGA: Yeah. I think we're okay with oil in terms of needs.

DR. ANSELL: So, it's the method of manufacture, right? Because I do believe that the difference between the oil and water is not the extraction method but rather the final preparation.

DR. SLAGA: Okay.

DR. ANSELL: The oil is actually just the water without the water.

DR. PETERSON: That doesn't make sense why they would call it water when it's oil. Jay, what you're saying is that the water is oil, right?

DR. ANSELL: No.

DR. COHEN: No.

DR. ANSELL: I'm saying, is that they all arise from a water extract, and it's the further processing which would distinguish a water from an oil. Juice would typically be squeezed, but an oil and water would be more of a concentration -- a post-extraction concentration. I think that's a very valid question. And I think it's one that we would take on and give a little more clarity.

DR. PETERSON: Yeah. That would be great because from what you said -- just let me repeat so that I make sure that I understand. So, the water is basically the tea, or whatever, that's used to then do the distillate to get the oil?

DR. ANSELL: That is my understanding.

DR. PETERSON: Okay.

DR. ANSELL: But I do believe that that's a great question. And we will address that for the next report, clarify a method of manufacturing to distinguish them.

DR. COHEN: So, might we get more specific and say flower/leaf/stem water and leaf water, we want method of manufacturing, composition, and impurities?

DR. PETERSON: Yep.

DR. COHEN: And it looks like we need -- do we need tox on it, I think? I don't think we -- oh, we have some.

DR. SLAGA: Dermal irritation, sensitization, and genotox.

MS. RAJ: Well, just --

DR. COHEN: Okay.

MS. RAJ: -- just to remind, once we do the change, or if we move the data to the oil, I don't know how much data we'd have on these water ingredients. We would not have any.

DR. COHEN: So, we'll need dermal tox?

DR. SLAGA: Yes.

MS. RAJ: I think so.

DR. ANSELL: Well, if their --

DR. SLAGA: No.

DR. ANSELL: -- if the only difference is concentration, asking the compositions will -- once diluted in a natural product would end up being the driver and could end up being the same concentration. So, I think it's all going to come more clear once we have the method of manufacture.

DR. COHEN: I guess what's confusing me is, like, okay, you have this distillate and the oil goes to the top presumably. You take that off, there are going to be different components in the aqueous phase than in the oil phase, right?

DR. SLAGA: Right.

DR. COHEN: So, they seem like two different line items entirely.

DR. SLAGA: Right. I agree.

DR. PETERSON: If that's what water is, then yeah. But I'm still confused about what water is, so do have to define that? And then, depending on the method of manufacturing and what the water is, we're going to either need the components or not need the components depending on the method of manufacturing. So, can we specify that if it's this, we need that, or if it's that, we don't need anything at all? Because if it's --

DR. COHEN: Well, why don't we just ask for what we want. And when it comes back, we can fill in the blanks. Because if we do a lot of if/then statements, then it -- we have to give them a cutoff on what we want to see.

DR. PETERSON: Sure. Sure. Sure. And we can go back with another request for data.

DR. ANSELL: Yeah. And I think the question is clearer as opposed to hypothetical answers and then further questions. We would just need to know -- I think we need a distinction of what you're thinking of as an oil would be compressed as opposed to the concentration of the steam distillate. And that would resolve a number of the questions.

DR. BERGFELD: David, I have a question that's a little bit different, and that appears under dermal irritation and sensitization in vitro test. And it's called the RHE, R-H-E test, and the bottom result, it was not a corrosive. I'm not familiar with that particular statement. Not corrosive, do they mean not irritating or truly not corrosive?

MS. RAJ: That's probably how it was written in the source, Dr. Bergfeld. But perhaps that could also mean not irritating.

DR. BERGFELD: I think that's probably what it means.

DR. COHEN: Yeah.

MS. FIUME: And these tests are predictive tests; they're not absolute.

DR. BERGFELD: Yeah.

MS. FIUME: So, the in vitro tests are a prediction that it would not be considered corrosive --

DR. BERGFELD: Well corrosive (audio skip).

MS. FIUME: -- is the terminology they use.

DR. BERGFELD: Yeah. But does that mean irritating, Monice?

MS. FIUME: That's how I would interpret it but --

DR. BERGFELD: Irritation and corrosive are in the same line, one being more severe than the other.

MS. FIUME: I'm not extremely familiar with the toxicology of all of the in vitro tests. But I believe for some of these in vitro tests rather than -- sometimes there's data saying not predicted to be irritating. But predicted not to be corrosive does seem to be common in the conclusions that we get. So, we can only go with whatever wording was in the document that we had in front of us.

DR. COHEN: We don't tend to use that in the medical vernacular very much, corrosive.

DR. PETERSON: Yeah. That sounds like a chemistry lab concern.

DR. COHEN: Now, it looked like we have some sensitization and irritation at 8 percent in humans in the oil. And there were a few cases of allergic contact dermatitis in the lip balm and in aromatherapy oil. And in some late-breaking data that was sent, we have sensitization at 0.01 percent of the leaf extract at 110 subjects, but the max use of the leaf extract was 0.38 percent. So, it didn't satisfy our typical criteria.

And we had a max formulation of 0.015 percent for the oil in 105 subjects, but we have max use of 0.022. So again, we still need that max use -- well, we may not if we have the 8 percent oil. I'm sorry, I just want to make sure I'm covering all of that. We may be okay with oil and irritation and sensitization.

DR. PETERSON: Yeah. I mean, the chemical composition of the oil, it does have a chemical that's irritating and sensitizing. So, I think -- I mean, I have a note that we should have -- that it needs to be formulated not to be sensitizing or irritating. And then there's also a neurotoxicant in it.

And again, I don't think this is a concern when it's food, but if the concentrations are high enough in an oil, and it's used enough, then I guess you would worry about whether it penetrated or not. But, you know, I don't think there's any evidence of problems, but I just wanted -- from a chemist's perspective, there are chemicals in the oil that have some toxicological properties.

MS. FIUME: And David, if it's okay, I'd like to add, I know, Lisa, you had said earlier that we can go back and ask for more. Procedurally, we try and -- or I should say the panel tries to cover everything in the IDA so that we don't have to go back and do a second IDA. As I'm looking at the method of manufacture, it looks like the only information that we have for that, that is known to be a cosmetic ingredient, is on the leaf extract because that information was provided by suppliers. Where the others are general processes that were found in the published literature that we don't know how they necessarily apply to the cosmetic ingredients.

So, I don't know if that helps you as you're formulating your list or not. Because even in the irritation and sensitization part of the paper, I think a lot of that information came from a RIFM document that was done a long time ago on a sage oil.

MS. RAJ: Yes.

MS. FIUME: So, again, a generic name not exactly knowing if it's a one-for-one to what the current cosmetic ingredient is. So, I don't know if that helps you as you're forming your list for the IDA or not, but I did just want to point out those couple of items.

DR. COHEN: I think it does, then. So, are we going to ask for then, irritancy and sensitization on the other components at max use?

DR. SLAGA: Yes.

DR. PETERSON: And then we would want method of manufacturing for the cosmetic industry because I'm -- yeah, I'm still catching on this subtlety between what's okay to use and what's not okay. But it does make sense that it's possible the cosmetic industry is using something different than these references that you found. So then one would say we would need to have method of manufacturing on the items used in cosmetics.

DR. SHANK: I agree with that.

DR. SLAGA: Yeah.

MS. RAJ: Dr. Peterson, I just want to clarify from what you said before. So, does it sound like you would want to point out which of these components are, I guess, potential sensitizers or irritants or whatever? Because I know in our report, we kind of emphasized that we're reviewing these complex mixtures and not individual, you know, constituents --

DR. PETERSON: Right. Right. You have the -- I mean, you had that nice boilerplate sentences that talk about, you know, making sure that the reader understands that the cosmetic ingredient is a mixture and that, while there may be components of it that have some activity, we don't focus on the individual components. We focus on the mixture. And my only point for pointing them out is that, you know, that there's a sensitizer in there means that we have to think about the sensitizing potential of the overall cosmetic ingredient. You know what --

MS. RAJ: Yes.

DR. PETERSON: -- you need that data to, you know, you need to have the data to support that the cosmetic ingredient doesn't have the irritation, or it would have the irritation. And then we have to make a recommendation that anything using that ingredient needs to be formulated -- because the mixture is going into another mixture, and who knows what the interactions are between the chemical. Whether they enhance or -- you know, in some cases they can mute the biological activity of the individual component, depending on what else is in the mixtures.

And we don't really know that, so what we want is the safety information on the mixture. But, you know, to me it's an alert that there's a sensitizer in it, so we have to think about it.

MS. RAJ: Absolutely. And I'm kind of curious, too, because I'm also, you know, learning the world of botanicals. But would you say that perhaps -- I mean, it's hard to know, again, until you see the method of manufacture and, you know, I guess consider which constituents are maybe more prevalent in some ingredients more than others. But would you say as a panel that maybe you would, I guess, be more concerned about some ingredients than others in the group based on the level of these constituents in them?

DR. PETERSON: Yeah. I mean, if it turns out that it's 34 percent, or something like that, then it's a bigger concern than if it's less than 1 percent. You know, so I do think that knowing the composition helps you make your safety assessment, again, with the caveat you don't know how, you know, a lot of the testing of these individual components is done as a pure mixture. And when you start putting it in a mixture, there's other chemicals in the mixture that can either enhance or diminish the biological activity of the individual component.

MS. RAJ: Thank you.

DR. COHEN: So, just to circle back, we have method of manufacturing for the leaf extract, but we probably don't for anything else, then?

DR. PETERSON: Yep.

DR. COHEN: And, so, do we need the entire repertoire of requests for everything?

DR. SLAGA: The rest.

DR. COHEN: For the rest?

DR. PETERSON: Yep. Yep. And then we can see what we get, and then we can -- based on, you know, further clarification and --

DR. COHEN: All right.

DR. BERGFELD: The problem is just botanicals always is the composition and the impurity then.

MS. RAJ: So, am I hearing for everything besides the leaf extract, you want method of manufacture, composition, impurities, relevant tox data, and dermal irritation and sensitization data?

DR. COHEN: Yes.

DR. SHANK: And make sure that's for cosmetic ingredients.

MS. RAJ: Cosmetic ingredients.

DR. PETERSON: Right.

DR. BERGFELD: Cosmetic grade or ingredients, yeah.

MS. RAJ: Thank you.

DR. COHEN: All right. I'll put that together to articulate tomorrow. Okay.

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DR. COHEN: Okay, thank you. Sage, it's the first time we're reviewing this. It's used as a skin conditioning agent and a fragrance. And there are 12 derived ingredients. Leaf Extract is reported to have the greatest frequency. Leaf Extract also has the highest reported concentration of use, at .38 percent. And there are formulations that come in contact with the mucus membrane, such as sage oil, at 0.02 percent in bath soaps and detergents.

Our team suggested coming out with an insufficient data announcement. We have a lot of information about the oil component, and in fact it is a food. It's used as a seasoning.

For the aqueous components, we're asking for composition and impurities, dermal tox, genotox, irritation and sensitization at max use, for the Flower/Leaf/Stem/Water, Water and Leaf Water. And, additionally, for the Root, we would need the same things as above including the method of manufacturing since we had nothing for it.

DR. BERGFELD: And that's a motion?

DR. COHEN: That's a motion.

DR. BERGFELD: Is there a second or comment?

DR. BELSITO: We'll second the insufficiency. I'm not sure exactly if our lists match.

DR. BERGFELD: Okay, well, let me make an amendment here. It's going insufficient, and we'll vote on that. And then we'll discuss the needs, okay? Is that all right, David?

DR. COHEN: Yes.

DR. BERGFELD: All right. Any opposed to going insufficient? Abstaining? Hearing none, it's approved. Now, let's discuss the needs. Do you want to compare -- why don't you take one at a time, David, and let Don respond.

DR. COHEN: Okay, so, Don, for Flower/Leaf/Stem/Water composition and impurities, dermal tox, genotox, irritation and sensitization at max use.

DR. BELSITO: So, we asked for a 28-day dermal and if absorbed then those.

DR. COHEN: Okay.

DR. BELSITO: Those are rather extensive test we're getting.

DR. COHEN: Okay. Ron, any concerns with that? Yeah, I think we're fine with that. I would say, we would duplicate that for Water and Leaf Water. And, all of those for Root, including method of manufacturing.

DR. BERGFELD: All right, for clarity again. For the group that you're going to ask for the 28-day dermal, is that the only one to be included there, or you're going to ask for anything else? The Flower/Leaf/Stem --

DR. BELSITO: We need sensitization for all except the Leaf Oil.

DR. COHEN: We agree.

DR. BERGFELD: Okay. So 28-day dermal in human, animal, or just sensitization?

DR. BELSITO: Sensitization, whatever is out there.

DR. BERGFELD: Okay. Anything else?

DR. BELSITO: We just had a question regarding, you know, the insufficiency on the 28-day dermal that we wanted to address with the panel. Do we need it for all of the ingredients, or can we choose a representative ingredient? And we wanted to hear Tom's and Ron's and Lisa's and David's comments on that.

DR. BERGFELD: Ron, you want to start?

DR. SHANK: If the chemists agree, if you have it on the Leaf Extract wouldn't that cover everything else?

DR. BERGFELD: Not the Root.

DR. SHANK: No, not the Root.

DR. PETERSON: I think if we had the composition of what's in the Water, you could read across -- I mean, I don't think you can read across to the Root, but I think if you had some composition information, which we don't have, I think, for the water.

DR. COHEN: Again, are we getting into the same discussion we will have with Tree Tea where there's an aqueous component with its attended set of constituents. And then the hydrophobic component with its constituents. And, perhaps, if we break them out into those two and ask for dermal tox on those two, we might be able to cover all of them.

DR. LIEBLER: My two-cent worth is that if we're going to lean on one thing to test we ought to get something that's (audio distortion), because it's going to have the constituents of concern that applies -- concern for sensitization. For example, the terpenoids which most frequently turn up as causative agents in that.

And, the problem with the waters, it's really hard to tell what it is. The opening description of the water says it an essential oil. So, you know, it's prepared by steam distillation. So if you do a steam distillation and you collect that in a little vial, it usually separates out into an aqueous and organic layer anyway.

So, if we had -- I guess I go back to Ron Shank's suggestion of the Leaf Extract. Because, most of the safe products are a leaf extract. And if it's an extract that captures the greatest percentage of the organics, that would be idea for a lead material for testing.

DR. SLAGA: Honestly, with that Leaf Extract would be the best.

DR. PETERSON: So, I just want to clarify, by Leaf Extract you mean the initial thing before distillation, or are you talking about the oil?

DR. LIEBLER: Oh, it would have to be a product.

DR. PETERSON: Okay.

DR. LIEBLER: Yeah. So, if we're choosing among the products, then, I think, based on the descriptions we had provided, either the Sage Extract or Leaf Extract would be best. And the Leaf Extract, bottom of PDF Page 11, it looks like they're pretty much hydroacoholic extracts, which I think would capture most of what we want. (Audio distorted).

DR. BELSITO: But the extracts, I mean, what's really left is -- is there a pure leaf extract?

DR. LIEBLER: It's one of the ingredients.

DR. SLAGA: Yeah.

DR. BELSITO: Okay.

DR. LIEBLER: Bottom of PDF Page 11, and there are multiple (audio distorted) reported, but they're all hydroacoholic extracts.

DR. BELSITO: Okay, so 28-day dermal on the Leaf Extract would cover all of the other extracts and the waters.

DR. SHANK: Except the Root?

DR. BELSITO: Except the Root.

DR. SLAGA: Except the Root, yeah.

DR. BERGFELD: So that's a consensus agreement? It's a Leaf Extract that we'll ask for the 28-day dermal. And the Root stands alone with all the needs listed.

DR. BELSITO: Right.

DR. COHEN: Yeah, I think it's pretty sensible. It's the highest use and the highest concentration, so it's highly representative.

DR. BERGFELD: I wonder if we could hear from Curt and Ron before we close this discussion. Curt?

DR. KLAASSEN: Yes, I agree with that.

DR. BERGFELD: Ron?

DR. SHANK: Yeah, I agree.

DR. BERGFELD: Okay. Any other discussion before we leave this ingredient? Wilbur are you satisfied with what you have? No, it's Preethi, excuse me.

MS. RAJ: Yes. No worries, no worries. Thank you Dr. Bergfeld. Just to confirm, so, it sounds like the panel would like a 28-day dermal tox on the Leaf Extract ingredient. But you would like method of manufacture, composition, impurities, relevant tox data, gentox and dermal irritation and sensitization data on the Root Extract ingredient.

DR. BERGFELD: That's correct.

DR. COHEN: Yes.

DR. BERGFELD: Everybody endorse that, David. Don?

DR. COHEN: We want composition and impurities on those other items, though, correct? We just narrowed down the dermal tox for the Leaf Extract, but we're not removing the ask for composition and impurities for the other ones as well, correct?

DR. BERGFELD: I don't -- Don? Dan?

DR. LIEBLER: I think we should maintain the request for that at this stage of the report.

DR. SLAGA: Yeah.

DR. BERGFELD: Yeah. Okay.

DR. COHEN: Thank you.

DR. BERGFELD: So, there's an agreement in that. Anything else that we missed in that list, David? Don? Ron? Curt? Lisa? Tom?

DR. SLAGA: No.

DR. BELSITO: No.

DR. BERGFELD: No? Okay, I think we've done it then.

MS. RAJ: Thank you.

DR. BERGFELD: Moving on to the next ingredient in this reports advancing is Levulinic Acid and Sodium Levulinate, Dr. Belsito.

MS. FIUME: First, Dr. Bergfeld, can I go back for a clarification on the safe ingredients?

DR. BERGFELD: Sure.

MS. FIUME: So, and you may have said it and I might've of missed it. So, irritation and sensitization, is that still for all ingredients except the Leaf Oil, or on the Leaf Extract?

DR. BELSITO: Dan, can comment but our feeling was that the Leaf Extract would really be the major ingredient in Flower/Leaf/Stem Extract, so. But, it could be sensitization and irritation, for us at least on the Leaf Extract.

DR. COHEN: We were still asking for it for the Flower/Leaf/Stem, the Water, and the Leaf Water.

DR. BELSITO: Well, we can ask for it and then decide.

DR. COHEN: We can adjudicate it once we have more information to make a better decision.

DR. BELSITO: All right.

DR. BERGFELD: Okay.

MS. FIUME: Thank you.

DR. BERGFELD: Preethi, are you clear on this? Because this has changed a little bit since the beginning of the discussion. Are you clear on what the needs are now?

MS. RAJ: Are you talking to me? Yes.

DR. BERGFELD: Yes.

MS. RAJ: Yes, I think so. So, it sounds like the main ask is for the Leaf Extract the 28-day dermal. It sounds like you also want dermal irritation and sensitization for the Leaf Extract. And you want the whole almost profile of data needs for the Root Extract ingredient.

DR. BERGFELD: Now, I do believe that you added composition and impurities for all the things -- Flower/Leaf/Stem.

DR. COHEN: Yeah, Flower/Leaf/Stem/Water, Water, Leaf Water.

MS. RAJ: Okay, thank you.

DR. BERGFELD: Did we miss anything?

DR. COHEN: I think we got those now.

DR. BERGFELD: Okay. All right. Monice, did we answer the questions?

MS. FIUME: Yes, I believe so. I still think -- I believe the ask for irritation and sensitization data are all ingredients except the Leaf Oil, but then depending on what comes in you'll decide at the next meeting if that's correct -- if you need additional data at least on what was submitted. Is that correct?

DR. BERGFELD: Correct. Well, the needs were as listed but they were very interested in the Leaf Oil getting the 28-day dermal and sensitization and irritation.

DR. BELSITO: Water, not oil.

DR. LIEBLER: Leaf Extract.

DR. BELSITO: Leaf Extract.

DR. COHEN: Actually, thank you for asking again. Just one quick point. Is it possible to get some more information about the eight percent in petrolatum sensitization study and the 25 subjects. Because that one is way over max use and if we had some more data that might (audio distorted) valuable, but --

MS. RAJ: Dr. Cohen, I appreciate you bringing that up. I do think that study was like summary data coming from maybe an even outdated source. So, it might be hard.

DR. COHEN: Okay. Okay, and, yeah, so we can always consider a formulate not to be sensitizing discussion later on.

DR. BERGFELD: Now, I just want to make sure that we know what we've asked for. I need to have you go over it again, Preethi.

MS. RAJ: So, the ask was for a 28-day dermal tox for the Leaf Extract as well as dermal irritation and sensitization for the Leaf Extract. You want composition and impurities for the Flower/Leaf/Stem/Water, and the Leaf Water. Basically all the Flower/Leaf/Stem ingredients, sounds like. And for the Root Extract you kind of want the whole profile because there's nothing.

DR. BERGFELD: Right. I think we got it.

DR. COHEN: We got it.

DR. BERGFELD: Okay. I'm satisfied.

MS. RAJ: Thank you.

DR. BERGFELD: Thank you, very much. All right, so, the next big one that we have, Dr. Cohen, you lucky boy you, Red Algae.

DR. BELSITO: No, we have Levulinic Acid, Wilma.

DR. BERGFELD: Oh, I'm sorry. Oh, we had to go back, so Levulinic. Pardon me, thank you. Don, you're on. I'm sorry, you're waiting.

DECEMBER 2021 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – December 6, 2021

DR. BELSITO: In March of 2021, we issued an insufficient data announcement. We asked for a number of data needs. Let me just pop those up here.

MS. RAJ: I can share those, Dr. Belsito.

DR. BELSITO: I have it right here. Twenty-eight-day dermal tox for the leaf extract; dermal irritation and sensitization for the leaf extract; composition and impurities for flower, leaf, stem water, and leaf water; and basically, the usual tox endpoints for the flower, leaf, stem ingredients. Is that correct?

MS. RAJ: Actually, I have here, Dr. Belsito, that for all ingredients, you would ask for composition and impurities data, and dermal irritation and sensitization data at the maximum concentration of use. For the leaf extract ingredient, you had asked for a 28-day dermal tox and additional endpoints if absorbed. For the root extract ingredient, you had asked for method of manufacture and the 28-day dermal tox, again with additional endpoints if absorbed. That's what I have.

DR. BELSITO: Okay. We have a different list, but it doesn't matter. We look at all the data again, so let's see what we have this time. On PDF page 27, it says some of the ingredients consumed as foods, but it's only sage leaf, correct?

MS. RAJ: Yes. I know in the other group, they were curious about what the GRAS was referring to, so it seems like one GRAS qualification is for the oil of sage, which would be the oil of the sage leaf. Then the other is for spices and natural seasonings and flavoring.

DR. BELSITO: Which is also leaf.

MS. RAJ: Yes.

DR. BELSITO: Right, so the GRAS status is just for leaf components.

MS. RAJ: Yes, it doesn't explicitly say so, but that's, I guess, what we would gather.

DR. BELSITO: The oil is derived from the leaf.

MS. RAJ: Yes.

DR. LIEBLER: Correct.

DR. BELSITO: So GRAS is just the leaf.

DR. LIEBLER: Root is not used.

DR. BELSITO: Right. The next comment is on, again, PDF 27 with the ECHA definition. When I went through the ECHA report, they were just talking about the essential oil, which was from the leaves, flowers, and stalks by steam distillation, but not all the components of the plant. They were just looking at the oil. So I don't know that that helps us with anything else from the flower, the stem, or any other component of the plant because they threw it all in. It says the essential oil of *Salvia Officinalis* obtained from leaves, flowers, and stalks by steam distillation. So, they didn't look at the components of flowers and stalks, other than the essential oil, which we know is GRAS.

DR. EISENMANN: They gave the top 14 constituents.

DR. BELSITO: Right.

DR. EISENMANN: That is not listed in the CIR report yet.

DR. BELSITO: Right, and that will contain some dermal sensitizers as well.

DR. LIEBLER: Don, if you think of the essential oil as GRAS, and then the main concern would be skin sensitization, right?

DR. BELSITO: Well, yeah, but I mean, we don't know what the other components are of the flowers and the stalks.

DR. LIEBLER: Well, they're all contained in the oil.

DR. BELSITO: Are they? I mean, this --

DR. LIEBLER: I thought the essential oil was described as flowers, leaves, stems.

DR. BELSITO: Yeah, so in the ECHA report, they were looking at an essential oil that was derived from those, but they didn't look at any of the other components of leaves, flowers, or stalks. They simply looked at the steam distillation component that was the oil.

DR. LIEBLER: Yeah. See, this is where I got kind of hung up trying to think about this because literally by definition, it contains the sort of the oil-soluble components of the flowers, leaves, and stems.

DR. BELSITO: Right.

DR. LIEBLER: One of the hang-ups I had previously was flower ingredients were -- we didn't have any data on method of manufacture or composition impurities. But, on the other hand, flower ingredients are part of this essential oil. If the essential oil is GRAS, that means it mitigates any concern about systemic toxicity and leaves us with just the question of sensitization, irritation in the skin.

MS. RAJ: I do have a question.

DR. BELSITO: Why would it alleviate your systemic toxicity since we don't know what else is in the flowers and stalks other than just this oil component? There's got to be something more than just the oil, right?

DR. LIEBLER: Yeah, no, that's a good point. The oil really contains the terpenes --

DR. BELSITO: No, for --

DR. LIEBLER: -- (inaudible).

DR. BELSITO: I agree, but what about for other tox endpoints?

DR. LIEBLER: No, you're right. I think you're right. That's the problem. So we still don't have a solution for the flower.

MS. RAJ: I'm sorry to interject, but I do wonder though because, I mean, obviously, you must have dealt with this in other botanicals. I mean, we're more familiar with the use of the leaf in food. If the GRAS citations don't explicitly state that it's from the leaf, could it perhaps be the whole plant?

DR. BELSITO: Well, if you've ever looked at sage that you buy in a grocery store, or anyplace else, it's just the leaf. I've never seen any other part of sage.

DR. LIEBLER: You really have to go with Table 1 definitions, and so the sage extract is the extract of the whole plant, which includes stem, leaves, flowers.

DR. BELSITO: Roots.

DR. LIEBLER: Possibly root, yeah. Then, the next three items are flower/leaf/stem extract, juice, and water. That's got flower in it and stem. We don't have any method of manufacture or composition/impurities on either of those. Then everything else that's leaf oil, leaf extract, leaf powder, leaf water, sage oil is from the plant. Then the root, we don't have. Then the water is from the plant. The only thing that we really have good data on --

DR. BELSITO: Is leaf.

DR. LIEBLER: -- method of manufacture, composition, and impurities are the leaf ingredients.

DR. BELSITO: Yeah. I agree.

DR. SNYDER: Only ones used. The root is not used.

DR. LIEBLER: Yeah. Right.

DR. BELSITO: Okay.

MS. RAJ: But based on council's comment about, I guess, the classification of the ECHA data, did the Panel feel that perhaps the data should be reclassified or --

DR. LIEBLER: Remind me, what are they classified as?

MS. RAJ: So, because we weren't entirely sure of the method of manufacture of what was described in ECHA as an essential oil or an extract, like whether it was, I guess, just the leaf water on its own or whether it was a byproduct of the steam distillation to make oil, I think it was left as a flower, leaf, stem water throughout the report. According to council, it should -- they thought it should come under leaf oil or oil or even extract.

DR. LIEBLER: It would be great if it was more precisely defined, but it isn't and our attempting to read the sage leaves on this is not supportable.

DR. EISENMANN: Well, ECHA does say it's an essential oil. They clearly say it's an essential oil and they give 14 major components of it.

DR. LIEBLER: Right, but, Carol --

DR. EISENMANN: (Inaudible).

DR. BELSITO: They state that they looked at the essential oil that was derived by steam distillation, right?

DR. EISENMANN: Right.

DR. BELSITO: They don't say what else is in the flower, the stem, the other parts of the plant.

DR. EISENMANN: Right, right, I understand that. The essential oil of the -- if more than one essential oil, so I don't know which one it coordinates with, but it's an essential oil. It's not a water, so maybe it should be put down as an essential oil of as how it's defined, and it's defined as those -- the flower, leaf, and stem.

DR. BELSITO: I agree. Right.

DR. EISENMANN: How it coordinates with an INCI ingredient, I don't know for sure, but it also gives composition. It gives the 14 major components in it.

DR. BELSITO: For the oil.

DR. EISENMANN: Right, of the essential oil they tested.

DR. BELSITO: Right.

DR. LIEBLER: The problem I think is we just -- it's an essential oil of what? We just really don't know.

DR. BELSITO: Well, it's essential oil that's derived probably primarily from the leaf, but also somewhat from the flower and stem.

DR. LIEBLER: These are all assumptions.

DR. EISENMANN: No, it says that.

DR. BELSITO: We know that the leaf is GRAS. We know that the essential oil and, presumably, the leaf will contain dermal sensitizers. If we use our botanical boilerplate, we're going to say formulated to be non-sensitizing. So the only problem that I had with the leaf components at all was that they're used, the maximum leave-on is 0.38 and the data that we have is an HRIPT at 0.005 and another one at 0.03.

But we're going to say when formulated to be non-sensitizing, so I'm not bothered by the sensitization data. So I was thinking we could go safe as used for the leaf components and insufficient for the others. Right? I mean, because even if we got data at 0.38 and it was negative, we're still going to say it's a botanical and it has sensitizers, right? You need to formulate to not sensitize.

DR. LIEBLER: So, Carol, I don't see what the European classification, the European ingredient description essential oil, how that helps us with our deficiencies or method of manufacture or composition/ impurities because the holes that we have are the root --

DR. EISENMANN: I'm not saying it helps you for those; I'm just saying, in the report, it should not be called a water. It's an essential oil.

DR. LIEBLER: Oh, okay.

DR. BELSITO: Right.

DR. LIEBLER: I'm questioning whether it even belongs in the report.

DR. EISENMANN: No, it belongs in the report because that's got to be the material of commerce, or they never would have registered with ECHA.

DR. BELSITO: Correct.

DR. LIEBLER: It doesn't -- we can't make it clearly correspond to any of our ingredients, can we?

DR. BELSITO: Well, yes and no, Dan, because in terms of sensitization, as you pointed out before, we're concerned about the oil and now we have composition, and we know there are sensitizers. So our usual botanical boilerplate with formulated to be non-sensitizing comes into place, which I think obviates the need for sensitization data at a higher level than what we have.

DR. LIEBLER: Okay, so I guess the one ingredient in our list that corresponds to that European essential oil is our *Salvia Officinalis* sage oil, which is described as derived from the herbal plant.

DR. BELSITO: Well, and we also have GRAS status for the leaf.

DR. LIEBLER: Yeah, but that's beside this point.

DR. BELSITO: Can't you go safe as used for all the leaf components?

DR. LIEBLER: Oh, yeah, already we were there.

DR. BELSITO: Oh, yeah. So then insufficient --

DR. LIEBLER: Yeah, no, we were already there on that. I'm just trying to figure out where this European ingredient matches up to our ingredient list.

DR. BELSITO: It doesn't help us with any of the other non-leaf components.

DR. LIEBLER: Except for this sage oil.

DR. BELSITO: Right. I mean, I think the oil is fine.

DR. LIEBLER: Page (audio skip) at the bottom.

DR. BELSITO: Right. The leaf and the oil are fine when formulated to be non-sensitizing, and all the others we need manufacturing, impurities, composition if significantly different from the leaf and the oil, other data endpoint. No?

DR. LIEBLER: Yeah, so the sage oil has 87 uses for us, and now we've got method of manufacture, composition, and impurities for that because of the European ingredient.

DR. BELSITO: Right.

DR. LIEBLER: Okay. Sorry for leading us on a wild goose chase through this, Carol. I just needed to follow the logic to get to one of our ingredients, and I hadn't made that connection until just now.

DR. SNYDER: Don, on page 27 for the 12 ingredients, we're saying all of them are safe except for the root extract. What about the sage water?

DR. BELSITO: I was just looking at how that was made. We're not saying all of them because --

DR. SNYDER: Well, it's all -- oh, okay, I guess leaf, stem.

DR. BELSITO: For all the leaf/stem extract, flower/leaf/stem juice, flower/leaf/stem water, we don't know.

DR. SNYDER: Well, I thought a lot of those compositions said for the aerial part of the plant, which would include the flower, leaf, and stem. Did it not?

DR. LIEBLER: You mean the above-ground part of the plant?

DR. SNYDER: Yes, that's what I thought. I read that in a report. I thought it was this report, but maybe it was a different report because I wrote aerial part of the plant, safe as used. It says (audio skip) the flower/leaf/stem extract -- on Page 28, it says the flower extract, fresh flowers -- because we have flower under there. We have the flower extract, the leaf extract.

DR. BELSITO: Well, it tells us how it was made. It doesn't tell us the composition and impurities, does it? No. We have leaf water. We have leaf oil, sage oil. We don't have composition and impurities for those other ingredients, Paul. We just have a method of manufacture.

DR. SNYDER: I guess I'm having trouble linking back, like, the leaf oil back to, and the sage oil back to exactly what part of the plant that is.

DR. HELDRETH: Hey, Paul, I think what you're referring to is on PDF page 29 for the description of the salvia officinalis sage oil. It does talk about making that using the aerial parts.

DR. SNYDER: Oh, there it is, yeah. Okay, yeah.

DR. BELSITO: Yeah, but we already know that from the ECHA document, Bart, but they're not telling us what else is in there other than the oil, right?

DR. HELDRETH: But they're saying that the oil is comprised from using the aerial parts: the flower, the leaf, the stem.

DR. SNYDER: Yeah, so I take that to mean that would cover all that.

DR. BELSITO: Why? If it's just the oil, they're not looking at the other components. I thought we already decided that the oil was fine, we're not having an issue with wherever it comes from. But we're having issue --

DR. SNYDER: No, but I thought we were equating oil to leaf, but I think the oil is stem and flower also.

DR. BELSITO: Yeah, we agree.

DR. SNYDER: Oh, okay, okay. I'm sorry.

DR. BELSITO: From the ECHA document, we have the ingredients for the oil, but we don't have the ingredients for the flower, stem, other than the oil part.

DR. LIEBLER: I think part of the confusion is we got multiple plant parts and then we got multiple kinds of chemical products produced from them. The multiple plant parts are obvious. Then the products are the essential oil, which contains mainly the terpenes and other very nonpolar hydrocarbons. Then we've got the extracts, which are usually hyper-alcoholic extracts, and they contain the flavonoids and phenols. Then we have the waters, which are the leftover from steam distillation that don't contain all the terpenes and all that hydrocarbon stuff. Those are the three bins that we have.

Then the question of which of those three chemical product bins matches up to which plant parts? That's where I've kind of gotten lost.

DR. BELSITO: Well, I don't think we know, other than the sage leaf is GRAS, and the oil we have composition for. But we don't have composition and impurities for flower or for stem, and the water, it just says an aqueous solution of steam distillate obtained from salvia, so it's the whole plant. So I don't think we have data to support the water either.

DR. LIEBLER: Let me put it to you this way. The flower and the stem never apparently stand on their own. They're either part of the sage extract, which is the whole plant that may or may not contain flowers, and then the flower/leaf/stem extract that is most likely mostly leaves, or this flower/leaf/stem juice, which is most likely from mostly leaves.

Then we have this European essential oil that comes from the whole plant. That comes from the whole plant, and that's the terpene, hydrocarbon layer. Then we've got the sage extract, which is our first ingredient, and we do have method of manufacture. It's pretty sketchy. We do have also very brief composition/impurities. We have a lot of uses for that.

DR. BELSITO: Well, but do we have sufficient composition and impurities for the extract? It just gives us a total phenolic count.

DR. LIEBLER: Right. All I'm saying is we've got something, but not much.

DR. BELSITO: We don't have any tox data. We do have DART on the extract and on the flower/leaf/stem extract. We have some genotox data on the flower/leaf/stem water. I just don't quite honestly know where to go. I mean, from the dermal endpoint, I think the leaf and the oil present the greatest concern, and I'm fine clearing them with our botanical boilerplate because they contain sensitizers, even though our HRIPT data was lower than the use concentration. But I'm just not sure about the other tox endpoints because I just don't think we have the data on what they're made of. But, Dan, I hear you sort of arguing that they're all fine except possibly the root.

DR. LIEBLER: That's kind of where I'm leaning. I'm just looking for enough interlocking bits of logic to support this. I'm looking at the non-cosmetic use again. The sage oil is GRAS. The leaf and leaf oil are GRAS. Then the plant is a common pot herb *Salvia Officinalis* leaves used for flavoring meat, traditional medicine, medicinal uses, various forms, but it doesn't specify what parts of the plant except occasionally to mention leaves.

DR. BELSITO: Yeah, but, you know, for traditional medicine, cava's a traditional medicine too, right? It induces hallucinogenic experiences.

DR. LIEBLER: Yeah. Well, "*Salvia Officinalis* oil and extract consumption is contraindicated during pregnancy due to its abortifacient and emmenagogic properties."

DR. SNYDER: 0.38 percent (audio skip). Yeah, so I mean, we're kind of -- I thought at 0.38 percent, we had enough data to think everything above ground was safe as used, and that the root was insufficient for composition. No reported concentration of use, or no use is reported.

DR. LIEBLER: Yeah, thank you, Paul, I mean, that's where I've been leaning. I've just been trying to justify it.

DR. BELSITO: Yeah, how do we justify the flower and the stem?

DR. LIEBLER: Well, they're part of the sage whole plant extract.

DR. BELSITO: Right. What tox data do we have for that? We just have the DART studies, and we have a --

DR. SNYDER: We have an eight-week, short-term oral, Don, with sage oil or sage leaf oil, with a NOAEL of 250 milligrams per kilogram. Pretty darn high.

DR. BELSITO: That's leaf and oil.

DR. SNYDER: Yeah.

DR. BELSITO: It's not stem and flower.

DR. LIEBLER: So we got the DART for the flower, leaf, stem, and I think that's pretty good, right?

DR. BELSITO: We have a 14-day for the flower/leaf/stem extract for oral tox. Then we have the DART data, correct, for the flower and stem.

DR. SNYDER: Don, I got to go back to that method, the sage oil says it's prepared by drying and grinding the aerial parts of the plant.

DR. BELSITO: Right, but then they're only looking at the oil, Paul, they're not looking at the other parts.

DR. LIEBLER: We do have, on PDF 31 at the bottom, under oral tox.

DR. BELSITO: Right.

DR. LIEBLER: We got the flower/leaf/stem extract.

DR. BELSITO: Right. It's 14 days, is that sufficient?

DR. SNYDER: Yeah. Yeah, yeah. Two-week study? Yeah. I mean, that's not a -- yeah. That's a short-term study, yeah. I mean, that's consistent with the eight-week study. I mean there's nothing here -- I guess, I'm having the same problem that Dan is having. We have a fair bit of data here, we just --

DR. BELSITO: Which eight-week study are you talking about, Paul?

DR. SNYDER: The oral under short term, eight-week with the oil and the leaf oil.

DR. BELSITO: Oh, yeah.

DR. SNYDER: The leaf --

DR. BELSITO: Not the flower, leaf, stem.

DR. SNYDER: No, that's a 14-day also.

DR. BELSITO: Right.

DR. SNYDER: The pulp was, for 14 days, was considered non-toxic at the maximum dose, 2,000 milligrams per kilogram.

DR. BELSITO: Right, so the only data we have for flower, leaf, stem is that 14-day. We don't have a 28-day.

DR. SNYDER: No, I meant -- yeah, I'm sorry, yeah. I misspoke. Fourteen-day and eight-week.

DR. BELSITO: Eight-week.

DR. LIEBLER: That's the only thing we have to hang our hat on for an extract. The extract contains the phenolics and the flavonoids, but --

DR. EISENMANN: It was a single-dose study with a 14-day observation period.

DR. SNYDER: Yeah, that's true. That's right.

DR. BELSITO: Yeah.

DR. SNYDER: Still, there's no signal there. It is GRAS.

DR. BELSITO: Well, the leaf is GRAS.

DR. LIEBLER: We just don't have much tox data on either the flower/leaf/stem or just the sage extract, which is the whole plant.

DR. BELSITO: Right.

DR. LIEBLER: We just -- that's our shortcoming on tox. If we had either of those, I think we'd be smooth sailing to safe as used for all of the leaves except the root.

DR. BELSITO: Right.

DR. LIEBLER: But we just can't quite justify it.

DR. SNYDER: Well, then that's consistent with our previous insufficient data announcement where we needed a 28-day dermal for the leaf extract and the root extract. Just leave it at that.

DR. LIEBLER: For the flower/leaf/stem.

DR. SNYDER: Yeah.

DR. BELSITO: Yeah, flower/leaf/stem extract, not the --

DR. SNYDER: Yeah, yeah. I'm sorry, yeah.

DR. LIEBLER: That's where it sits. But I think that the sage extract, which is defined as the whole plant, if we say that that's okay, but flower/leaf/stem is not. I think that's inconsistent because the whole plant is the leaves and stems, and if it's flowering, then the flowers too.

DR. BELSITO: Yeah, I'm not saying that the whole plant extract is safe. I'm saying the leaf components and the essential oil are safe.

DR. LIEBLER: Okay. I think that's the only thing that we can strictly justify.

DR. BELSITO: The others are insufficient for 28-day dermal for the whole plant and the root.

DR. LIEBLER: Got it.

DR. SNYDER: I'd probably rephrase it to say safe as used for all leaf-derived ingredients.

DR. BELSITO: And essential oil.

DR. SNYDER: And essential oils, yes. Yeah, insufficient for root extract and the leaf/stem/flower extract.

DR. BELSITO: Okay. And aerosol, how are handling that?

DR. SNYDER: Scrolling to the use table.

DR. LIEBLER: Very low concentrations.

DR. SNYDER: Yeah, low across the board.

DR. LIEBLER: Yeah.

DR. KLAASSEN: Extremely, extremely low.

DR. SNYDER: Yeah.

DR. BELSITO: So that's discussion.

DR. LIEBLER: Right.

DR. BELSITO: The insufficiency is we want a 28-day dermal on the flower/leaf/stem extract.

DR. SNYDER: Yeah, or the whole plant extract.

DR. BELSITO: Or whole plant.

DR. SNYDER: Including the root extract and the leaf/stem extract or the whole plant extract.

DR. LIEBLER: Correct.

DR. BELSITO: So the whole plant would cover the root.

DR. SNYDER: Yes.

DR. BELSITO: Is that correct? Okay. So safe for all the leaf ingredients and the oil, insufficient for the others. The insufficiency is a 28-day dermal for the flower/leaf/stem and root extracts or a 28-day dermal for the whole plant to cover all.

DR. LIEBLER: Yep.

DR. BELSITO: Okay. And in the discussion, we're going to handle the respiratory endpoint by stating low concentration of use.

DR. SNYDER: Even incidental exposure through cosmetic use at these concentrations are not concerned or something like that. Again, we'll pull out the (audio skip) as it go forward.

DR. BELSITO: Okay. Then, Preethi, the botanical boilerplate will cover the sensitization issue.

MS. RAJ: Okay, and, thank you, Dr. Belsito. Should there be any language in the discussion about why the Panel feels that safety is covered for the leaf and essential oil ingredients?

DR. BELSITO: Because we have the ingredients and the essential oil, and the leaf is GRAS.

MS. RAJ: Okay, so leaf is GRAS and, sorry, what else did you say?

DR. BELSITO: We have the components for the essential oil.

MS. RAJ: Okay.

DR. BELSITO: If we have some sensitization data for the leaf, it's lower than the concentration of use, but the sensitization would be limited by our botanical boilerplate anyway.

MS. RAJ: Okay. Great. Then that means we're leaving the categorization of ECHA data as-is, right? Or are we changing it?

DR. BELSITO: I don't understand the question.

MS. RAJ: Well, again, I mean, Carol has brought up, right, about the data that came from ECHA whether it should possibly come under oil, but am I hearing --

DR. BELSITO: Yes, it should come under oil.

MS. RAJ: Okay. Did the Panel want -- I know Carol had mentioned that in ECHA they have the top 14 constituents in oil, should that be mentioned in the composition section?

DR. BELSITO: Yes, because some of those are sensitizers.

MS. RAJ: Okay.

DR. BELSITO: Which is why we're keeping the botanical boilerplate as it's been used previously.

MS. RAJ: Thank you. Can I then categorize this ECHA data under the leaf oil and oil ingredients? I think there're two of them here.

DR. BELSITO: No, it's not just leaf oil, but, for the ECHA, it was flower/leaf/stem, so it has to be under just a category, I think, of essential oil. It's what I would say. Team members?

MS. RAJ: Okay.

DR. LIEBLER: I agree.

DR. BELSITO: Yeah, okay.

MS. RAJ: Okay. Thank you.

DR. BELSITO: Anything else for sage? Or have all of our sage comments been made? Okay. I think we can close that out and save this. Then we're going to move to Portulaca oleracea. If that's the correct pronunciation.

Cohen Team – December 6, 2021

DR. COHEN: Okay, sage. This is a draft tentative report. In March we issued an IDA, included all possible data categories for the ingredient group as well as method of manufacturing for the leaf extract; 28-day dermal tox for the leaf extract, the root extract; and if these were found to be absorbed, we'd want other toxicologic endpoints. And I think we were looking for dermal irritation and sensitization data on the root extract ingredient. I think that was some of the things that we were asking for.

MS. RAJ: Yes, Dr. Cohen. If you'd like me to reiterate the IDA, it was for composition and impurities data, dermal irritation and sensitization data at the maximum concentration of use for all ingredients.

DR. COHEN: Yeah.

MS. RAJ: Then specifically for the leaf extract it was a 28-day dermal toxicity data and, if absorbed, other toxicological endpoints. And for the root extract it was method of manufacture and the 28-day dermal toxicity data.

DR. COHEN: Yes, yes, thank you. So, the data added was the contents of the leaf oil which included limonene linalool in low concentrations. We have a 0.005 leaf extract HRIPT, but that was diluted at one percent. We have a new HRIPT on a body lotion containing 0.03 percent, but we don't have HRIPT on max use for it. I'll open it up. We got some information. Lisa?

DR. PETERSON: I think the missing impurities can be covered by the boilerplate pesticides/heavy metals. I mean, those are the big concerns.

DR. COHEN: Got it. Tom?

DR. SLAGA: I lost my page. Let me get it back.

DR. COHEN: I'll go to Ron, and then we can get it back.

DR. SHANK: Okay. I have just what Preethi said about the data needs. And including the 28, I was just trying to find is this not a GRAS?

DR. COHEN: Food?

DR. SHANK: The extracts would be great.

DR. BERGFELD: The leaf extract.

DR. SHANK: The leaf itself is a food.

DR. SLAGA: Yeah, it's GRAS.

DR. SHANK: Because it's an herb. It's food. And then the extracts would be GRAS. I'm trying to find -- is that right?

DR. SLAGA: Right.

DR. COHEN: And our sensitization still isn't near max use. Ron, do you agree with that?

DR. SHANK: Yeah. I'm trying to find where I am here.

DR. SLAGA: Yeah, Tom here. I agree with that. I think we still need sensitization data.

DR. PETERSON: Of what?

DR. COHEN: Leaf extract.

DR. SHANK: The oil and the leaf are natural seasonings. Now it says -- in the report it says these are GRAS. Unless FDA has changed the definition, GRAS refers to food additives, not foods. So, a leaf would be a food, not an additive.

DR. SLAGA: Right.

DR. SHANK: The oil and the extracts would be additives, and their GRAS. It's a little confusing there.

MS. RAJ: Dr. Shank, as far as I remember I think when I saw those CFR citations it is referring to the leaf directly, not necessarily as a food additive.

DR. SHANK: Right. It's not a food additive. It's a food.

DR. SLAGA: Food.

DR. SHANK: Yes. So, it wouldn't be GRAS because GRAS -- we can check with FDA but --

DR. ANSELL: No, that's correct.

DR. SHANK: I can still -- GRAS has always been referring to food additives, not to whole foods. Rice, barley, wheat, those are not additives. Those are foods. They're GRAS.

DR. ANSELL: Correct. And the GRAS is added --

DR. SHANK: The leaf is added as a leaf, so that's a food. But the extracts would be food additives.

DR. SLAGA: Under GRAS.

DR. COHEN: Okay. So --

DR. SHANK: Now what's needed -- I can't remember why we said we need data for 28 dermal toxicity for the leaf extract and the root extract.

DR. BERGFELD: Not much on the root.

DR. SHANK: Maybe somebody else can remember, and the sensitization data you want more, right?

DR. ANSEL: Right.

DR. COHEN: Yeah, I think we need it at max use. We're pretty far off.

DR. SHANK: Uh-huh. Yes.

DR. COHEN: So, we want that but what else do we need? The root isn't food, though, right?

DR. PETERSON: No. I thought we needed -- it's still insufficient for root.

DR. COHEN: So, we need all the same things for root.

DR. SLAGA: Right.

DR. PETERSON: Yup.

DR. COHEN: Okay. But the leaf we're okay with because it's GRAS -- or not GRAS but --

DR. SLAGA: Food.

DR. COHEN: It's food.

DR. SLAGA: Yeah, so it's safe and the extract.

DR. SHANK: The leaf is a food. I would think all of the extracts, at least the leaf extract -- the leaf oil, leaf powder, leaf water would all be covered by GRAS.

DR. SLAGA: Right.

DR. SHANK: Maybe not the root extract or whole plant extract.

DR. COHEN: Okay. I think I know what we want.

DR. SHANK: Okay.

DR. COHEN: And there's a question, does the European data -- should it be moved or left where it was in the report?

DR. PETERSON: I thought it was fine where it was because basically it's the water from the distillation, so it made sense to me to be under water.

DR. SLAGA: Sure, that's fine.

DR. COHEN: Okay. Any further comments on sage? All right.

DR. BERGFELD: Can you repeat what you're going to ask for?

DR. COHEN: Yeah, sure. So, we still need 28-day dermal tox on the root, and we want dermal irritation/sensitization on the root and sensitization at max use on the leaf extract.

DR. PETERSON: Yeah, can I just add -- I'm sorry finish the needs, and then I'll --

DR. COHEN: No, that's where I finished. And the missing impurities would be covered by the boilerplate.

DR. PETERSON: Yup. And I just want to say the way that -- I like the way the inhalation issue was dealt in this particular one because they aren't all this nuanced, but it includes a particle size. And then it has the coupled with a small actual exposure in the breathing zone and the concentrations at which the ingredients are used. The valuable information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory and systematic effects.

I really like that, and I thought that this kind of nuance needs to be added to all of the documents going through to have not just the particle size but consideration of the type of exposures, the concentrations at which the chemicals are used. I thought this was awesome and that, to me -- if you just argue particles, it's not a good argument. This is where putting in all of the pieces of information when it comes to inhalation is really what should happen in all documents that deal with this inhalation issue.

MS. FIUME: David, can I clarify that this report is going tentative report inefficient for all ingredients, is that correct?

DR. COHEN: I think so because I don't think -- where we have satisfaction on the tox, we don't have satisfaction on sensitization.

DR. SLAGA: Correct.

MS.FIUME: I just want to clarify we are at the tentative stage.

DR. COHEN: Yes.

MS. RAJ: And based on what Dr. Peterson said, I guess the discussion on inhalation -- the Panel is satisfied with it in the text?

DR. SLAGA: Yes. Yes.

DR. COHEN: Agreed. Okay, can we leave sage?

DR. SLAGA: Yes.

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DR. BELSITO: Okay. Salvia officinalis group, so at the March 2021 meeting, we issued an IDA. We're asking for manufacturing information for the leaf extract, 28 dermal tox for both the officinalis leaf extract and the officinalis root extract ingredients and, if they were absorbed, additional tox endpoints. We received a number of data that I won't review here. We'll look when we look at the report. I think the one issue was the data coming from ECHA, which, yes, was a distillation product of the flower/leaf/stem, but it was really essential oil.

So in response to the question that was posed as to where that information should appear, we felt that it should be appearing under the salvia officinalis oil, which is also listed as a specific ingredient here. Having said all that and looking at all the new data we received, we thought we could go with a safe as used for all the leaf uses, as well as the oil and insufficient for the other parts of the plant that are reported as cosmetic ingredients. And the data needs would be a 28 day dermal for the flower/leaf/stem and root extracts or a 28 day dermal for the whole plant that would cover all of them and, depending on those results, additional tox endpoints might be needed.

DR. BERGFELD: David?

DR. COHEN: So before I second that -- so you were safe as used for the leaf extract?

DR. BELSITO: For leaf and essential oil.

DR. COHEN: And, Don, is the max use on that 0.38 percent, and how do you reconcile the sensitization data we have with that?

DR. BELSITO: Yeah. So the sensitization data that we have is at a lower level. However, this is a botanical where we will have the botanical boilerplate stating that it needs to be formulated to be non-sensitizing since there are allergens or potential allergens present in these materials. So that would cover the fact that we don't have the data at the expected or the level of use that's stated here because our conclusion will state that it has to be formulated to be non-sensitizing.

DR. COHEN: Okay. Then I could second that motion.

DR. BERGFELD: All right. So we have a second. Do we have any other discussion or additions to the text or edits that we need to discuss?

DR. BELSITO: So, again, this is an issue where we have, you know, respiratory boilerplate where we feel that there is potential inhalation. We need to use the boilerplate but discuss that there's a low concentration of use in the products that could be applied -- that could be incidentally inhaled. So again, the idea that our boilerplates -- like here we're using the full botanical boilerplate and we're using a respiratory boilerplate and explaining why that is of (inaudible).

DR. BERGFELD: No concerns? Of no concern, is that what you meant?

DR. BELSITO: Pardon? No, no concerns for respiratory and low concentration of use in products that could be potentially inhaled.

DR. BERGFELD: Okay. David, comment on that?

DR. COHEN: No. We're okay with that.

DR. BERGFELD: Okay. So we have a safe for the leaf and the oil, an insufficient for the other with a list that's been generated. Preethi, do you understand the list? Do you want to repeat --

MS. RAJ: Yes. So the data needs appear to be either a 28-day dermal tox for the flower, leaf, and stem extract or for the whole plant; is that right?

DR. BERGFELD: I think that's what he said.

DR. BELSITO: Yeah. Flower/leaf/stem and also a 28-day dermal for the root or for the whole plant.

MS. RAJ: Okay.

DR. BELSITO: So two data needs if we're only getting parts of the plant that don't represent the whole plant or one data need if we're getting something for the whole plant.

MS. RAJ: Okay. And is the Panel in consensus about moving the ECHA data under the oil ingredient, then?

DR. BELSITO: Our team was.

DR. BERGFELD: David?

DR. COHEN: I didn't have any specific notation on that. Lisa, are you okay with that?

DR. BELSITO: You're muted, Lisa.

DR. PETERSON: Yes, I'm okay with it.

DR. BERGFELD: Okay. All right. I'd like to call a vote, though. All those in favor of this safe as stated conclusion with the exception of insufficiency -- all those in favor of moving to a tentative final?

DR. BELSITO: I think we all --

DR. BERGFELD: Opposed? Sorry. Abstaining? Okay. Unanimously addressed. Thank you. Then our next ingredient, another tentative file -- another botanical -- yes?

MS. FIUME: Can I just clarify? Don, I thought in the beginning you said safe as used, but was it safe as used when non-sensitizing on a total of six ingredients? Is that correct?

DR. BELSITO: Yeah. So the safety is going to be our usual botanical boilerplate, which will specify formulated to be non-sensitizing.

MS. FIUME: Thank you.

DR. BERGFELD: For clarification, are you putting the boilerplate also into the discussion regarding manufacturing, pesticides, heavy metals, et cetera?

DR. BELSITO: Yes. That part of the boilerplate for pesticides, heavy metals, et cetera, goes with any botanical. Usually --

DR. BERGFELD: But we didn't put one for one of the last ones.

DR. BELSITO: We did. We just removed the part of the botanical boilerplate that dealt with sensitization and other tox endpoints because there were no materials there that presented a concern.

DR. BERGFELD: Right. Okay. Is that all we have to do to discuss now with sage? Can we move on? Okay. All right. Dr. Cohen.

Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 12 *Salvia officinalis* (sage)-derived ingredients as used in cosmetic formulations. These ingredients are most commonly reported to function as skin conditioning agents and fragrance ingredients. Because final product formulations may contain multiple botanicals, each containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. The Panel noted terpenes as potential sensitizers. Industry should use current good manufacturing practices to minimize impurities. The Panel reviewed data relevant to the safety of these ingredients in cosmetic formulations, and concluded that 6 of the ingredients (those derived from the leaves and the oil) are safe in cosmetics in the present practices of use and concentrations described in this safety assessment when formulated to be non-sensitizing, and that the data are insufficient to make a determination that the remaining 6 ingredients are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This assessment reviews the safety of 12 *Salvia officinalis* (sage)-derived ingredients as used in cosmetic formulations:

Salvia Officinalis (Sage) Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice
Salvia Officinalis (Sage) Flower/Leaf/Stem Water
Salvia Officinalis (Sage) Leaf
Salvia Officinalis (Sage) Leaf Extract
Salvia Officinalis (Sage) Leaf Oil
Salvia Officinalis (Sage) Leaf Powder
Salvia Officinalis (Sage) Leaf Water
Salvia Officinalis (Sage) Oil
Salvia Officinalis (Sage) Root Extract
Salvia Officinalis (Sage) Water

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), various functions are reported for these ingredients, with skin-conditioning agent and fragrance ingredient being the most common; other reported functions include as an antioxidant, oral care agent, a flavoring agent, and exfoliant (Table 1).[1] No cosmetic function is reported for Salvia Officinalis (Sage) Leaf.

The Panel does not typically review ingredients that function only as fragrance ingredients, because, as fragrances, the evaluation of the safety of these ingredients is the purview of the Research Institute for Fragrance Materials (RIFM). Salvia Officinalis (Sage) Flower/Leaf/Stem Water and Salvia Officinalis (Sage) Water are reported to function only as fragrance ingredients in cosmetics, according to the wINCI *Dictionary* (see Table 1). Although RIFM published a monograph on Sage Oil, Dalmatian in 1979,[2] it appears the sage ingredients are not currently scheduled for review by RIFM; thus, the Panel is reviewing the safety of these ingredients.

These ingredients are all derived from the same species, and have therefore been grouped together in this assessment. *Salvia officinalis* may contain hundreds of constituents, some of which have the potential to cause toxic effects. For example, terpenes have the potential to cause dermal sensitization.[3] In this assessment, the Panel is reviewing the potential toxicity of each of *Salvia officinalis*-derived ingredients as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical ingredients.

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

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/ supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment is described on the European Chemicals Agency (ECHA) website[4] and in the 2016 European Medicines Agency (EMA) monographs on *Salvia officinalis*.[5,6] Please note that the ECHA website and EMA monographs provide summaries of information from the industry and toxicological studies, and it is those summary data that are reported in this safety assessment when ECHA and EMA are cited. The CAS No. 84082-79-1 referenced in the ECHA dossier is generic, and corresponds to several of the ingredients in this report. However, based on the definition for this substance in ECHA, these data were deemed to refer to the Salvia Officinalis (Sage) Oil ingredient, and have been described as such, when cited in this report.

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, without italics. In many of the published studies, it is not known how the substance being tested compares to the cosmetic ingredient. Therefore, if it is not known whether the chemicals being discussed are cosmetic ingredients, the test substances will be identified by the standard taxonomic practice of using italics to identify genus and species (i.e., *Salvia officinalis* extract). However, if it is known that the substance is a cosmetic ingredient, the International Nomenclature Committee (INC) terminology (i.e., title case and no italics) "Salvia Officinalis…" (e.g., Salvia Officinalis (Sage) Extract) will be used. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics will be followed (i.e., *Salvia officinalis*).

CHEMISTRY

Definition and Plant Identification

The definitions of the 12 *Salvia officinalis* (sage)-derived ingredients reviewed in this assessment are presented in Table 1.[1] All of the ingredients included in this assessment have the generic CAS No. 84082-79-1; however, both Salvia Officinalis (Sage) Leaf Oil and Salvia Officinalis (Sage) Oil also have the CAS No. 8022-56-8 (generic).

Generically, the root is defined as a plant organ that lacks leaves and nodes, is usually underground, and absorbs and transports water and nutrients.[1] The flower is defined as the reproductive shoot in flowering plants, and is usually composed of sepals, petals, stamens, and pistil(s). The stem is defined as a slender or elongated structure, which supports a plant, fungus, or plant organ. The leaves are defined as the flattened photosynthetic organs of a plant, which are attached to the plant stems.

Salvia officinalis is a plant in the Lamiaceae (i.e., mint) family and Nepotoideae subfamily.[7] Commonly referred to as sage, or Dalmatian sage, *Salvia officinalis* is native to the Mediterranean and Middle Eastern regions, and is cultivated throughout the Americas and Europe, including, Spain, Italy, Yugoslavia, Greece, Albania, Argentina, Germany, France, Malta, Turkey, England, and Canada.[8,9] It is a medium-size perennial evergreen herb, which grows as a bush, having a quadrangular base, with many branches.[9] The plant can grow up to 60 - 70 cm in height. The leaves are arranged in an opposite and whorled pattern, and are oblong, 2.5 - 6.0 cm long, wrinkled, and light green to silver gray in color. *Salvia officinalis* blooms in early summer, and has blue, white, or purple flowers that have two lips, are up to 3 cm long, and are attached in whorls on short, upright flower spikes.

Chemical Properties

Ingredients with reported properties (only 3) are provided as liquids, with densities comparable to water. A summary of chemical properties described for these *Salvia officinalis* (sage)-derived ingredients are provided in Table 2.

Method of Manufacture

Some of the methods below are general to the processing of *Salvia officinalis* (sage), and it is unknown if they apply to cosmetic ingredient manufacturing.

<u>Salvia Officinalis (Sage) Flower/Leaf/Stem Extract</u>

In the preparation of an aqueous *Salvia officinalis* leaf extract, 1 g of dried aerial *Salvia officinalis* was added to 200 ml of boiling water, and the solution was left to stand at room temperature for 5 min, filtered under reduced pressure, frozen, and lyophilized.[10] A preparation of a methanolic *Salvia officinalis* extract was then obtained by stirring a 1 g sample of dried aerial *Salvia officinalis* with 30 ml of a methanol/water (80:20 v/v) solvent at 25 °C and 150 rpm for 1 h, and then filtering the extract. A second step extraction was obtained with an additional 30 ml of the solvent; extracts from both steps were combined, evaporated at 35 °C under reduced pressure, and further lyophilized. The lyophilized methanolic *Salvia officinalis* extracts were re-dissolved in methanol/water (80:20 v/v); the aqueous *Saliva officinalis* extracts were re-dissolved in water. The resulting stock solutions contained a 20 mg/ml concentration of *Salvia officinalis* extract.

<u>Salvia Officinalis (Sage) Flower/Leaf/Stem Juice</u>

Salvia Officinalis (Sage) Flower/Leaf/Stem Juice is the juice expressed from the flowers, leaves, and stems of *Salvia officinalis*.[1]

<u>Salvia Officinalis (Sage) Flower/Leaf/Stem Water</u>

Salvia Officinalis (Sage) Flower/Leaf/Stem Water is the aqueous solution of the steam distillate obtained from the flowers, leaves, and stems of *Salvia officinalis*.[1]

<u>Salvia Officinalis (Sage) Leaf Extract</u>

One supplier described a trade mixture containing Salvia Officinalis (Sage) Leaf Extract (dry extract between 1.8 – 3%), propylene glycol, and water as a hydroglycolic extract obtained from *Salvia officinalis* leaves, via controlled extraction using propylene glycol and water.[11] In another method of manufacture for Salvia Officinalis (Sage) Leaf Extract, described by a supplier, dried leaves are extracted with eluent(s), such as water, butylene glycol, glycerin, propylene glycol, or carthamus tinctorius (safflower) seed oil, under appropriate temperature conditions, to yield a concentrate.[12] This concentrate is then blended with the desired diluent(s) and is preserved to yield the final ingredient. Both the intermediate concentrate and the final ingredient are evaluated for physiochemical properties, contaminants, and specification requirements.

A supplier provided 5 methods of manufacture for 5 separate Salvia Officinalis (Sage) Leaf Extracts.[13] In general, dried *Salvia officinalis* leaves were extracted with either a 30% or 90 vol% ethanolic solution or with a 50 vol% 1,3-butylene glycolic solution, and filtered to produce a filtrate. The resulting filtrate (sometimes called a concentrate) went through a sedimentation process, and was filtered and adjusted as needed, prior to packaging. In one of the described methods, the extract concentrate was dissolved in squalane prior to sedimentation.

Salvia Officinalis (Sage) Oil

A *Salvia officinalis* oil sample was prepared by first drying and grinding the aerial parts of *Salvia officinalis* to yield 250 g of powder.[14] The powder was subject to hydrodistillation for 3 h using a Clevenger apparatus; the eluted oil was dried over anhydrous sodium sulfate and preserved in a sealed vial at 4 °C.

Salvia Officinalis (Sage) Leaf Water

Salvia Officinalis (Sage) Leaf Water was described by a supplier as an aqueous extract obtained by steam distillation of the *Salvia officinalis* leaves.[15]

Salvia Officinalis (Sage) Water

Salvia Officinalis (Sage) Water is the aqueous solution of the steam distillate obtained from the leaves of Salvia officinalis.[1]

Composition and Impurities

The determination of individual constituents and natural content in *Salvia officinalis*-derived ingredients varies considerably depending on the extraction solvent and method, part of the plant, growth stage, and time of harvest.[16-20]

The European Food Safety Authority issued a recommended maximum residue level of 20 mg/kg ametoctradin, a fungicide, in *Salvia officinalis*.[21,22] In an analysis of pesticide residues, commercial samples of *Salvia officinalis* in Poland were found to have boscalid, chlorpyrifos, 1,1,1-tricloro-2,2-*bis*(4-chlorophenyl)ethane, dimethoate, and indoxacarb in negligible amounts (0.02 - 0.05 mg/kg).[23] The researchers concluded that the presence of these contaminants in herbal infusions would be minimal.

Salvia Officinalis (Sage) Extract

An aqueous extract of *Salvia officinalis* was reported to have a total phenolic compound content of 158.9 ± 38.0 µg gallic acid equivalents.[24]

Salvia Officinalis (Sage) Leaf Extract

Theoretical calculations made by a supplier indicate that a trade mixture of propylene glycol, water, and Salvia Officinalis (Sage) Leaf Extract contains less than 10 ppm geraniol, less than 125 ppm limonene, and less than 225 ppm linalool.[11] Borneol, cineol, luteolin, apigenin, caffeic acid, and rosmarinic acid were identified as being present in this extract.

In an industry assessment conducted on the concentrate in an alcohol base, no heavy metals or pesticide residues were detected in Salvia Officinalis (Sage) Leaf Extract.[12] Similarly, testing the concentrate of Salvia Officinalis (Sage) Leaf Extract, in an alcohol base, for the 26 allergens identified by the European Union yielded a universal threshold of < 10 ppm – 0.001%.[12]

Flavonoids and tannins were the primary components identified in 4 Salvia Officinalis (Sage) Leaf Extracts, prepared using 30% or 90% ethanol, or 50% 1,3-butylene glycolic solution.[13] The levels of heavy metals and arsenic found in 4 of these Salvia Officinalis (Sage) Leaf Extract samples were not more than 20 ppm and 2 ppm, respectively. In a fifth sample of Salvia Officinalis (Sage) Leaf Extract, in which the intermediate concentrate was dissolved in squalane, the primary components were also flavonoids and tannins, and detected heavy metal and arsenic levels were no more than 10 ppm and 2 ppm, respectively.

Salvia Officinalis (Sage) Leaf Water

Theoretical calculations made by a supplier, indicate that a Salvia Officinalis (Sage) Leaf Water contains less than 10 ppm geraniol, less than 125 ppm limonene and less than 225 ppm linalool.[15] The presence of borneol was also identified in this ingredient.

Salvia Officinalis (Sage) Leaf Oil

The main classes of constituents identified in an Albanian sample of *Salvia officinalis* leaf oil were monoterpene hydrocarbons (21.5%), oxygenated monoterpenoids (66.5%), sesquiterpene hydrocarbons (9.4%), and oxygenated sesquiterpenoids (2.4%).[25] The major components in this *Salvia officinalis* leaf oil sample were α- and β-thujone, of which α-thujone was proportionally higher.

Salvia Officinalis (Sage) Oil

According to the EMA monograph, the principal components of *Salvia officinalis* oil are thujone, 1,8-cineole, and camphor; in 25 different commercial sources of sage leaves, camphor levels varied from 7 - 50% .[5] The main classes of constituents in *Salvia officinalis* oil are identified as terpenoids, hydroxycinnamic acid derivatives, flavonoids, phenolic glycosides, and polysaccharides. According to the 49th Amendment of the International Fragrance Association (IFRA) standards, in the absence of analytical data, thujone is expected to occur naturally from 2-10% in *Salvia officinalis* oleoresin and from 8 – 33% in *Salvia officinalis* oil.[26]

An essential oil of *Salvia officinalis* is described as being obtained from leaves, flowers, and stalks by steam distillation.[4] The major components in this oil were identified as 1-isopropyl-4-methylbicyclo[3.1.0]hexan-3-one; DL-bornan-2-one; cineole; (1*S*, 4*S*, 5*R*)-4-methyl-1-(1-methylethyl)bicyclo[3.1.0]hexan-3-one; camphene; humulene; pin-2(3)-ene; caryophyllene; (1*S*-endo)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol; pin-2(10)-ene; *p*-mentha-1,4-diene; dipentene; L-born-2-yl acetate; and 7-methyl-3-methyleneocta-1,6-diene.

The major components of a *Salvia officinalis* oil from Iran were identified as α-thujene (13.96%), α-pinene (12.91%), and 1,8-cineole (22.91%).[14] Percent composition of both *Salvia officinalis* leaf oil and *Salvia officinalis* oil samples is provided in Table 3.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. The cosmetic product categories named in the VCRP database indicate the intended uses of cosmetic ingredients, and are identified in 21 CFR Part 720. Data are submitted by the cosmetic industry in response to a survey conducted by the Personal Care Products Council (Council) of maximum reported use concentrations, also by product category. Neither the categories provided by the VCRP, nor those provided by the Council survey, include a designation for use via airbrush application. Airbrush devices, alone, are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, used in airbrush devices, are within the jurisdiction of the FDA. As airbrush technology use for cosmetics has neither been evaluated by the CPSC, nor the use of cosmetic ingredients in airbrush technology by the FDA, no US regulatory authority has evaluated the safety of this delivery methodology for cosmetic ingredients. Moreover, no consumer habits and practices data are available to evaluate the risks associated with this use type.

According to 2022 VCRP survey data, Salvia Officinalis (Sage) Leaf Extract is reported to have the greatest frequency of use; it is reported to be used in 211 formulations, 114 of which are rinse-off formulations[27] (Table 4). The other ingredients have 105 or fewer reported uses. The results of the concentration of use survey conducted by the Council in 2020 indicate Salvia Officinalis (Sage) Leaf Extract also has the highest reported concentration of use; it is used at up to 0.38% in other skin care preparations.[28,29] The 5 *Salvia officinalis* (sage)–derived ingredients which are not reported to be in use are listed in Table 5.

A few of the *Salvia officinalis* (sage)-derived ingredients are reported to be used in products applied near the eye, such as Salvia Officinalis (Sage) Leaf at up to 0.0001% in eye lotions, and in products that can result in incidental ingestion (e.g., Salvia Officinalis (Sage) Oil at up to at 0.011% in dentifrices). Additionally, some of the ingredients are used in formulations that could come in contact with mucous membranes, such as Salvia Officinalis (Sage) Oil at up to 0.02% in bath soaps and detergent.

Furthermore, some of the *Salvia officinalis* (sage)-derived ingredients are used in cosmetic spray formulations, and could possibly be inhaled. For example, Salvia Officinalis (Sage) Leaf Extract is reported to be used in pump and aerosol hair sprays at up to 0.0001% and 0.002%, respectively, Salvia Officinalis (Sage) Extract is reported to be used in underarm deodorant spray at up to 0.0011%, and Salvia Officinalis (Sage) Leaf Oil is reported to be used in pump spray suntan formulations at up to 0.012%. Salvia Officinalis (Sage) Leaf Extract is reported to be used in 1 face powder formulation (concentration of use not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. 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 technology, 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 related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

All of the ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[30] However, IFRA limits the levels of thujone in finished products, depending on the product category, ranging from 0.0053% to 9.5%.[26]

Non-Cosmetic

Salvia officinalis L. is generally recognized as safe (GRAS) as an essential oil, oleoresin (solvent-free), and natural extractive (including distillates), and, as a spice, natural seasoning and flavoring for human consumption, according to the US FDA [21CFR § 182.20; 21CFR § 182.10, respectively]. *Salvia officinalis L.* is also GRAS as a spice and other natural seasoning and flavoring for use in animal feed [21CFR § 582.10]. Additionally, *Salvia officinalis* oil is listed as a GRAS flavoring substance by the Flavor Extract Manufacturers Association.[2] Also, sage oil may have previously been used as an active ingredient in over-the-counter, astringent drug products; however, the FDA citation states that there are inadequate data to establish general recognition of the safety and effectiveness of the ingredient for this specified use [21CFR § 310.545]. The *Salvia officinalis* plant is a common potherb; *Salvia officinalis* leaves are typically used for flavoring meat, fish, and poultry dishes.[31]

According to a 2016 EMA herbal monograph of *Salvia officinalis* L., folium, an aqueous infusion of *Salvia officinalis* is applied to the skin in traditional medicine for the relief of minor inflammation.[6] The monograph also describes *Salvia officinalis* being consumed orally as a dry/liquid extract or tincture, for the treatment of heartburn, bloating, excessive sweating, and relief of inflammation of the mouth or throat. Most medicinal uses of *Salvia officinalis* products in Europe are marketed in varied forms, at a daily dose of 1.5 - 2.5 g/d.[5] In Spain, a dry extract of *Salvia officinalis* is marketed for the treatment of excessive sweating at a dose of 360 mg/d (equivalent to 500 - 800 mg of dried *Salvia officinalis* leaves). Pure *Salvia officinalis* oil and extract consumption is contraindicated during pregnancy, due to its abortifacient and emmenagogic properties.[5]

TOXICOKINETIC STUDIES

No relevant toxicokinetic studies on *Salvia officinalis* (sage)-derived ingredients were found in the published literature, and unpublished data were not submitted. In general, toxicokinetic 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

The acute dermal and oral toxicity studies summarized below are described in Table 6.

The acute dermal LD_{50} values for Salvia Officinalis (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, and *Salvia officinalis* oil or *Salvia officinalis* leaf oil were determined to be > 2000 mg/kg in mice and > 5000 mg/kg in rabbits, respectively.[2,13] No visible signs of toxicity were observed in groups of 6 female Swiss mice administered a single oral dose of up to 5000 mg/kg hydroalcoholic *Salvia officinalis* extract.[32] No visible signs of toxicity were observed. All animals in the 5000 mg/kg group showed piloerection and diarrhea lasting up to 3 h after treatment. One animal from the 5000 mg/kg group died before 48 h. The acute oral LD_{50} in female Swiss mice was extrapolated to be 44,760 mg/kg. In one study, a *Salvia officinalis* leaf and stem extract was determined to be non-toxic when administered to 6 female albino rats at the maximum dose of 2000 mg/kg bw.[33] The acute oral LD_{50} of *Salvia officinalis* oil or *Salvia officinalis* leaf oil was determined to be 2600 mg/kg bw in rats.[2] Groups of 10 male Wistar rats were administered an oral, undiluted, dose of *Salvia officinalis* oil at 1290, 2020, 3200, or 5000 mg/kg bw.[4] One animal died from the 1290 mg/kg group, 4 died from the 2020 mg/kg group, 7 died from the 3200 mg/kg group, and 9 animals died from the 5000 mg/kg group. The calculated LD_{50} was determined to be 2600 mg/kg bw.

Short-Term Toxicity Studies

Oral

Salvia Officinalis (Sage) Oil or Salvia Officinalis (Sage) Leaf Oil

In an 8-wk study using groups of 5 white rats (sex and strain not specified), a daily dose of 250 mg/kg bw *Salvia officinalis* oil was well tolerated when given by oral administration.[5] Upon increase of the daily dose to 500 mg/kg bw/d, convulsions occurred in some animals. Upon increase to 1000 mg/kg bw/d, most animals died, and all animals died when the dose was increased to 1250 mg/kg bw/d (timing and duration of all 3 dose increases not provided). The no-observed-adverse-effect-level (NOAEL) of *Salvia officinalis* oil was determined to be 250 mg/kg bw/d, under the conditions of this study.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details of the developmental and reproductive toxicity studies summarized below are described in Table 7.

Groups of 7 female Wistar rats were administered either distilled water or 30 mg/kg bw/d hydroalcoholic extract (70% ethanol) of *Salvia officinalis*, orally, for 30 d.[34] No significant differences in blood estradiol or progesterone were observed, and a decrease in the duration of estrous cycles in *Salvia officinalis* extract-treated rats was not statistically significant. An increased number of alveolar buds and lobules in the whole mount slides, as well as an increase in the number and diameter of ducts in the histological sections of rats treated with *Salvia officinalis* extract, were statistically significant. In a study evaluating the estrogenic effects of up to 200 mg/kg bw, orally administered, ethanolic *Salvia officinalis* leaf and stem extract in immature ovariectomized female rats for 7 d, vaginal smears collected on day 8 exhibited varying estrus cycle phases, compared to controls, and significant increases in the percentage of positively stained cells were seen in the uterine tissue of rats treated with 100 and 200 mg/kg bw leaf and stem extract.[33] Similarly, treatment with the *Salvia officinalis* leaf extract exhibited a significant dose-dependent increase in uterine weights. Twenty-four female ICR mice received a daily dose of 0.25% *Salvia officinalis* oil (equivalent to 375 mg/kg/d), in rodent feed, for 14 d.[35] A significant decrease in embryo cell distribution, according to nucleus number, was observed in dams which consumed *Salvia officinalis* oil (until day 4 of gestation), compared to control females fed with 1% edible soya oil. Dam weights and the proportion of dead cells in embryos were not affected.

GENOTOXICITY STUDIES

Details of the in vitro genotoxicity studies summarized below are described in Table 8.

Salvia Officinalis (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, was not genotoxic in a reverse mutation test using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or *Escherichia coli* WP2 uvrA at up to 5000 µg/0.1 ml/plate.[13] *Salvia officinalis* oil was not found genotoxic when tested at concentrations up to 5000 µg/plate, in two bacterial reverse mutation assays.[4,36] *Salvia officinalis* oil was not found genotoxic in a chromosome aberration test at doses up to 0.15 mg/ml.[37] In one Ames test, *Salvia officinalis* oil, in concentrations of 91, 183, or 457 µg, was shown to significantly inhibit bacterial growth, however, was not considered genotoxic.[38]

ANTI-MUTAGENICITY STUDIES

In Vitro

Salvia Officinalis (Sage) Extract

The anti-mutagenic potential of *Salvia officinalis* extract was tested in 3 groups of 5 male C3H mice.[39] Animals were first intraperitoneally dosed with 1 mg/kg of a positive mutagen, mitomycin C (MMC), and then with 25, 50, or 100 µl/kg *Salvia officinalis* extract. Bone marrow was extracted 24 h after treatment and tested for aberrations. Treatment with 25 and 50 µl/kg *Salvia officinalis* extract immediately after MMC exposure significantly decreased the frequency of cells in metaphase with chromosome aberrations, relative to cells only treated with MMC. However, the 100 µl/kg dose of *Salvia officinalis* extract was shown to be cytotoxic by itself, and when administered after MMC (confirmed in a preliminary test).

CARCINOGENICITY STUDIES

No relevant carcinogenicity studies on *Salvia officinalis* (sage)-derived ingredients were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

Animal

Salvia Officinalis (Sage) Leaf Extract

In a tumorigenesis study, 20 female Wistar rats, which were previously induced with dimethyl-benzanthracene to develop breast cancer, were orally dosed with 3 mg/kg/d of an hydroalcoholic *Salvia officinalis* leaf extract for 6 mo.[40] The control group consisted of 8 rats which received 3 ml of sunflower oil, every 2 d, for 3 consecutive wk. Cancer stage and progression was analyzed throughout the course of the study. Cancerous lobule counts were significantly lower in the *Salvia officinalis* leaf extract treated group, compared to controls in the fourth and sixth mo of treatment.

OTHER RELEVANT STUDIES

Cytotoxicity

Salvia Officinalis (Sage) Leaf Oil

The cytotoxic activity of *Salvia officinalis* leaf oil in various cancer cell lines was determined using half maximal inhibitory concentration (IC_{50}) values.[41] The IC_{50} values of *Salvia officinalis* leaf oil were 554.5 ± 1.5 µg/ml against the MCF-7 breast cancer cell line, 394.6 ± 1.4 µg/ml, against the HCT-116 colon cancer cell line, and 207.5 ± 0.8 µg/ml against the RAW264.7 murine macrophage cell line.

Salvia Officinalis (Sage) Oil

Salvia officinalis oil was determined to have an IC_{50} value of 367.43 µg/ml ± 1.5 µg/ml against a C32 human melanoma cell line, and an IC_{50} of 108.70 ± 1.2 against an ACHN renal carcinoma cell line.[42]

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below are described in Table 9.

In an in vitro skin corrosion reconstituted human epidermis (Rhe) test, performed according to Organization for Economic Cooperation and Development (OECD) test guideline (TG) 431, 50 µl *Salvia officinalis* oil did not cause irritation to Rhe tissue surfaces, epiCS®.[4] In another in vitro skin irritation Rhe test, performed in accordance with OECD TG 439, 16 µl of *Salvia officinalis* oil was applied neat to 3 separate, 0.50 cm^2 reconstituted human epidermis tissue surfaces (EpiSkin SA, RHE/S/17); cell viability was measured in a MTT assay.[4] Mean percent viability of the treated tissues was 2.1%, compared to 2.9% in the positive control replicates exposed to 5% sodium dodecyl sulfate. Under these test conditions, the test substance was classified as "irritating to the skin" or "corrosive to the skin". Undiluted and 10% Salvia Officinalis (Sage) Leaf Extract (eluted in 50% 1,3-butylene glycolic solution) were not irritating when applied to rabbit skin.[13] *Salvia officinalis* oil, or *Salvia officinalis* leaf oil was moderately irritating when applied under occlusion to intact, or abraded rabbit skin for 24 h.[2] One irritation reaction occurred in a 24-h patch test of undiluted *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, using 20 subjects;[2,43] In another study, *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, tested at 8% in petrolatum, did not produce irritation in a 48-h occlusive patch test of human subjects.[2] A product containing 0.005% Salvia Officinalis (Sage) Leaf Extract, applied at a 1% dilution in distilled water, and a product containing 0.03% Salvia Officinalis (Sage) Oil were not irritating or sensitizing in two separate occlusive human repeated insult patch tests (HRIPT) completed in 53 subjects.[44,45] A maximization test was carried out on 25 subjects, using *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, tested at a concentration of 8% in petrolatum.[2] The test article was deemed non-sensitizing.

OCULAR IRRITATION STUDIES

In Vitro

Salvia Officinalis (Sage) Oil

The potential of *Salvia officinalis* oil to cause eye irritation was evaluated in a reconstructed human cornea-like epithelium test.[4] The test was performed in accordance with OECD TG 492, using an EpiOcular™ three-dimensional human cornea model. Fifty µl of the undiluted test article was applied to 2 living tissue models (duplicate runs), pretreated with DPBS, for 30 min. The treated tissue was then washed out with DPBS and post-incubated under normal medium and culture conditions for 2 h. Cell viability was measured via an MTT assay; positive controls were treated with methyl acetate. In the first test, viability was 60.34%, compared to 24.44% in positive controls. In the second test, viability was 80.96% compared to 18.36% in the positive controls. The test substance was not considered an ocular irritant.

CLINICAL STUDIES

Case Reports

Salvia Officinalis (Sage) Extract

An 83-yr old woman presented with swelling and redness of the lips and the surrounding area, followed by tightness and a burning sensation, which persisted for 3 mo.[46] The allergic reaction was attributed to a lip balm she had previously used. The subject was patch tested with the European baseline, cosmetic and bakery series, and with the suspected lip balm. On day 2 and 4, positive reaction readings were noted only for the lip balm. The subject was then patch tested with manufacturer-supplied *Salvia officinalis* extract and polygonum, each separately in water and in petrolatum. Positive reactions only occurred to *Salvia officinalis* extract. Patch tests of the lip balm, *Salvia officinalis* extract, and polygonum were negative in 20 other subjects.

Salvia Officinalis (Sage) Oil

A 65-yr old healthy woman, a professional aromatherapist, with no prior history of skin disease, presented with eczema on her arms and upper trunk, which later spread to the legs, face, and hands.[47] The hand eczema became chronic and was associated with handling household cleansers, sealing wax and paints, as well as customary dilution of essential oils. The subject tested positive to a fragrance mix (++) in the European standard series, and to lemongrass oil (++), neroli oil (+), and peppermint oil (+), in a perfume series. When patch tested with personally-used essential oils, diluted in petrolatum at 1% and 5%, the subject tested positive to 17 out of 20 oils, of which *Salvia officinalis* was one (++, at both concentrations). The subject recalled lemongrass being the first oil she had used in aromatherapy, which the researchers surmised had induced primary sensitization, and lead to later development of dermatitis to the other essential oils.

SUMMARY

According to the *Dictionary*, various functions are reported for these 12 *Salvia officinalis* (sage)-derived ingredients as used in cosmetics, with skin-conditioning agent and fragrance ingredient being the most common. Other reported functions include as an antioxidant, oral care agent, flavoring agent, and exfoliant. Salvia Officinalis (Sage) Leaf Extract is reported to have the greatest frequency of use, in 211 formulations, more than half (114) are rinse-offs. The highest reported concentration of use amongst these ingredients is for Salvia Officinalis (Sage) Leaf Extract, at up to 0.38% in other skin preparations.

The acute dermal LD_{50} of Salvia Officinalis (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, was determined to be > 2000 mg/kg in 5 mice. The acute dermal LD_{50} of *Salvia officinalis* oil, or *Salvia officinalis* leaf oil (unclear from source), was determined to be > 5000 mg/kg in rabbits. Of 6 female Swiss mice administered a single oral dose of 5, 50, 500, or 5000 mg/kg bw hydroalcoholic *Salvia officinalis* extract, one mouse in the 5000 mg/group died; the acute oral LD_{50} was extrapolated to be 44,760 mg/kg. No mortality or signs of toxicity were observed in 6 female albino rats dosed with up to 2000 mg/kg bw of an ethanolic *Salvia officinalis* leaf and stem extract; the extract was considered non-toxic at the maximum dose of 2000 mg/kg bw. The acute oral LD_{50} of *Salvia officinalis* oil or *Salvia officinalis* leaf oil in rats was determined to be 2600 mg/kg bw. Lethargy was observed in all groups of 10 male Wistar rats administered an undiluted oral dose of 1290, 2020, 3200, or 5000 mg/kg bw *Salvia officinalis* oil. One animal from the 1290 mg/kg group, 4 animals from the 2020 mg/kg group, 7 animals from the 3200 mg/kg group, and 9 animals from the 5000 mg/kg group died. The calculated LD_{50} was determined to be 2600 mg/kg bw.

In an 8-wk study, white rats were administered a progressively increasing oral dose of *Salvia officinalis* oil (250, 500, 1000, or 1250 mg/kg bw/d), convulsions and mortality were observed with increasing dosage. The NOAEL was determined to be 250 mg/kg bw/d, under the study conditions.

A group of 7 female Wistar rats administered a 30-d oral dose of 30 mg/kg bw/d hydroalcoholic *Salvia officinalis* extract did not exhibit significant differences in hormone levels or estrous cycle lengths, as compared to controls administered distilled water. However, a significant increase in alveolar buds, lobules, and the diameter of mammary ducts was observed. Groups of 6 immature, ovariectomized rats orally dosed with 50, 100 or 200 mg/kg bw *Salvia officinalis* leaf and stem extract for 7 d exhibited significant increases in positive staining for estrogen receptors in the 100 mg/kg group. Serum levels of LH and FSH were also significantly lower (41.7% and 49.1%) in the 200 mg/kg group, compared to ovariectomized controls. In a reproductive toxicity study with 13 gravid female ICR mice, a 14-d diet containing 0.25% *Salvia officinalis* oil caused significant decreases in embryo cell distribution, collected on day 4 of gestation, according to nucleus number.

Salvia officinalis oil and Salvia Officinalis (Sage) Leaf Extract were not found genotoxic when tested at concentrations of up to 5000 µg/plate in bacterial mutation assays; *Salvia officinalis* oil was not genotoxic at up to 0.15 mg/ml in a chromosome aberration test. When tested at doses of up to 457 µg, *Salvia officinalis* oil significantly inhibited bacterial growth, however, it was not considered genotoxic, in an Ames test. C3H mice intraperitoneally dosed with up to 100 µl/kg *Salvia officinalis* extract, after exposure to MMC, had a significant decrease in the frequency of cells in metaphase with chromosome aberrations. The 100 µl/kg dose of *Salvia officinalis* extract exhibited cytotoxicity, even in the absence of MMC.

Twenty female Wistar rats, that were induced with dimethyl-benzanthracene to develop breast cancer, saw significant reductions in cancerous lobules during the fourth and sixth month of being orally dosed with 3 mg/kg/d of an hydroalcoholic *Salvia officinalis* leaf extract for 6 mo, compared to sunflower oil controls. *Salvia officinalis* leaf oil yielded IC_{50} values of 554.5 ± 1.5 µg/ml, 394.6 ± 1.4 µg/ml, and 207.5 ± 0.8 µg/ml against breast cancer, colon cancer, and murine macrophage cell lines, respectively. *Salvia officinalis* oil was determined to have an IC_{50} of 367.45 ± 1.5 µg/ml and 108.70 ± 1.2 µg/ml against C32 human melanoma and ACHN renal carcinoma cell lines, respectively.

A 50 µl dose of undiluted *Salvia officinalis* oil did not cause irritation in an in vitro Rhe test. In another in vitro Rhe test, the mean percent cell viability of tissues treated with 16 µl of undiluted *Salvia officinalis* oil was 2.1%, compared to 2.9% in positive controls exposed to 5% sodium dodecyl sulfate; the test substance was classified as a skin irritant or dermally corrosive. Undiluted and 10% Salvia Officinalis (Sage) Leaf Extract, eluted in 50% 1,3-butylene glycolic solution, were not irritating to rabbit skin. Undiluted *Salvia officinalis* oil, or *Salvia officinalis* leaf oil, was moderately irritating when applied to intact and abraded rabbit skin under occlusion for 24 h. One irritation reaction occurred in a 24-h patch test of undiluted *Salvia officinalis* oil, or leaf oil, using 20 subjects. The sensitization potential of a product containing 0.005% Salvia Officinalis (Sage) Leaf Extract, tested at a 1% dilution in distilled water and of a body lotion containing 0.03% Salvia Officinalis (Sage) Oil was tested in 2 separate occlusive HRIPTs completed in 53 subjects; no adverse reactions were observed, and the test substances were deemed non-irritating and non-sensitizing. No irritation or sensitization was observed when 8% *Salvia officinalis* oil, or leaf oil, in petrolatum was tested via a 48-h occlusive patch test or a maximization test using 25 subjects, respectively. *Salvia officinalis* oil was not considered an ocular irritant when tested at a dose of 50 µl in an EpiOcular™ model.

An 83-yr old woman had positive reactions in a patch test to a lip balm containing *Salvia officinalis* extract. Upon separate patch testing with two of the manufacturer-supplied ingredients, *Salvia officinalis* extract and polygonum, in water and in petrolatum, positive reactions only occurred to *Salvia officinalis* extract. Patch test results for the lip balm, *Salvia officinalis* extract, and polygonum were negative in 20 other subjects. A 65-yr old woman, with no prior skin disease, presented with eczema on her arms, upper trunk, legs, face, and hands; when patch tested with personally-used essential oils diluted in petrolatum, the subject tested positive to *Salvia officinalis* oil at 1% and 5%. Primary sensitization was attributed to lemongrass oil, and subsequent dermatitis to the frequent use of other essential oils as an aromatherapist.

DISCUSSION

This assessment reviews the safety of 12 *Salvia officinalis* (sage)-derived ingredients as used in cosmetic formulations. The Panel concluded that the data are sufficient for determining the safety of 6 ingredients, i.e., those ingredients derived from the leaves and the oil, due to negative human irritation and sensitization data for these ingredients. The Panel, alternately, discussed that additional data would be needed to determine the safety of the remaining 6 ingredients that are derived from the whole plant, flowers, stems, and roots. Specifically, the Panel acknowledged the need for a 28-day dermal toxicity study of Salvia Officinalis (Sage) Flower/Leaf/Stem Extract, Salvia Officinalis (Sage) Root Extract, or the whole plant; dependent on the results of that study, additional toxicity data may be needed.

The Panel noted the GRAS status and historical food uses of *Salvia officinalis* (sage)-derived ingredients, especially *Salvia officinalis* leaves, and agreed that systemic exposures from food would be much higher than those from cosmetic use. Additionally, the Panel was reassured by the 250 mg/kg/d NOAEL seen in an 8-wk study of rats orally dosed with *Salvia officinalis* oil. Furthermore, the Panel acknowledged the negative human irritation and sensitization data for leaf-derived ingredients, which provided reassurance of the safety of these ingredients because *Salvia officinalis* leaves are the most constituent-rich ingredients, and therefore, would contain the highest levels of potential sensitizers.

Because final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For *Salvia officinalis* (sage)-derived ingredients, the Panel was concerned about the presence of terpenes/ terpenoids in cosmetics, which have dermal sensitization potential. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

The Panel also expressed concern about pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., Salvia Officinalis (Sage) Leaf Oil is used at up to 0.012% in pump spray suntan formulations, Salvia Officinalis (Sage) Extract is used at up to 0.0011% in underarm deodorant spray, and Salvia Officinalis (Sage) Leaf Extract has 1 confirmed use in face powders (concentration of use not reported)). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. As indicated in the respiratory exposure resource document and in the Cosmetic Use section of this report, airbrush application of cosmetic products is not assessed by the Panel. 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.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 6 *Salvia officinalis* (sage)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment, when formulated to be non-sensitizing:

Salvia Officinalis (Sage) Leaf
Salvia Officinalis (Sage) Leaf Extract
Salvia Officinalis (Sage) Leaf Oil
Salvia Officinalis (Sage) Leaf Powder*
Salvia Officinalis (Sage) Leaf Water
Salvia Officinalis (Sage) Oil

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

The Panel also concluded that the available data are insufficient to make a determination that the following 6 ingredients are safe under the intended conditions of use in cosmetic formulations:

Salvia Officinalis (Sage) Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract**
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice**
Salvia Officinalis (Sage) Flower/Leaf/Stem Water**
Salvia Officinalis (Sage) Root Extract**
Salvia Officinalis (Sage) Water

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

TABLES

Table 1: Definitions and functions of *Salvia officinalis* (sage) - derived ingredients[1]

Ingredient/CAS No.	Definition	Function
Salvia Officinalis (Sage) Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Extract is the extract of the whole plant, *Salvia officinalis*.	Skin-conditioning agents-miscellaneous
Salvia Officinalis (Sage) Flower/Leaf/Stem Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Flower/Leaf/Stem Extract is the extract of the flowers, leaves, and stems of *Salvia officinalis*.	Fragrance ingredients; Skin-conditioning agents - miscellaneous
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice 84082-79-1 (generic)	Salvia Officinalis (Sage) Flower/Leaf/Stem Juice is the juice expressed from the flowers, leaves, and stems of *Salvia officinalis*.	Antioxidants
Salvia Officinalis (Sage) Flower/Leaf/Stem Water 84082-79-1 (generic)	Salvia Officinalis (Sage) Flower/Leaf/Stem Water is the aqueous solution of the steam distillate obtained from the flowers, leaves, and stems of *Salvia officinalis*.	Fragrance ingredients
Salvia Officinalis (Sage) Leaf 84082-79-1 (generic)	Salvia Officinalis (Sage) Leaf are the leaves of *Salvia officinalis*.	not reported
Salvia Officinalis (Sage) Leaf Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Leaf Extract is the extract of the leaves of *Salvia officinalis*.	Oral care agents; Skin-conditioning agents-miscellaneous
Salvia Officinalis (Sage) Leaf Oil 84082-79 -1 (generic) 8022-56-8	Salvia Officinalis (Sage) Leaf Oil is the volatile oil obtained from the leaves of *Salvia officinalis*.	Flavoring agents; Fragrance ingredients; Skin-conditioning agents - miscellaneous
Salvia Officinalis (Sage) Leaf Powder 84082-79-1 (generic)	Salvia Officinalis (Sage) Leaf Powder is the powder obtained from the dried ground leaves of *Salvia officinalis*.	Exfoliants
Salvia Officinalis (Sage) Leaf Water 84082-79-1 (generic)	Salvia Officinalis (Sage) Water is an aqueous solution of the steam distillate obtained from the leaves of *Salvia officinalis*.	Fragrance ingredients; Skin-conditioning agents - miscellaneous
Salvia Officinalis (Sage) Oil 84082-79-1 (generic) 8022-56-8	Salvia Officinalis (Sage) Oil is the essential oil derived from the herbal plant, *Salvia officinalis*.	Fragrance ingredients; Skin-conditioning agents-miscellaneous
Salvia Officinalis (Sage) Root Extract 84082-79-1 (generic)	Salvia Officinalis (Sage) Root Extract is the extract of the roots of *Salvia officinalis*.	Skin-conditioning agents-miscellaneous
Salvia Officinalis (Sage) Water 84082-79-1 (generic)	Salvia Officinalis (Sage) Water is an aqueous solution of the steam distillate obtained from *Salvia officinalis.*	Fragrance ingredients

Table 2. Chemical properties of *Salvia officinalis* (sage) – derived ingredients and a tradename mixture

Property	Value	Reference
Salvia Officinalis (Sage) Leaf Extract (aqueous)		
Physical Form	Liquid	12
Color	Medium to dark amber	12
Density (g/ml @ 25 °C)	0.99 – 1.02	12
Refractive Index (@ 25 °C)	1.320 – 1.3450	12
pH (@ 25 °C)	4 – 7	12
Solubility	In water	12
Salvia Officinalis (Sage) Leaf Extract (1.8 -3% dry extract, in a tradename mixture, containing propylene glycol and water)		
Physical Form	Liquid, with slight precipitate	11
Color	Brown to brown-orange	11
Density (g/ml)	1.045 – 1.058	11
Refractive Index (@ 20 °C)	1.410 – 1.420	11
Miscibility	In water and 50 % v/v alcohol	11
Non-miscibility	Mineral and vegetal oils	11
pH	4 - 5	11
Salvia Officinalis (Sage) Leaf Oil or Oil		
Physical Form	Liquid	4
Color	Light yellow to yellow	4
Density (g/ml @ 20 ºC)	0.9153	4
Odor	Camphoraceous, herbal, spicy, floral, pine, thujone-like	48
Boiling Point (ºC @ 1013 kPa)	189.3	4

Table 2. Chemical properties of *Salvia officinalis* (sage) – derived ingredients and a tradename mixture

Property	Value	Reference
	Salvia Officinalis (Sage) Leaf Water	
Physical Form	Liquid	15
Color	colorless	15
Density (g/ml @ 20°C)	0.999 – 1.002	15
Refractive Index	1.332 – 1.339	15
Miscibility	In water and 50% v/v alcohol	15
Non-miscibility	Mineral and vegetal oils	15
pH	4 – 6.5	15

Table 3. Composition of *Salvia officinalis* (sage) oils, measured via gas chromatography- mass spectrometry

	Salvia officinalis leaf oil*[25]	**Salvia officinalis oil*[14]**
Compound	**Percentage (%)**	
cis-salvene	-- (not reported)	0.40
(*Z*)-salvene	0.2	--
(*E*)-salvene	trace	--
tricyclene	0.2	0.09
α-thujene	0.3	**13.9**
α-pinene	5.0	**12.91**
camphene	5.2	4.74
sabinene	0.1	--
trans-sabinene hydrate	--	0.13
β-pinene	4.1	5.93
β-thujene	--	8.91
1-octen-3-ol	trace	--
β-myrcene	--	0.69
myrcene	2.8	--
α-phellandrene	0.1	--
1-phellandrene	--	0.15
α-terpinene	0.5	0.31
α-terpinolene	--	0.20
p-cymene	0.6	--
limonene	1.5	--
1-napthalenepropanol	--	0.11
1,8-cineole	**26.9**	**22.91**
(*Z*)-β-ocimene	0.1	0.1
γ-terpinene	0.7	0.41
cis-sabinene hydrate	0.1	--
terpinolene	0.2	--
p-cymenene	trace	--
linalool	0.3	--
α- thujone	**17.2**	--
β- thujone	3.8	--
chrysanthenone	trace	--
3-*iso*-thujanol	trace	--
camphor	**12.8**	3.28
neo-iso-3-thujanol	trace	--
trans-pinocamphone	0.1	--
3- thujanol	0.2	--
borneol	1.2	6.18
δ- terpineol	0.4	--
terpinen-4-ol	0.5	--
α- gurjunene	--	0.1
α- terpineol	1.1	--
linalyl acetate	0.2	--
endobornyl acetate	--	0.77
bornyl acetate	1.1	0.39
trans-sabinyl acetate	0.1	--
trans-caryophyllene		7.41
2,3- pinanediol	trace	--
α- terpinyl acetate	0.6	--
α- copaene	0.1	--
β- caryophyllene	4.9	--
6-oxobornyl acetate	trace	--
α- maaliene	0.1	--

Table 3. Composition of *Salvia officinalis* (sage) oils, measured via gas chromatography- mass spectrometry

	Salvia officinalis leaf oil[*] [25]	**Salvia officinalis oil[*] [14]**
Compound	**Percentage (%)**	
aromadendrene	0.4	0.56
myltayl-4 (12)-ene	trace	--
5-oxobornyl acetate	0.1	--
α- humulene	3.1	3.19
9-*epi*-β- caryophyllene	0.1	--
trans-cadina 1(6)-4-diene	0.1	--
guaia-1(10)-11- diene	0.1	--
viridiflorene	0.3	--
δ- amorphene	0.1	--
δ- cadinene	0.1	0.24
Caryophyllene oxide	0.1	--
viridiflorol	2.0	3.08
humulene epoxide II	0.2	--
carylophylla-4(12),8(13)-dien-5α-ol	0.1	--
manool	0.2	--

Table 4. Frequency (2022)[27] and concentration of use (2020)[28,29] of *Salvia officinalis* (sage)-derived ingredients according to duration and exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Salvia Officinalis (Sage) Extract		**Salvia Officinalis (Sage) Leaf**		**Salvia Officinalis (Sage) Leaf Extract**	
Totals*	**70**	**0.000028-0.078**	**1**	**0.0001-0.1**	**211**	**0.000004-0.38**
Duration of Use						
Leave-On	*44*	*0.001-0.078*	*1*	*0.0001*	*95*	*0.0001-0.38*
Rinse-Off	*26*	*0.000028-0.01*	*NR*	*0.1*	*114*	*0.000004-0.08*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*2*	*0.004*
Exposure Type						
Eye Area	NR	NR	NR	0.0001	3	NR
Incidental Ingestion	3	NR	NR	NR	5	NR
Incidental Inhalation-Spray	14[a]; 21[b]	0.02[b]	NR	NR	1; 50[a]; 24[b]	0.0001-0.002; 0.001-0.018[a]
Incidental Inhalation-Powder	21[b]	0.02[b]	NR	NR	1; 24[b]	NR
Dermal Contact	36	0.001-0.078	1	0.0001-0.1	140	0.0002-0.38
Deodorant (underarm)	1[a]	Not spray: 0.001% Spray: 0.0011%	NR	NR	NR	NR
Hair - Non-Coloring	31	0.000028-0.003	NR	NR	51	0.000004-0.08
Hair-Coloring	NR	NR	NR	NR	15	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	4	0.0035-0.01	NR	NR	31	0.004-0.01
Baby Products	NR	NR	NR	NR	NR	NR
	Salvia Officinalis (Sage) Leaf Oil		**Salvia Officinalis (Sage) Leaf Water**		**Salvia Officinalis (Sage) Oil**	
Totals*	**2**	**0.0028-0.02**	**3**	**0.00071**	**105**	**0.000097-0.22**
Duration of Use						
Leave-On	*NR*	*0.0028-0.02*	2	*0.00071*	69	*0.012-0.22*
Rinse Off	*1*	*0.02*	1	*NR*	30	*0.000097-0.18*
Diluted for (Bath) Use	*1*	*NR*	NR	*NR*	6	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	1	NR
Incidental Ingestion	1	NR	NR	NR	3	0.005-0.011
Incidental Inhalation-Spray	NR	0.012	1[a]	0.00071[b]	1; 30[a]; 15[b]	0.005[a]
Incidental Inhalation-Powder	NR	NR	NR	0.00071[b]	15[b]	0.22[c]
Dermal Contact	1	0.0028-0.02	3	0.00071	88	0.0097-0.22
Deodorant (underarm)	NR	NR	1[a]	NR	1[a]	NR
Hair - Non-Coloring	NR	NR	NR	NR	14	0.000097-0.0049
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	NR	NR	10	0.005-0.02
Baby Products	NR	NR	NR	NR	NR	NR
	Salvia Officinalis (Sage) Water					
Totals*	**1**	**NR**				
Duration of Use						
Leave-On	*1*	*NR*				
Rinse-Off	*NR*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*				
Exposure Type						
Eye Area	NR	NR				
Incidental Ingestion	NR	NR				
Incidental Inhalation-Spray	1[b]	NR				
Incidental Inhalation-Powder	1[b]	NR				
Dermal Contact	1	NR				
Deodorant (underarm)	NR	NR				
Hair - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Mucous Membrane	NR	NR				
Baby Products	NR	NR				

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.
NR – not reported

Table 5. *Salvia officinalis* (sage) - derived ingredients not reported to be in use[27-29]

Salvia Officinalis (Sage) Flower/Leaf/Stem Extract
Salvia Officinalis (Sage) Flower/Leaf/Stem Juice
Salvia Officinalis (Sage) Flower/Leaf/Stem Water
Salvia Officinalis (Sage) Leaf Powder
Salvia Officinalis (Sage) Root Extract

Table 6. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50} Results	Reference
			DERMAL			
Salvia Officinalis (Sage) Leaf Extract	mice	5 mice	1, 3-butylene glycolic solution	50%	>2000 mg/kg	13
Salvia officinalis oil or *Salvia officinalis* leaf oil	rabbits	NR	NR	NR	>5000 mg/kg	2
			ORAL			
Salvia officinalis extract	Female Swiss mice	6/group	Hydroalcoholic extract	5, 50, 500, or 5000 mg/kg	Extrapolated to be 44, 760 mg/kg. No visible signs of toxicity were observed. All animals in the 5000 mg/kg group showed piloerection and diarrhea lasting up to 3 h after treatment. One animal from the 5000 mg/kg group died before 48 h.	32
Salvia officinalis leaf and stem extract	albino rats	6 females	Ethanol	1% v/v Tween 80 in distilled water (control), or 500 -2000 mg/kg bw test article. Animals were observed for symptoms of toxicity or mortality for 14 d.	The extract was considered non-toxic at the maximum dose of 2000 mg/kg bw. No mortality or signs or toxicity were observed over 14 d.	33
Salvia officinalis oil or *Salvia officinalis* leaf oil	rats	NR	NR	NR	2600 mg/kg bw	2
Salvia officinalis oil	Male Wistar rats	10/group	none	1290, 2020, 3200, or 5000 mg/kg bw. Mortality was observed for up to 14 d after treatment, after which all surviving animals were killed.	Calculated to be 2600 mg/kg bw. One animal died from the 1290 mg/kg group, 4 died from the 2020 mg/kg group, 7 died from the 3200 mg/kg group, and 9 animals died from the 5000 mg/kg group. Lethargy was observed in all rats	4

Abbreviations: NR- not reported

Table 7. Developmental and reproductive toxicity studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
ORAL						
Salvia officinalis extract	7 female Wistar rats/group	70% ethanol	Distilled water or 30 mg/kg bw/d, via gavage for 30 d	Estrous cycle changes were monitored with daily vaginal smears. At the end of the observation period, animals in the estrus phase of the estrous cycle were dissected under deep anesthesia. Blood samples were taken to be analyzed in a hormonal assay. Right and left mammary glands from the pelvic region were excised, from which whole mount and formalin-fixed slides were prepared, respectively.	No significant differences in blood estradiol or progesterone were observed, and a decrease in the duration of estrous cycles in Salvia officinalis extract-treated rats was not statistically significant. An increased number of alveolar buds and lobules in the whole mount slides, as well as an increase in the number and diameter of ducts in the histological sections of rats treated with Salvia officinalis extract, were statistically significant.	34
Salvia officinalis leaf and stem extract	6 female rats	ethanol	1% v/v Tween 80 in distilled water (controls) 50, 100, or 200 mg/kg bw/d, via gavage for 7 d	One control group was not ovariectomized, while a second control group served as ovariectomized controls; both control groups were administered 1% v/v Tween 80 in distilled water. An additional group was administered an i.p. dose of 1 µg/d of estradiol, as standard drug treatment. On day 8, vaginal smears were collected from all animals for evaluation of estrus cycle phase and blood samples were drawn to assess serum levels of luteinizing hormone and follicle-stimulating hormone. Then, after the animals were killed, the uteri underwent immunohistochemical staining for estrogen receptors, dissection to examine uterine histology, and were weighed to calculate relative uterus weights.	Vaginal smears from rats treated with the Salvia officinalis leaf and stem extract exhibited varying estrus cycle phases, compared to ovariectomized controls. Serum levels of LSH and FSH were also significantly reduced in the 200 mg/kg bw group (41.7% and 49.1%, respectively). While a decreased percentage of cells stained positively for estrogen receptors in the 50 mg/kg group (compared to the non-ovariectomized controls), significant increases in the percentage of positively stained cells were seen in the uterine tissue of rats treated with 100 and 200 mg/kg bw leaf and stem extract. Increased endometrial thickness, associated with stromal inflammation, was seen in both rats treated with estradiol and the Salvia officinalis leaf and stem extract, and dose-dependent increases in endometrial thickness, were seen in the latter group of treated rats, suggesting uterotrophic effects. Similarly, treatment with the Salvia officinalis leaf extract exhibited a significant dose-dependent increase in uterine weights.	33
Salvia officinalis oil	24 female ICR mice	rodent feed	0.25% (equivalent to 375 mg/kg/d), in diet, for 14 d	After the initial 2-wk period, 3 females were housed with 1 male for 8 d, to induce fertilization. Unfertilized dams were excluded. Post-mating, 13 fertilized females pretreated with Salvia officinalis oil were fed, ad libitum, a diet containing Salvia officinalis oil, while 13 control females were fed a diet with 1% edible soya oil (vehicle), till day 4 of gestation. Dams were killed on day 4 of gestation, and the embryos were recovered at the blastocyst stage of development and prepared for morphological analyses. The number and distribution of pre-implantation embryo nuclei, and the percentage of normal and dead cells, were measured as markers of growth and development.	A significant decrease in embryo cell distribution, according to nucleus number, was observed in dams which consumed Salvia officinalis oil. Dam weights and the proportion of dead cells in embryos were not affected.	35

Abbreviations: FSH- follicle-stimulating hormone; ICR – Institute of Cancer Research; LH-luteinizing hormone

Table 8. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Salvia Officinalis Leaf Extract (50 vol% 1,3-butylene glycolic solution)	5000 µg/0.1 ml/plate	none specified	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA1537 and *Escherichia coli* WP2uvrA	Bacterial reverse mutation assay	Not genotoxic	13
Salvia officinalis oil or *Salvia officinalis* leaf oil	Up to 5000 µg/plate; with and without metabolic activation	Paraffin oil	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and *E. coli* WP2	Bacterial reverse mutation assay, in accordance with OECD TG 471.	Not genotoxic	4
Salvia officinalis oil	91, 183, or 457 µg, with and without metabolic activation	DMSO	*S. typhimurium* strains TA 98 and TA 100	Ames test	Not genotoxic. Significantly inhibited bacterial growth.	38
Salvia officinalis oil	0.25, 0.5, or 1 µl/plate	DMSO	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA1537	Bacterial reverse mutation assay	Not genotoxic	36
Salvia officinalis oil	Up to 0.15 mg/ml	Ethanol	*S. typhimurium* strains TA92, TA 94, TA 98, TA 100, TA 1535, TA 1537	Chromosomal aberration test	Not genotoxic	37

Abbreviation: DMSO- dimethyl sulfoxide

Table 9. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN CHEMICO / IN VITRO STUDIES		
Salvia officinalis oil	50 µl	epiCS®	OECD TG 431. Skin corrosion test and MTT assay. Two separate tissue samples were exposed to the test article, applied neat, for 3 min and 1 h, and were then rinsed with DPBS after each exposure. Cell viability was measured in an MTT assay.	Not corrosive; mean percent cell viability of both tissue replicates were 100% and 39.83%, compared to 20.26% and 0% in positive control replicates.	4
Salvia officinalis oil	16 µl	EpiSkin SA	OECD TG 439. In vitro skin irritation test. Three separate tissue samples were exposed to the test article for 42 min, rinsed with DPBS, and incubated for 42 h in fresh medium. Cell viability was measured in an MTT assay.	Irritating or corrosive to the skin. The mean percent viability of treated tissue was 2.1% compared to 2.9% in the positive controls exposed to 5% sodium dodecyl sulfate	4
			ANIMAL		
Salvia officinalis leaf extract	Undiluted, and 10%, in 50% 1,3-butylene glycolic solution	3 rabbits	NR	Not irritating	13
Salvia officinalis oil or *Salvia officinalis* leaf oil	NR	rabbits	24-h occlusive patch test, performed on intact and abraded rabbit skin. The test article was applied neat.	Moderately irritating	2
			HUMAN		
Salvia officinalis oil or *Salvia officinalis* leaf oil	NR	20 subjects	24-h occlusive patch test. The test article was applied neat.	Not irritating. One irritation reaction occurred.	2,43
Salvia officinalis oil or *Salvia officinalis* leaf oil	8%, in petrolatum	NR	48-h occlusive patch test	Not irritating or sensitizing	2
Salvia Officinalis (Sage) Leaf Extract	0.2 ml; 1%, in water	53 subjects	HRIPT. Nine, 24-h applications of the test article were made to the back over a 3-wk induction period. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site, and was scored after 24 and 72 h.	Not irritating or sensitizing	44
Sage Officinalis (Sage) Oil	0.1-0.15 g	53 subjects	HRIPT. Nine, 24-h applications of the test article were made to the back over a 3-wk induction period. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site and was scored after 24 and 72 h.	Not irritating or sensitizing	45

Abbreviations: epiCS®- reconstituted human epidermis tissue surfaces; HRIPT – human repeated insult patch test; MTT - 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; OECD- Organization for Economic Cooperation and Development; TG – test guideline

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2022 VCRP Frequency of Use Data – *Salvia officinalis* (Sage)- Derived Ingredients

INGREDIENT NAME	CATEGORY CODE	CATEGORY DESCRIPTION	CPIS COUNT
Salvia Officinalis (Sage) Extract Total Uses: 70			
Salvia Officinalis (Sage) Extract	05A	Hair Conditioner	5
Salvia Officinalis (Sage) Extract	05F	Shampoos (non-coloring)	11
Salvia Officinalis (Sage) Extract	05G	Tonics, Dressings, and Other Hair Grooming Aids	10
Salvia Officinalis (Sage) Extract	05I	Other Hair Preparations	5
Salvia Officinalis (Sage) Extract	09A	Dentifrices	3
Salvia Officinalis (Sage) Extract	10A	Bath Soaps and Detergents	1
Salvia Officinalis (Sage) Extract	10B	Deodorants (underarm)	1
Salvia Officinalis (Sage) Extract	12A	Cleansing	3
Salvia Officinalis (Sage) Extract	12C	Face and Neck (exc shave)	15
Salvia Officinalis (Sage) Extract	12D	Body and Hand (exc shave)	6
Salvia Officinalis (Sage) Extract	12F	Moisturizing	2
Salvia Officinalis (Sage) Extract	12H	Paste Masks (mud packs)	3
Salvia Officinalis (Sage) Extract	12I	Skin Fresheners	2
Salvia Officinalis (Sage) Extract	12J	Other Skin Care Preps	3
Salvia Officinalis (Sage) Leaf Total Uses: 1			
Salvia Officinalis (Sage) Leaf	12J	Other Skin Care Preps	1
Salvia Officinalis (Sage) Leaf Extract Total Uses: 211			
Salvia Officinalis (Sage) Leaf Extract	02A	Bath Oils, Tablets, and Salts	2
Salvia Officinalis (Sage) Leaf Extract	03D	Eye Lotion	3
Salvia Officinalis (Sage) Leaf Extract	05A	Hair Conditioner	13
Salvia Officinalis (Sage) Leaf Extract	05B	Hair Spray (aerosol fixatives)	1
Salvia Officinalis (Sage) Leaf Extract	05F	Shampoos (non-coloring)	24
Salvia Officinalis (Sage) Leaf Extract	05G	Tonics, Dressings, and Other Hair Grooming Aids	8
Salvia Officinalis (Sage) Leaf Extract	05I	Other Hair Preparations	5
Salvia Officinalis (Sage) Leaf Extract	06C	Hair Rinses (coloring)	7
Salvia Officinalis (Sage) Leaf Extract	06D	Hair Shampoos (coloring)	8
Salvia Officinalis (Sage) Leaf Extract	07B	Face Powders	1
Salvia Officinalis (Sage) Leaf Extract	07D	Leg and Body Paints	2
Salvia Officinalis (Sage) Leaf Extract	07F	Makeup Bases	1
Salvia Officinalis (Sage) Leaf Extract	09A	Dentifrices	4
Salvia Officinalis (Sage) Leaf Extract	09B	Mouthwashes and Breath Fresheners	1
Salvia Officinalis (Sage) Leaf Extract	10A	Bath Soaps and Detergents	22
Salvia Officinalis (Sage) Leaf Extract	10D	Feminine Deodorants	1
Salvia Officinalis (Sage) Leaf Extract	10E	Other Personal Cleanliness Products	1
Salvia Officinalis (Sage) Leaf Extract	11A	Aftershave Lotion	1
Salvia Officinalis (Sage) Leaf Extract	11E	Shaving Cream	1
Salvia Officinalis (Sage) Leaf Extract	12A	Cleansing	29

2022 VCRP Frequency of Use Data – *Salvia officinalis* (Sage)- Derived Ingredients

Salvia Officinalis (Sage) Leaf Extract	12C	Face and Neck (exc shave)	20
Salvia Officinalis (Sage) Leaf Extract	12D	Body and Hand (exc shave)	3
Salvia Officinalis (Sage) Leaf Extract	12F	Moisturizing	37
Salvia Officinalis (Sage) Leaf Extract	12H	Paste Masks (mud packs)	4
Salvia Officinalis (Sage) Leaf Extract	12I	Skin Fresheners	4
Salvia Officinalis (Sage) Leaf Extract	12J	Other Skin Care Preps	8
Salvia Officinalis (Sage) Leaf Oil **Total Uses: 2**			
Salvia Officinalis (Sage) Leaf Oil	02A	Bath Oils, Tablets, and Salts	1
Salvia Officinalis (Sage) Leaf Oil	09A	Dentifrices	1
Salvia Officinalis (Sage) Leaf Water **Total Uses: 3**			
Salvia Officinalis (Sage) Leaf Water	10B	Deodorants (underarm)	1
Salvia Officinalis (Sage) Leaf Water	12A	Cleansing	1
Salvia Officinalis (Sage) Leaf Water	12I	Skin Fresheners	1
Salvia Officinalis (Sage) Oil **Total Uses: 105**			
Salvia Officinalis (Sage) Oil	02A	Bath Oils, Tablets, and Salts	2
Salvia Officinalis (Sage) Oil	02B	Bubble Baths	1
Salvia Officinalis (Sage) Oil	02D	Other Bath Preparations	3
Salvia Officinalis (Sage) Oil	03D	Eye Lotion	1
Salvia Officinalis (Sage) Oil	05A	Hair Conditioner	2
Salvia Officinalis (Sage) Oil	05B	Hair Spray (aerosol fixatives)	1
Salvia Officinalis (Sage) Oil	05F	Shampoos (non-coloring)	3
Salvia Officinalis (Sage) Oil	05G	Tonics, Dressings, and Other Hair Grooming Aids	6
Salvia Officinalis (Sage) Oil	05I	Other Hair Preparations	2
Salvia Officinalis (Sage) Oil	07D	Leg and Body Paints	2
Salvia Officinalis (Sage) Oil	09A	Dentifrices	1
Salvia Officinalis (Sage) Oil	09C	Other Oral Hygiene Products	2
Salvia Officinalis (Sage) Oil	10A	Bath Soaps and Detergents	1
Salvia Officinalis (Sage) Oil	10B	Deodorants (underarm)	1
Salvia Officinalis (Sage) Oil	11B	Beard Softeners	2
Salvia Officinalis (Sage) Oil	11E	Shaving Cream	2
Salvia Officinalis (Sage) Oil	11G	Other Shaving Preparation Products	1
Salvia Officinalis (Sage) Oil	12A	Cleansing	9
Salvia Officinalis (Sage) Oil	12C	Face and Neck (exc shave)	8
Salvia Officinalis (Sage) Oil	12D	Body and Hand (exc shave)	7
Salvia Officinalis (Sage) Oil	12F	Moisturizing	23
Salvia Officinalis (Sage) Oil	12G	Night	1
Salvia Officinalis (Sage) Oil	12H	Paste Masks (mud packs)	9
Salvia Officinalis (Sage) Oil	12J	Other Skin Care Preps	15
Salvia Officinalis (Sage) Water **Total Uses: 1**			
Salvia Officinalis (Sage) Water	12C	Face and Neck (exc shave)	1