Safety Assessment of *Rosa centifolia*-Derived Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: February 10, 2023
Panel Meeting Date: March 6-7, 2023

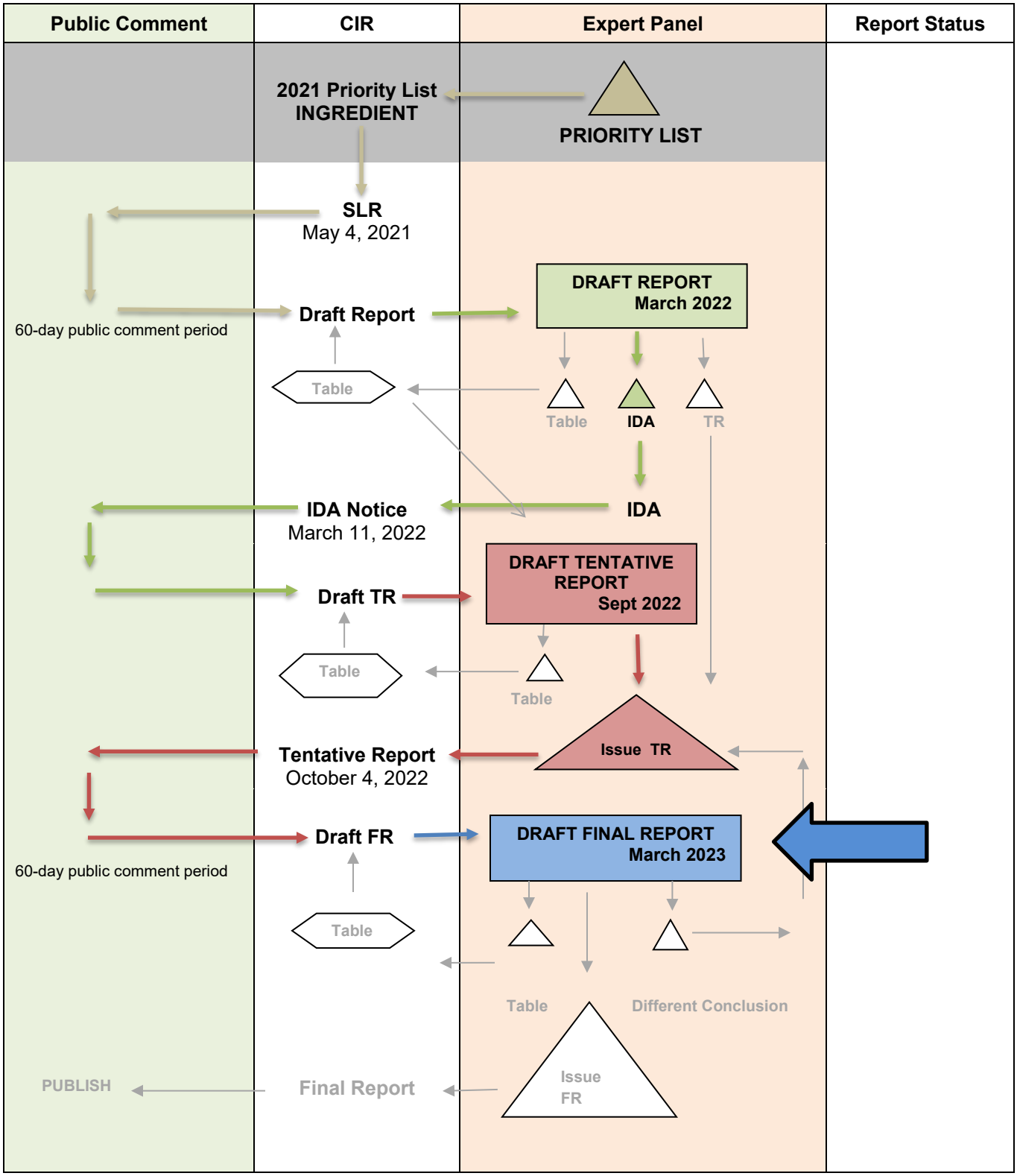
The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Daniel C. Liebler, Ph.D. and Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., former Senior Scientific Analyst/Writer, and Regina Tucker, M.S., Scientific Analyst/Writer, CIR.

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651
CIRINFO@CIR-SAFETY.ORG

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Rosa centifolia*-derived ingredients

MEETING March 2023



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Regina Tucker, M.S., Scientific Analyst/Writer, CIR
Date: February 10, 2023
Subject: Safety Assessment of *Rosa centifolia*-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of *Rosa centifolia*-Derived Ingredients as Used in Cosmetics. (It is identified in this report package as *report_RosaCentifolia_032023*.) At the September 2022 meeting, the Expert Panel for Cosmetic Safety (Panel) issued a Tentative Report for public comment with the conclusion that the following 9 *Rosa centifolia*-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:

Rosa Centifolia Bud Extract
Rosa Centifolia Flower
Rosa Centifolia Flower Extract
Rosa Centifolia Flower Juice
Rosa Centifolia Flower Oil
Rosa Centifolia Flower Powder
Rosa Centifolia Flower Water
Rosa Centifolia Flower Wax
Rosa Centifolia Stem Extract

The Panel also concluded the available data are insufficient to make a determination that the following 3 *Rosa centifolia*-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Rosa Centifolia Callus Culture Extract
Rosa Centifolia Extract
Rosa Centifolia Leaf Cell Extract

The additional data needed to determine safety for these 3 ingredients are:

- Method of manufacturing
- Composition and impurities data
- Dermal irritation and sensitization data
- Dermal toxicity (28-day dermal)
    - If positive, other toxicological endpoints (e.g., developmental and reproductive toxicity, genotoxicity, carcinogenicity, etc.) may be needed.

No new data were received or found. Comments on the Tentative Report that were provided from the Council *(PCPCcomments_RosaCentifolia_032023)*, as well as CIR response to these *comments (response-PCPCcomments_RosaCentifolia_032023)* are included in this packet.

As per the Panel's request at the December 2022 meeting, an updated use table format has been implemented. The frequency and concentration of use for each ingredient is presented both cumulatively by likely duration and exposure and individually by product category.

Also included in this package for your review are the report history (*history_RosaCentifolia_032023*), flow chart (*flow_RosaCentifolia_032023*), literature search strategy (*search_RosaCentifolia_032023*), data profile (*dataprofile_RosaCentifolia_032023*), and transcripts from previous meetings (*transcripts_RosaCentifolia_032023*).

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: October 20, 2022

SUBJECT: Tentative Report: Safety Assessment of *Rosa centifolia*-Derived Ingredients as Used in Cosmetics (release date: October 4, 2022)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of *Rosa centifolia*-Derived Ingredients as Used in Cosmetics.

Introduction – In the Introduction, it would be helpful to note that the re-review summary is also available on the CIR website.

Method of Manufacture, Rosa Centifolia Stem Extract – Please revise: "An extract was harvested…" The "epicormic, new, and old shoots" were harvested and the extract was made from the shoots.

Acute, Oral – In the first paragraph, "route of administration not stated" should be deleted. The route of administration is oral and OECD TG 425 states that the rats should be treated by gavage.

Short-Term, Oral – Rather than saying "route of administration not stated" it should state that the "method of oral administration was not stated".

Table 6, first row – Please add the units in the Concentration/Dose column.

Table 6, second row – In the Procedure column, please correct "24 hand for 3h" to "24 h, and for 3h".

Table 7 – Has RIFM been asked about the concentrations tested in the studies they submitted (references 8, 10, 11, 12, 13,7)? If the studies do not discuss dilution of the test materials, they were likely tested undiluted.

Draft Report Comment Responses

Rosa Centifolia – March 2023-Regina Tucker	
Comment Submitter: Personal Care Products Council **Date of Submission: October, 2022**	
Comment	**Response/Action**
(1) Introduction – In the Introduction, it would be helpful to note that the re-review summary is also available on the CIR website.	Addressed
(2) Method of Manufacture, Rosa Centifolia Stem Extract – Please revise: "An extract was harvested…" The "epicormic, new, and old shoots" were harvested and the extract was made from the shoots.	Addressed
(3) Acute, Oral – In the first paragraph, "route of administration not stated" should be deleted. The route of administration is oral and OECD TG 425 states that the rats should be treated by gavage.	Addressed
(4) Short-Term, Oral – Rather than saying "route of administration not stated" it should state that the "method of oral administration was not stated"	Addressed
(5) Table 6, first row – Please add the units in the Concentration/Dose column.	Addressed
(6) Table 6, second row – In the Procedure column, please correct "24 hand for 3h" to "24 h, and for 3h"	Addressed
(7) Table 7 – Has RIFM been asked about the concentrations tested in the studies they submitted (references 8, 10, 11, 12, 13,7)? If the studies do not discuss dilution of the test materials, they were likely tested undiluted	Addressed

CIR History of:

Rosa centifolia-derived Ingredients

May 2021

A Scientific Literature Review (SLR) on Rose centifolia-derived ingredients was issued on May 4, 2021.

January 2022

Updated (2022) VCRP data were received and incorporated.

March 2022

Comments on the draft report were received from The Personal Care Products Council

The Panel issues an Insufficient Data Announcement, with the following data needs:

The additional data needed to determine safety for these cosmetic ingredients and address data insufficiencies include:

- Method of manufacturing
- Composition and impurities data for all, except the flower and bud ingredients
- Dermal toxicity (28 day dermal)
    - If positive, other toxicological endpoints (e.g., developmental and reproductive toxicity, genotoxicity, carcinogenicity, etc.) may be needed

September 2022: Draft Tentative Report

The following unpublished data were received:

- Anonymous. 2014. Clinical safety evaluation Repeated insult patch test (eye serum containing 0.1% Rosa Centifolia Flower Extract).
- Method of manufacture Mexoryl SDA (Rosa Centifolia Stem Extract).
- Certificate of analytical composition Mexoryl SDA (Rosa Centifolia Stem Extract).
- Mexoryl SDA (Rosa Centifolia Stem Extract): Bacterial reverse mutation assay.
- Mexoryl SDA (Rosa Centifolia Stem Extract): In vitro human lymphocyte micronucleus assay.
- EpiSkin™ Micronucleus assay Mexoryl SDA (Rosa Centifolia Stem Extract)

The Panel issued a Tentative Report for public comment with the conclusion that the following 9 Rosa centifolia-Derived ingredients are safe in cosmetics in the present practices of use and concentrations described in the safety assessment when formulated to be non-sensitizing: Rosa Centifolia Bud Extract, Rosa Centifolia Juice, Rosa Centifolia Flower Water, Rosa Centifolia Flower, Rosa Centifolia Flower Oil, Rosa Centifolia Flower Wax, Rosa Centifolia Flower Extract, Rosa Centifolia Stem Powder, and Rosa Centifolia Stem Extract.

The Panel also concluded the available data are insufficient to make a determination that the following 3 Rosa centifolia-Derived ingredients are safe under the intended conditions of use in cosmetic formulations: Rosa Centifolia Callus Culture Extract, Rosa Centifolia Extract, and Rosa Centifolia Leaf Cell Extract.

The additional data needed to determine safety for these 3 cosmetic ingredients are:

- Method of manufacture
- Composition and impurities data
- 28-day dermal toxicity data o if positive additional toxicological endpoints may be needed
- Dermal irritation and sensitization data.

March 2023: Draft Final Report

Comments on the Draft Tentative Report were received from The Personal Care Products Council.

Rosa centifolia-derived Ingredients Data Profile* –March 2023 – Wilbur Jonhnson/Regina Tucker																														
						Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents	Impurities	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Silico	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Case Report	Other Clinical Reports
Rosa Centifolia Bud Extract		X																												
Rosa Centifolia Callus Culture Extract																														
Rosa Centifolia Extract			X																										X	
Rosa Centifolia Flower	14	X																				X			X					
Rosa Centifolia Flower Extract	174	X	X	X	X				X			X													X					X
Rosa Centifolia Flower Juice	1	X	X	X	X																									
Rosa Centifolia Flower Oil	25	X	X					X	X												X	X			X					
Rosa Centifolia Flower Powder	5	X	X																											
Rosa Centifolia Flower Water	99	X	X	X	X																									
Rosa Centifolia Flower Wax	10	X	X																											
Rosa Centifolia Leaf Cell Extract																														
Rosa Centifolia Stem Extract			X	X	X												X													

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

Rosa centifolia-derived Ingredients

Ingredient	CAS #	InfoBase	PubMed	TOXNET	FDA*	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Rosa Centifolia Bud Extract		Yes	0/0			No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Callus Culture Extract		Yes	0/0		Yes*	No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Extract		Yes	6/6		Yes*	No	No	No	No	No	No	No	No	No	No	No	Yes**
Rosa Centifolia Flower		Yes	4/4			No	No	No	No	No	No	No	No	No	No	No	No
Rosa Centifolia Flower Extract	84604-12-6	Yes	1/1		Yes*	No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Flower Juice		Yes	0/0			No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Flower Oil		Yes	1		Yes	No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Flower Powder		Yes	0/0			No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Flower Water		Yes	1/1			No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Flower Wax		Yes	0/0			No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Leaf Cell Extract		Yes	0/0		Yes*	No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa Centifolia Stem Extract		Yes	0/0		Yes*	No	No	No	No	No	No	No	No	No	No	No	Yes
Rosa centifolia (genus and species, not an ingredient)			/22		Yes*	No	No	No	No	No	No	No	No	No	No	No	Yes

*Rose Absolute (can also be Rosa centifolia): Essential oil, oleoresins (solvent-free), and natural extractants (including distillates) GRAS for use in foods for human consumption (21 CFR 182.20). Same derivatives GRAS for use in foods, drugs, and related products for animal consumption (21 CFR 582.20) – Need to determine if any of other ingredients covered by 12 CFR 182.20 and 21 CFR 582.20.

**Search Rosa Centifolia Extract – Cosmetic Analysis

Dr. Duke's has composition data on Rosa centifolia

No IFRA standard in Standards Library

Rosa Centifolia Flower Extract has fragrance function also listed

Qualifiers

Absorption
Acute
Allergy
Allergic
Allergenic
Cancer
Carcinogen
Chronic
Development
Developmental
Excretion
Genotoxic
Irritation
Metabolism
Mutagen
Mutagenic
Penetration
Percutaneous
Pharmacokinetic
Repeated dose
Reproduction
Reproductive
Sensitization
Skin
Subchronic
Teratogen
Teratogenic
Toxic
Toxicity
Toxicokinetic
Toxicology
Tumor

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- Chemical information | Australian Industrial Chemicals Introduction Scheme (AICIS)
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - Flavor Extract Manufacturers Association (FEMA) (femaflavor.org) Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

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

Fragrance Websites, if applicable

IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

MARCH 2022 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT
Belsito's Team Meeting – March 7, 2022

Dr. Donald Belsito
Alright. Let me save this before I lose everything. Then we're going to Rosa Centifolia. So this is the first time we're seeing this. And a we've got a bunch of data, looks like a lot of it was sent in from the Cosmetic are from RIFM. Let me find it here. We have a wave, three comments from
Personal Care Products Council as well on this, so looks like we can clear the flower ingredients. It's grass and there's some sensitization data. Oh, no, we have an issue with flower oil, it absorbs and it's phototoxic. And there's no photo allergy data. Where he's going to go across all the flower because, right, I mean. Dan you're the chemist. Major components in the oil better photosensitizing could come out with other extraction methods or no?

Dr. Dan Liebler
The oil comes from the oil layer of steam distillation. So the that is separate from the juice. And, let's see. I would argue it's also separate from the act, the flower extract.

Dr. Donald Belsito
Or with photoallergy, even a small component could be an issue.

Dr. Dan Liebler
So what's the endpoint test endpoint for photoallergy?

Dr. Donald Belsito
We don't have one now.

Dr. Dan Liebler
Well, when we're in trouble for this ingredient.

Dr. Donald Belsito
Unless we want to do it on animals. But you know, that's probably why RIFM hasn't taken this up because there is no photo allergy data. There is very good photo toxicity data for the flower oil.

Dr. Dan Liebler
So the flat. Yeah. So you just said the flower oil has good photo tox data.

Dr. Donald Belsito
Yeah, showing it's quite phototoxic.

Dr. Dan Liebler
OK, so if we have photo tox data then we assume that we have a higher risk of photo allergenicity until proven otherwise?

Dr. Donald Belsito
Right.

Dr. Dan Liebler
OK.

Dr. Donald Belsito
We know it can absorb, so we and we don't have photo allergy data or.

Dr. Dan Liebler
There's something in it that was photo tox. I thought I heard. Carol starts to talk.

Carol Eisenmann (PCPC)
Yes, but they actually tested the concrete, not the oil. She's put the concrete under the oil, which really shouldn't be.

Dr. Dan Liebler
Ah.

Carol Eisenmann (PCPC)
It's called upon. It's the concrete that's positive photo tox.

Dr. Dan Liebler
K.

Dr. Donald Belsito
Yeah.

Dr. Dan Liebler
I was going to.

Dr. Donald Belsito
Does it really matter?

Dr. Dan Liebler
Well, the concrete is a is derivative of the oil.

Dr. Donald Belsito
Right.

Dr. Dan Liebler
And the process sort of bifurcates from steam distillation to give you the flower oil and then whatever becomes of it including a concrete, whereas the others are the aqueous layer, which have a different composition.

Dr. Donald Belsito
But not completely different. I mean, we don't know what the photo absorbing component is. Isn't it possible that there could be small amounts in the other factions?

Dr. Dan Liebler
Ah, it's of course it's always possible that there's a small amount. I mean they these fractions are very distinct in the compositions, but not in the absolute amounts. Ah, and so I guess the question it would be, do we have any photo tox, negative photo tox data for any other component of this Rosa centifolia?

Dr. Donald Belsito
No. Right. I'm trying to find the page with the photo tox.

Dr. Dan Liebler
Because, if we don't, then the logic that a teeny tiny will count something.

Dr. Paul Snyder
Page 18.

Dr. Dan Liebler
Yeah.

Dr. Donald Belsito
Excellent. Correct. You have the concrete. I mean, it was only at a very high dilution 33%, you know, I mean you can deal with, you know, as you know from experience with the RIFM panel Dan, that you can deal with phototoxicity by going 110th below the minimum phototoxic dose but photo allergy are a complete no, no. And we don't have any photo allergy data.

Dr. Dan Liebler
So the Rosa centifolia, flower oil was strongly phototoxic, but only at the highest concentration, 33% in benzene.

Dr. Donald Belsito
Right.

Dr. Dan Liebler
All responses.

Dr. Curtis Klaassen
Does it help us any? Does it help us in the non-cosmetic section? It says that, ah, the Rosebuds and rose flowers are generally recognized as safe as for use for food for human consumption.

Dr. Donald Belsito
Yeah, but you're not putting it on skin.

Dr. Curtis Klaassen
Yeah, he has also determined that these are grass for use in foods, drugs and related products for animal consumption.

Dr. Donald Belsito
Yeah, but it's consumption, not putting on your skin and getting exposed to sunlight.

Dr. Dan Liebler
Like lime.

Dr. Donald Belsito
Right.

Dr. Dan Liebler
So what does it mean when it says all responses were abolished as the result of binary dilution? Is that just mean a one to one delusion? Did you Regina, did you take that line verbatim out of the reference or did you rephrase that from something? Do you know what they mean by binary dilution here?

Regina Tucker (CIR)
No, I'm not certain what they meant by that.

Dr. Donald Belsito
Usually it's log dilutions, no?

Dr. Dan Liebler
I'm just unfamiliar with that term.

Dr. Donald Belsito
Yeah, me too.

Dr. Dan Liebler
I mean if there's log deletion via tenfold.

Dr. Donald Belsito
Right would be 3.3, which is a big difference.

Dr. Dan Liebler
Yeah. No, but there's still a whole lot more higher concentration that would be used in. Cosmetic ingredients, I think?

Dr. Donald Belsito
Yeah, I agree Dan. But the problem is that if it's photoallergy then concentration becomes less important.

Dr. Dan Liebler
Well, let's just cut to the chase and Don is this ingredient saveable period.

Dr. Donald Belsito
I don't know.

Dr. Dan Liebler
I mean, we've got the Guilty. Ah. This is the proof you're not guilty. Review approach when we get to photo allergenicity if there's a photo tox response.

Dr. Donald Belsito
Right. Yeah, Dan, to answer your question, just doing a quick Google search, it looks binary delusions or keep cutting it in half.

Dr. Dan Liebler
OK, so one to one. So if you went from 33 to you know?

Dr. Donald Belsito
16.5.

Dr. Dan Liebler
16 or so, yeah. Then you're the effect went away.

Dr. Donald Belsito
Right.

Dr. Dan Liebler
You know you're the dermatologist, or you're one of the dermatologists on the panel, but, it seems to me that the solution here might be in the concentration applied.

Dr. Donald Belsito
For Phototoxicity but. Yeah, it's just there's something that's absorbing.

Dr. Dan Liebler
Right, you know, but if it's absorbing it mean photo allergenicity still, at least our understanding of the adverse outcome pathway is something becomes photo excited and then reacts with some protein to form a Hampton.

Dr. Donald Belsito
Right.

Dr. Dan Liebler
That then sensitizes and so mechanistically it's very similar to the photoactive photo tox adverse outcome pathway or where an excited species either binds to a protein or produces oxidants that causes damage to some critical molecules. And if you're able to take that mechanism out by a one to one delusion, then it suggests that you could dramatically decrease the hapten formation. Similarly, in fact, you know, if you extrapolate that down too, I don't know how many logs we are above the maximum use concentration here, but if you're, you know, talking about 1000 fold, let's say, you may not realistically have a concern about photo allergenicity mechanistically.

Dr. Donald Belsito
OK, so I'm just looking at point 025.096 for the flower water. .002 for the flower oil. I mean, the concentrations are very low. Very low.

Dr. Dan Liebler
Yeah. So I think that you know, I think we have an approach we could take to assess the risk.
Without knocking all the ingredients out, you know as possible that we take the oil and the concrete out of, you know, out or we. Because the if it's. If it's something that's in the concrete, it's got to be really, really organic lipid soluble. So it's, you know, whatever that is its going to be present in the sort of the more aqueous ingredients and very negligible concentrations. And then we have a very low overall use concentration. So I think that provides the logic that we might employ. To consider you know the photo allergenicity issue. I'd love to hear what David and Wilma had to say about this as well, of course. But ah.

Dr. Donald Belsito
OK.

Dr. Dan Liebler
Let's see.

Dr. Donald Belsito
Yeah. OK. So.

Dr. Dan Liebler
So this is David is presenting first on this.

Dr. Donald Belsito
So centralization is cleared, photo tox was seen at 33% but not 16.5%.

Dr. Dan Liebler
And Regina, I just have one more question about the wording here in the paper. So did they actually show data that was negative at in a one to one delusion or it was just something that was said in the text or? You know. It'll be good to know what that actually was in that report, because that's a critical piece of information for our line of thinking is, you know, if you heard us talking about it.

Dr. Donald Belsito
You could send me that paper. Or it's not a paper, right? It's data from RIFM.

Regina Tucker (CIR)
It was, it was data. It was data from RIFM. And if you would like that data, yes, I will be able to send that over.

Dr. Donald Belsito
OK.

Monice Fiume (CIR)
You have the data it's PDF page that it where it says Davies. Or between PDF page 72 and 80 are the studies.

Dr. Donald Belsito
Temple University.

Monice Fiume (CIR)
But they are Davies and Forbes, I believe. It may actually be the one starting on page 7, PDF page 75.

Dr. Donald Belsito
So it it's a shoulder at 3:20. Right. So this is Rose Bulgari concrete is what we're talking about here. Was irritating at high concentrations when a phototoxic response not strongly dose related apparently superimposed on the irritant background. No clear photo toxic threshold.

Dr. Dan Liebler
So you're looking at PDF 77 here.

Dr. Donald Belsito
Well, I'm looking at page 79, which is even more. Says the Rose Bulger concrete had an unusual response, with had the appearance of a phototoxic reaction is localized in most cases to the light exposed area, but had the appearance of multiple petechiae rather than the can fluent edema or erythema normally observed. Moreover, the response was first seen prior to radiation.

Dr. Dan Liebler
Wow.

Dr. Donald Belsito
Maybe suspected localization was related to occlusion rather than light exposure.

Dr. Dan Liebler
Well, this is ambiguous then?

Dr. Donald Belsito
Yeah. And, they concluded, was mildly phototoxic, but some other reaction unrelated to light was a greater significance. Ah. Almost think that study, is a poor study. And shouldn't be, I mean, they were reporting it as to contact irritant at 33% and 16%. And you any radiating areas. I'm not even getting a dose response. It's two out of six and three out of six, for 33 and 16 and then it goes away.
I think this is a crummy study. And probably even should not be referenced. I mean, it's just very confusing it to what they're describing is more urgency than phototoxicity. I mean phototoxic reactions are more severe clinically than photoallergic reactions. Photoallergic reactions look like allergy phototoxic reactions very frequently cause blisters when severe. So I just think that this is a study that shouldn't be included? I mean, it was sent to us, but I just don't see the relevance of it. Looking at all the details. In which case all that concerned about sent Photosensitization goes away.

Dr. Dan Liebler
Yep. OK, so I you know defer to your judgment on this whether to include I think there are certainly big question marks about this study. It certainly isn't on him is not on ambiguous evidence for photo tox.

Dr. Donald Belsito
No, I mean not at all. The response was seen before light. The same response that is seen after light, which just gave it more time to develop, it was severely irritating at 16% and 33%. There was no dose response in the sense that two out of six at 33 and three out of six at 16 and then it all goes away at 8. So I. I think we just get rid of this study and don't even quote it.

Dr. Paul Snyder
What about the clinical studies on page 18, PDF page 18.

Dr. Donald Belsito
Which clinical study?

Dr. Paul Snyder
For the case reports, I'm sorry. Do yuppies 18?

Dr. Donald Belsito
Right. But that when patch tested, it was a positive patch test, not.

Dr. Donald Belsito
So, eptopic female patient with a history of polymorphous light eruption, two week history of a rash after using rose absolute and their non scented body lotion with Rosa Center folio. So let's talk about these reactions and then they patched, tested them. It wasn't a photo patch, so this was just patch test positive.

Dr. Paul Snyder
OK.

Dr. Donald Belsito
So one case report of an allergin. Not a photo allergy. Yeah, I mean, I, I, Regina, I would just get rid of that photo tox study. It's a very poor study and not interpretable.

Regina Tucker (CIR)
Yes, I can do that. So just to be clear. I will be getting rid of the photo tox, the photo tox study from your PDF, page 77.

Dr. Donald Belsito
Well, that's this. You'll be getting rid of that and then you'll be getting rid of in the documents itself that photosensitization phototoxicity that whole area will go away. Because it's.

Regina Tucker (CIR)
OK, thank you. I understand that now. So the whole section that whole section will be taken out of the report.

Dr. Donald Belsito
Yes, that's what I would recommend. That study is I mean to me what they're reporting is irritation, not phototoxicity.

Regina Tucker (CIR)
Thank you.

Dr. Donald Belsito
So having gotten rid of that.

Dr. Dan Liebler
So Don and with respect to the plant parts and the data on.

Dr. Donald Belsito
Right.

Dr. Dan Liebler
Chemistry. You know, method of manufacture impurities and so forth. I think we're OK on everything except. On the callous cell culture and the Leafs of cell culture extracts. Everything else, I think we've got covered. By appropriate by either direct at or appropriate inference from related plant perhaps.

Dr. Donald Belsito
OK, well I had come, looks like we can clear the flower ingredients, their grass, and we have the sensitization data. But the others I thought were insufficient for manufacturing, except the extract, composition impurities. And depending upon these photo tox endpoints.

Dr. Dan Liebler
Let's see, leaves all the Leafs , leaf cells, Akalis and stem extract. I think the buds OK because, that's flower.

Dr. Donald Belsito
Right.

Dr. Dan Liebler
And. So everything Rosa centifolia extract. Yeah, that's whole plant. Isn't that whole plant? Yeah, whole plant. So that's going to be leaves and stems and stuff. So. Yeah. OK. Let me just restate everything. Flower derived is OK. And then everything including the bud. So we're going to group that will flower, I think.

Dr. Donald Belsito
Yeah.

Dr. Dan Liebler
And then everything else is not, because.

Dr. Donald Belsito
We need.

Dr. Dan Liebler
Now we've got method of manufacture Rosa Centifolia, but no composition impurities.

Dr. Donald Belsito
Right. We have method of manufacture except the extract. So we have the extract?

Dr. Dan Liebler
Yep.

Dr. Donald Belsito
So we don't have method of manufacture for the stem, extract the leaf cell extract.

Dr. Dan Liebler
And the callus.

Dr. Donald Belsito
And the callus extract, we need those three.

Dr. Dan Liebler
Yep.

Dr. Donald Belsito
The leaf cell and stem. And then we need composition and impurities. For all except the flowering Bart, correct.

Dr. Dan Liebler
See I think the flower extract, a flower juice flower water collectively clears all the other flower related stuff.

Dr. Donald Belsito
Yeah, I think all the flowers stuff is fine. But I'm saying is composition and impurities for the non flower ones.

Dr. Dan Liebler
Yep. Correct. We don't have that.

Dr. Donald Belsito
So that would include the whole extract.

Dr. Dan Liebler
Correct.

Dr. Donald Belsito
That would be bud extract cell culture extract the extract, the leaf cell extract the stem extract.

Dr. Dan Liebler
Yeah. So I'm keeping the bud with the flowers. Because my understanding is, the bud is an unopened flower.

Dr. Donald Belsito
I mean, I'm fine with that.

Dr. Dan Liebler
I mean, it's perhaps a little bit less developed and you know, maybe depending on where you cut off, how old its bud is relative to flowering, but I'm just lumping the button with the flower.

Dr. Donald Belsito
I'm good with that, Curt, Paul.

Dr. Curtis Klaassen
Sure, go ahead.

Dr. Paul Snyder
Yeah, I'm fine with that.

Dr. Donald Belsito
OK.

Dr. Dan Liebler
Since we're reviewing it in the early spring.

Regina Tucker (CIR)
Yeah. OK. So just to be clear, so I just want to make sure I have this correct. So on the flower in the bud is OK, but everything else is not. So we need the composition and impurities, method of manufacture for the stem leaf callus cell extracts. Is that correct?

Dr. Dan Liebler
That's right.

Dr. Donald Belsito
Right. So we have we need manufacturing for Callus leaf cell and stem extract, then we need composition and impurities for those three plus the whole plant extract.

Regina Tucker (CIR)
OK. so you need the whole plant, extract the composition and impurities for the whole plant, extract the stem, the leaf, the callous in the cell extracts, yes. Thank you.

Dr. Donald Belsito
Yeah. And then in the discussion, so it's going to be formulated to be non sensitizing because these have sensitizing component. We have the botanical boilerplate. We have the respiratory boilerplate. We clearing Bay flowering bug based upon grass status and sensitization data. And the others, obviously we're going insufficient. This is our first go around so this is a really.

Dr. Dan Liebler
Yep.

Dr. Donald Belsito
Anything else with this? So Regina, you also have the sort of early discussion botanical respiratory and then the sensitization boilerplate for botanicals.

Regina Tucker (CIR)
Yes, I had it botanical respiratory and sensitization boilerplate.

Dr. Donald Belsito
Right.

Regina Tucker (CIR)
Yes, I have that.

Dr. Donald Belsito
And. OK. And are safe as used for the flour and butter based upon graph status and sensitization data that clears them.

Monice Fiume (CIR)
I'm sorry I missed. What were the constituents of concern, so we can make sure it makes it into the abstract and discussion.

Regina Tucker (CIR)
Yep.

Dr. Donald Belsito
I'm. Off the top of my head. Then once I'm remembering as citronellol geraniol. Let me just do a search for such an ally. I think they were all in the orgeraniol. They're all in the same.

Monice Fiume (CIR)
Yes, and phenethyl alcohol, would that also be one?

Dr. Donald Belsito
Phenethyl alcohol near all, I think was there right? A whole bunch of sensitizers. I don't think we need to list them all.

Dr. Dan Liebler
Table 3.

Dr. Donald Belsito
Yeah, I'm.

Monice Fiume (CIR)
And I would like to point to some examples. So I just wanted to make sure we had some.

Dr. Donald Belsito
Yeah. So citronellol, you know geraniol are the real big ones, but you have phenethyl alcohol, even pining's you have, wellimitinglula when they're oxidized, you have myrcene. So I would, you know, the 26 that need to be labeled in Europe would be citronellal, geraniol, eugenol, farnesol, among other potential sensitizers, I would just put those four.

Dr. Dan Liebler
Those are three of those are the top three by concentration in Table 3.

Dr. Donald Belsito
Yeah.

Monice Fiume (CIR)
Thank you.

Dr. Donald Belsito
Anything else on those? OK, that was quicker than I thought then. Let me just save this, and then we're moving to starch phosphates, which is also a first go around. Ah we had wave 3 for the Rosa centifolia that I was fine with the Council made some comments on placement of, concrete in the oil and also the extraction right, the extraction medium does not always need to be volatile. I think they're really pretty straightforward. Starch phosphates. And we have wave three comments here as well. And then, we have comments that were made before Wave 3. And that they they've been addressed on PDF page 5.

Cohen's Team Meeting - March 7, 2022

Dr. David Cohen
Alright, let's move on to Rosa. Rosa centifolia. So, Regina, this is yours as well. This is a draft report. This is the first time we've reviewing it. Of note, in 1990 the panel had a safety assessment on phenethyl alcohol. At up to 1%. As safe as used and they reaffirm that conclusion in 2008. We don't have method of manufacturing that is clear. Is this the whole plant or not on the extract? Although I guess that was in the setting of us getting that barley

information. But Bud callus, culture leaf and stem, I don't know if we have that and we have one maximization study. That showed that it can induce contact sensitization, as we might expect with this type of product. Ah. Tom, you want to comment?

Dr. Thomas Slaga
Yeah. We got some data and you know all of flower parts are grass just to bring that out and we have data to go with that. So. They only thing we didn't have data on is this stem

Dr. Wilma Bergfeld
No leaf.

Dr. Thomas Slaga
In Leaf. The rest we have, you know irritation and sensitization, we have a good bit of data.
But and so, in a way, I think we can go for safe for all the flower parts. And insufficient for the rest.

Dr. Ron Shank
I agree.

Dr. Wilma Bergfeld
I do too.

Dr. Ron Shank
ICP says there's no supplier for the flower oil. Yet we list 25 uses.

Dr. David Cohen
25 yeah.

Dr. Thomas Slaga
Yeah.

Dr. Ron Shank
And we're going to say it's safe as used. This song sounds like a conundr. Or a difficulty.

Dr. Thomas Slaga
Yeah.

Dr. Bart Heldreth
Yeah.

Dr. Ron Shank
Is it used?

Dr. Bart Heldreth
But unfortunately we get our concentration of use and our frequency of use from two different sources. And so the 25 reported uses comes from FDA's voluntary cosmetic registration program. Talking with the someone that worked, there are just two years ago they've done a big clean up of their VCRP to make sure that things that aren't still in use, are not removed. They've made sure to pare down and we see that if you look at the VCRP numbers as a whole. Most of them have gone down to some extent, and that's because they've went through and cleaned them up. So my suspicion is that those 25, at least some of them, are real and that it is in use. It just may not be in use by member companies of the Council. Or member companies that want to report on it.

Dr. Ron Shank
OK. Thank you.

Dr. Bart Heldreth
As Carol mentioned, not everybody wants to respond.

Dr. David Cohen
So, I had safe as used when formulated to be non sensitizing.

Dr. Wilma Bergfeld
I agree.

Dr. David Cohen
But we are going to exclude leaf cell extract stem extract. Bud extract and callus culture extract?

Dr. Thomas Slaga
Yes.

Dr. Ron Shank
Yes.

Dr. David Cohen
Except. Bud callous leaf, cell and stem. What do we want? We want everything?

Dr. Thomas Slaga
Well, it's early in the game everything.

Dr. David Cohen
So we want that sort of manufacturing dermal tox.

Dr. Wilma Bergfeld
Chemical characterization.

Dr. Thomas Slaga
Yeah.

Dr. David Cohen
Composition and impurities, right?

Dr. Thomas Slaga
Yes.

Dr. David Cohen
Sensitization in irritation. Right.

Dr. Thomas Slaga
Right.

Dr. David Cohen
Got it.

Dr. Wilma Bergfeld
You don't need any tox data, you have enough there is Antimutagenic studies.

Dr. Thomas Slaga
Yeah. Well, like.

Dr. Wilma Bergfeld
Because it's the grass. Because it's a grass.

Dr. Thomas Slaga
Right. And if you have antimutagenic, it can't be mutagenics, so you know the.

Dr. Wilma Bergfeld
That's an assumption.

Dr. Thomas Slaga
Yeah.

Dr. David Cohen
Yeah. Yes, right.

Dr. Thomas Slaga
You can’t have both.

Dr. David Cohen
Right. Isn't the poison just by the dose?

Dr. Thomas Slaga
Yeah.

Dr. David Cohen
OK. All right. We'll move on to a starch phosphates.

Dr. Bart Heldreth
Alright Regina, did you get all of those presents efficiencies for the IDA?

Dr. Ron Shank
Before we move on, could somebody explain what is meant by absolute and concrete? In these extracts.
It's I couldn't find a net.

Dr. Wilma Bergfeld
And while you're doing that, I had the two, will you add need to I tried with any AG.

Dr. Ron Shank
Pardon, could you say that again?

Dr. Wilma Bergfeld
Add the word meat also meat at this first time this group of documents used it.

Dr. Ron Shank
OK, Meat usually means undiluted.

Dr. Bart Heldreth
OK, so.

Dr. Wilma Bergfeld
That's what I figured, but we never used it before.

Dr. Ron Shank
OK.

Dr. Bart Heldreth
Yeah, there there's a there's two common definitions for meat either one is undiluted and the other is water free.

Dr. David Cohen
Ah.

Dr. Bart Heldreth
I'm here if you go into a bar and you say I want this liquor neat. It means don't add any water to it, don't add any ice to it either.

Dr. Wilma Bergfeld
That's how I like my Scotch.

Dr. Bart Heldreth
Exactly.

Dr. David Cohen
Don't you call that straight? I thought that was straight.

Dr. Wilma Bergfeld
Yeah, I heard it straight.

Dr. Bart Heldreth
Yes. That was years ago, neat was the term of choice for that. The absolute and the concrete there are two, I guess extraction methodologies even the absolute is typically you're getting by one extraction method or another, you're getting the oil out. Not going to say with the essential oil, but something along the oil and wax line. And, whereas the concrete is usually you're going to get some sort of a solid residue out of the extraction process, but they're very general terms. They're not, they're not terms that are in the dictionary. And they're not terms that we use very frequently it's a, it's frustrating to try to put them into the terms of our ingredients, but because they're fairly brought in in terms, but.

Dr. Ron Shank
OK. Thank you.

Dr. Bart Heldreth
Alright, I can bring up the cosmetic dictionaries terms for those they do have it in their intro. Let me see if I can find that real quick.

Dr. Ron Shank
There was a question about sensitization. And on page 18. Something was tested. It was redacted out from the raw data. But it was a strong sensitizer.

Dr. David Cohen
Well, I think.

Dr. Ron Shank
Would be kind of nice and kind and nice to know what that was. And then there's a flower oil. Absolute. Rose French. And that was not a sensitizer. Does that help anything?

Dr. David Cohen
I think when you look at the Table 3, the chemical composition, you see sensitizers in there you see citronellol, you see geraniol. So I none of that surprised me, which is why we have the non sensitizing safe as used when formulated be non sensitizing.

Dr. Ron Shank
OK.

Dr. David Cohen
Right, I mean.

Dr. Ron Shank
But you asked for sensitization data, didn't you?

Dr. David Cohen
Well, on the on the parts that we don't know this represents right? Oh, right, because. It says whole plant leaf, well leaf we have but whole plant, we have not stated we don't. Ah. Well, the truth is, yeah, it says less than the stated PPMS for whole plant.

Dr. Ron Shank
So if we say formulated to be non sensitizing, that would cover the data in the.

Dr. David Cohen
Everything.

Dr. Wilma Bergfeld
Yeah.

Dr. Ron Shank
Would it not?

Dr. Wilma Bergfeld
Yes.

Dr. Bart Heldreth
Let me just remind the panel of our typical usage of formulated to be non sensitizing when it comes to botanicals. Typically we only say formulated to be non sensitizing for botanicals. One more concerned with cumulative effect. In other words you may put two or three or more botanical ingredients in one formulation, each containing the same constituents of concern and that the some of concentrations of that constitutional concern may go over a threshold of where we're concerned about it. Typically we only use when formulated to be non sensitizing and it's aimed at the specific ingredient as it's used by itself. When we're talking about discrete chemicals.

Dr. David Cohen
That helps, but there's a few discrete chemicals in here that at least know are a problem and that's a manufacturing

issue at that point, isn't it? It's, it's for the company to be aware, not to mix key Sensitizers that puts you over the threshold of concern, right?

Dr. Bart Heldreth
Well, in that that's why we put it in the conclusion by my one more worried about you know mixing those ingredients together and one formulation and taking the concentration of key sensitizer up to a level where could you know inducer illicit you know a response. But if you don't have enough data to say that that ingredient as used at the concentrations reported in the report, won't cause sensitization whether induction or licitation, then I would propose asking for that information.

Dr. David Cohen
Bart, can you translate that for me into what we're asking for? I think I understood it, but I'm not quite sure.

Dr. Bart Heldreth
Right. OK, so we try to look at botanicals as the whole mixture. So we try to say when we're looking at the safety of, let's say, the Rosa, Santa Foley a flower. We're not looking at, you know necessarily, the concentration of Citronelle or lemony or something in there specifically, we're typically looking at sensitization data on the whole mixture. We're typically looking at all the other tox endpoints on the whole mixture. Now we're aware of those constituents of concern. And that's why we have this cumulative type effect conclusion caveat when formulated to be non sensitizing because we're worried those levels might get too high. If the test data we have for the ingredient itself is showing sensitization. At those levels, then, that's a very different situation than the cumulative effect.

Dr. David Cohen
Yeah, but we had this issue with tea tree oil.

Dr. Bart Heldreth
Right, I mean, it's like if we don't know if the ingredient itself, if we don't have enough information to say the ingredient won't cause sensitization, then we should ask for that that information. That should be part of the insufficient data announcement that we put out saying we want to know. Can you give us a and HRIPT or can you give us one of these new methodologies that makes us feel confident that this ingredient, at least if it's not used with others that contain the stand constituents of concern, will not because it sensitization.

Dr. David Cohen
What would we have a maximization tests with sensitization? Although we don't have the concentration used we and maybe we should ask for that. So you're saying this early on, let's ask for more. Let's not go out with safe as used and say, what's the concentration of that maximization test that had 16 out of 25 people sensitized?

Dr. Bart Heldreth
Right.

Dr. Thomas Slaga
Right.

Dr. David Cohen
OK.

Dr. Bart Heldreth
Right because you know, what if it comes back and the concentration is, you know of that test is 85% and you know there way, way over the top of what we need, then we need a study that's closer to the maximum use concentration or worse. It comes back. And they were using it at 0.0005% and it cost sensitization then we have a different situation too.

Dr. David Cohen
Yeah, but wouldn't the discussion tomorrow then always lead back to, well, that's why we're saying safe as used when formulated to be non sensitizing. So at 85% were coming out with that and a .05% were coming out with that.

Dr. Bart Heldreth
I completely agree with you. However, if you looked at the discussion section of botanical reports, we always explain that the that the non sensitizing caveat is because of the cumulative effect of multiple ingredients sharing the same constituent of concern. And so that that language is always in there with the botanicals. If we're worried that a situation where a product just has one of these roses centifolia ingredients would cause sensitization, then that won't be covered in the discussion section we normally write for botanicals, so the panel has the, you know, the prerogative to come out with their botanical conclusion that says when formulated to be non sensitizing and have it not be a cumulative effect issue. But you will need to add something to the conclusion to alert the reader and the formulator to the fact that this ingredient alone may be a problem.

Dr. Wilma Bergfeld
Well, can't we say that in our discussion or we can call out this sensitizers that could be there?

Dr. Bart Heldreth
We can, but it would be it would be embarking on something different than that then the panel has been doing. It would be a change of a new conclusion *(inaudible).

Dr. Wilma Bergfeld
Well, we don't particularly have a threshold.

Dr. David Cohen
And I don't see any way we're going to know what constituent cause desensitization.

Dr. Wilma Bergfeld
Yeah.

Dr. David Cohen
I mean, there's like two dozen or three dozen listed here and at least a few of them are in a concentration that. Is significant enough I suppose to. Cause a problem.
Yeah, I mean we can ask for the concentration. Of use of that Max, you study that cause sensitization. I just suspect tomorrow I'm going to have a boomerang come back around me, and we're going to have. Is that's what the formulated to be non sensitizing and then Bart, you're going to have to j p in. Regarding the discussion component of it.

Dr. Bart Heldreth
Yep. I'll be happy to.

Dr. David Cohen
I guess one of the thing is if we have in Table 3 chemical composition of the whole plant, is it true? We have no then we're missing constituents. I guess there's other things like impurities and other components that we don't have. So. Yeah. And unfortunately with the botanicals and working with natural products chemist at pull, these things out, constituent data on botanicals is.

Dr. Bart Heldreth
Terribly, Inaccurate, it’s very hard to take, let's say, any botanical and separated into all the separate chemicals and identify them all up.

Dr. Thomas Slaga
Right.

Dr. Bart Heldreth
And that's why we rarely have very much of that kind of data. That's why you look at like what is it? Doctor Dukes? Information on what constituents are in botanicals and. They have a short list of what ingredients or what the constituents might be in there, but usually they don't say how much because they don't know, and it's really hard to it's really hard to make that separation and find out what it is.
Yes, that's why our approach has been to look at these botanicals as a whole instead of the separate constituents. If we can say that the. The you know the sensitization study at Maxis concentration didn't cause us any heartburn. Then it doesn't matter if you know. Citronella and laminin and MI and everything else was in there it's coming back as no sensitization. So that's why we not we normally ask for that specially at this stage we're in a draft report.

Dr. David Cohen
OK. So will it's an idea and we're asking for the concentrations we were asking for greater detail on the Max use studies. That were mentioned where concentration is not stated.

Carol Eisenmann (PCPC)
And if I believe correctly, those came from RIFM.

Dr. David Cohen
Yeah, and I don't think it would surprise anyone if we so different. Cultivars or locations of this will see all kinds of differences in the concentrations of. The chemical compositions and the phenethyl alcohol is nine, 100th of a percent, where there's known sensitizers in the mid teens. So I'm not sure that passed. Safety assessment on the phenethyl alcohol is all that. Comforting.

Dr. Bart Heldreth
Right.

Dr. David Cohen
Anyway, any other comments, Tom, Ron. I'm Wilma about. What we should ask for in the idea? We're going to ask for the full battery on the bud, callous Leafs cell and stem, and then we'll ask for further information about the Max use study protocols.

Dr. Wilma Bergfeld
On the oil. It's flower oil.

Dr. Ron Shank
Can't, can't we save the flower ingredients or safe?

Dr. David Cohen
You mean safe when formulated not to be sensitizing?

Dr. Thomas Slaga
Yeah.

Dr. Ron Shank
Well.

Dr. Thomas Slaga
The bud gives rise to the flowers, so to me. We could include the budcat way.

Dr. Ron Shank
Yeah, flower extract an oil, we have sensitization data.

Dr. David Cohen
And it's sensitizing.

Dr. Ron Shank
No.

Dr. David Cohen
The flower oil. Desensitizing, right?

Dr. Ron Shank
Oh, let me look.

Dr. Wilma Bergfeld
And looted. It's irritating. I mean. Rabbit.

Dr. Bart Heldreth
So. But if these ingredients are sensitizers themselves.

Dr. Thomas Slaga
16.

Dr. Bart Heldreth
Is it? But these instead be unsafe. Next ingredient itself is a sensitizer, and it's a botanical mixture and we don't really know the composition. How would we formulate it to be non sensitizing? It's showing that it's sensitizing it use concentration.

Dr. David Cohen
We don't know if it's it used concentration. It says concentration not stated. But more than half the people got sensitized.

Dr. Bart Heldreth
So then I went session.

Dr. David Cohen
Right. It's the same as the other botanical, particularly tea tree oil, which we know when it oxidizes, it becomes the sensitizer and but we were able to muscle through that. And come out with a very good report on it. I kind of look at this the same way. I think at the right concentration, it's probably can be safe as used as long as you don't. We don't know that. We don't know the concentration at that maximization test.

Dr. Bart Heldreth
Right.

Carol Eisenmann (PCPC)
Well, and actually the test is what was tested as the absolute in the concrete and those that absolute is not the same as the essential oil. And those are both RIFM tests.

Dr. David Cohen
So.

Dr. Thomas Slaga
Good.

Dr. David Cohen
It's absolute. It's absolute French flower oil. Is the test product but it doesn't say tested neat or?

Carol Eisenmann (PCPC)
Well. The court needs to be revised the absolute and concrete should not be presented under coil. It should be under extract. Their types of extracts or not, and then they're not the essential oil.

Dr. David Cohen
Right.

Carol Eisenmann (PCPC)
But yes, that was tested the absolute in the concrete and there was a RIFM studies and I suspect they were tested undiluted but Rep from needs to be contacted to clarify that.

Dr. Thomas Slaga
It.

Dr. David Cohen
Yeah. OK. So yeah, I. So we'll put that out and we'll wait for. A counter response.

Carol Eisenmann (PCPC)
But there are other sensitization study, so at 2% it was not sensitizing the flower oil which I think was actually the flower oil and not. The absolute.

Dr. David Cohen
Yeah, yeah. There's a flower extract at 20%.OK. Somehow I still think we wind up in the same place, but we'll have more information.

Dr. Thomas Slaga
Right.

Dr. David Cohen
OK. Any final comments before we close? This. Row center failure. Foliar. Kane will go to starch phosphates. We just close this other one.

Full Panel - March 8, 2022

Dr. David Cohen
So Rosa Centifolia, this is the first time we're reviewing this and it's a safety assessment on 12 derived ingredients or. Parts to use this as skin conditioning agent with some other additional uses as well described in the report. We have frequency of use and Max use of .096%. It has the potential for incidental exposure. As a side note, in in 1990 the panel published a safety assessment on phenethyl alcohol. However, keep in mind that phenethyl alcohol is a very small component of this plant, less than .1%. There is ample evidence of its sensitization potential with a list of constituent components that are known sensitizers, there's evidence of a mild phototoxicity, but this is at irritating concentrations. Well above Max use. We felt we needed some additional information before coming to a conclusion with caveats, and we are issuing, we're proposing an idea. Asking for concentrations. Of the tested materials in the sensitization studies. Method of manufacturing dermal talks. Composition and impurities and sensitization and derotation for Bud Callis leaf cell and stem. So that's our motion and I'm sure there will be some discussion.

Dr. Wilma Bergfeld
Done.

Dr. Don Belsito
Yeah. So, we thought the data were sufficient for all the flowering bud ingredients in terms of sensitization, it has citronellol and has geraniol and has farnesol. So, it's going to have our botanical sensitization boilerplate.

Dr. Don Belsito
Then it's going to need to be formulated to be non-sensitive that we didn't feel that we needed sensitization data, we did think that it was insufficient for manufacturing for all except the extract. So again, flowering bud ingredients safe as used with the botanical boilerplates. Insufficient for manufacturing for the others except the extract and come composition and impurities. And depending upon these other talks endpoints for all other than the flower and the. Bart and that's where we were.

Dr. David Cohen
Where there were not too far apart, the reason we didn't clear with a safe formulated not to be sensitizing is the concentrations on in the sensitization. Protocols weren't mentioned and we just wanted more information on that. Of course, the logical conclusion is safe when formulated to be non-sensitizing it. And we flirted with that, but we wanted a little more information about. What concentrations were used to demonstrate this sensitization?

Dr. Don Belsito
I mean, we're both in agreement that this is going to go in as out as insufficient. So fine. I I'm not going to argue. I mean include more or we can always drop it.

Dr. David Cohen
Yeah.

Dr. Wilma Bergfeld
So you're seconding the motion. Thank you. Any further discussion, comma?

Dr. Don Belsito
Awesome.

Dr. Dan Liebler -
And justice, just to clarify, we through the bud in with the flower because we looked at the bud is an unopened flower that's my.

Dr. Wilma Bergfeld
Yeah.

Dr. Dan Liebler -
Chemist version of botany.

Dr. Thomas Slaga -
Yeah.

Dr. Don Belsito
So we can start being bud light.

Dr. David Cohen
Hey.

Dr. Thomas Slaga -
That's true.

Dr. Dan Liebler -
Yeah.

Dr. David Cohen
Boy, what Will ask for some more information, and I don't know if we'll get it, but it might be interesting to see what changes from a bud to a flower and its constituents but.

Dr. Wilma Bergfeld
Or sprout enough and a seed.

Dr. Ron Shank
That's similar to a seat in a sprout, isn't it?

Dr. Wilma Bergfeld
Right, right.

Dr. Dan Liebler -
Yeah.

Dr. Wilma Bergfeld
OK. Any other subsequent comments?

Dr. Dan Liebler -
I think we're fresh out.

Dr. Wilma Bergfeld
OK. Regina, are you clear on everything?

Regina Tucker (CIR)
Yes, I have everything. Thank you.

Dr. Wilma Bergfeld
Alright, alright, I'll call the question then. All in favor of an insufficient Rep conclusion here and a request for added information as stated, those opposed Abstaining.

Dr. Don Belsito
Never, ever hand up someplace in the 36.

Dr. Wilma Bergfeld
Wait a minute. Wait a minute. I can't.

Dr. Don Belsito
I think Monice has her hand up.

Dr. Wilma Bergfeld
Who else?

Monice Fiume
I do.

Dr. Wilma Bergfeld
How many is, OK? Good. OK.

Monice Fiume
Wasn't sure if you were moving on or if you wanted.

Dr. Wilma Bergfeld
No, we didn't. We didn't have a vote yet finished.

Monice Fiume
OK. I'll let you finish the belt and then I have a question.

Dr. Wilma Bergfeld
OK, OK, abstaining. So approved. Alright, thank you. Go ahead Monice.

Monice Fiume
I just wanted to make sure before moving on to the next ingredient that yesterday and the Belsito team, the discussion about the photo toxicity studies. If that was going to be brought up today about excluding them from the document.

Dr. Don Belsito
Well, David said it discussed it yet dated. I thought that study was so crummy and so confusing with the irritation, and there was no dose response. There were more. It actually going from 33 to 16 1/2 for the numbers increased a little bit and then they totally disappeared that.

Dr. David Cohen
Right. And they're so far from the concentration of use.

Dr. Don Belsito
Reality. Yeah, I just thought that study shouldn't even be quoted and should be deleted from the document.

Dr. Wilma Bergfeld
David, what do you think? I said her payment with that.

Dr. Don Belsito
Maybe even investigators said that they couldn't understand it, that it, I forget the language they used. It was quirky or something.

Dr. Don Belsito
And it's just not it's study.

Dr. David Cohen
I'd have to go back to the study. We don't have to make that determination now. It's going to swing around again, and I'll read this study.

Dr. Don Belsito
Yeah, look. Yeah. Look at it.

Dr. Ron Shank
It's a very poor study.

Dr. Don Belsito
Right. Even the principal investigators said that they couldn't interpret the data essentially.

Dr. David Cohen
It.

Dr. Wilma Bergfeld
It sounded like it to air it before they even did the photo talks.

Dr. Ron Shank
That tells you something, it's.

Dr. Don Belsito
Yes.
Dr. David Cohen
Yeah, I looked at it being so far out of range that I didn't.
Dr. Don Belsito
And the response? The responses were particular. They were seen before a photo or ration. It was just bizarre.

Dr. David Cohen
Yes.

Dr. Wilma Bergfeld
Yeah.

Dr. David Cohen
No, my inclination would be to take it out because I didn't. Put much in in with it. So, I'm OK with that. I'll go back if we want to discuss it and put it back in. But I doubt that will occur.

Dr. Wilma Bergfeld
OK, so we can move on then and keep that in eyes view that we might want to discuss it again. OK, moving on to the last in ingredient in this group and that's the starch phosphates Dr Belsito.

SEPTEMBER 2022 PANEL MEETING – DRAFT TENTATIVE REPORT
Belsito's Team Meeting – September 26, 2022

[Due to technical difficulties, transcripts were not available for the Belsito team meeting.]

Cohen's Team Meeting – September 26, 2022

Dr. David Cohen - Good, good. Alright. So we'll carry that motion. I'll make a comment about the new data. Alright. Alright, Ross centifolia. So in March, we issued an IDA on the 12 Rosa Centifolia derived ingredients. With their data needs of method of manufacturing, composition and impurity for all accept the flower and bud. Dermal toxic and if positive, further toxicology needs. We received a fair amount of information. And I wonder what you thought about the new data and our capacity to clear this? We have method of manufacturing and composition and impurities on the stem, by the way. OK, sorry David.

Dr. David Ross I didn't think you got too much of what you asked for. You got a lot of data on the stem. I couldn't think you got. I mean you asked for, method of manufacture, composition and impurities. All except the flower and bud, I believe. You asked for a dermal tox that you didn't get. I think in your motion, David, you said you wanted the concentrations of materials used in the sensitivity studies that didn't quite make it into the request, I'm not sure, but anyway you didn't get the 28 dermal, you didn't get all the method of manufacture composition and impurities.

Dr. Tom Slaga - Right. And I agree.

Dr. David Cohen - I'm just. Susan?

Dr. Susan Tilton - Yes. I mean, I'm just looking through and not much of what was requested. There's other data that came through on my genotoxicity. But not much of the requested data.

Dr. David Cohen - We got our sensitization data on an (*inaudible). A point 1%. Point 1%, I'm sorry of a flower extract. I just wanted to pose a question. The extract is a whole plant extract and method of manufacturing, it's a whole plant extract. Right. So. What would that not cover a large number of items? We have the stem extract but we don't have the whole we don't have composition impurities of the.

Dr. Tom Slaga – (*inaudible).

Dr. David Cohen - Of the extract of the whole plant extract. Right, Tom? That's. Is that what you're saying? OK. So can we go through and reiterate what the insufficient data is our needs?

Dr. David Ross – I think it was in the original. Composition and impurities for all except the flower and bud. And I guess it now that would be, stem. You have the stem. Dermal tox. And that was asked for on the, what was the original request that was on the? I'm used to things, yeah.

Dr. David Cohen - On all on all of the derived products.

Dr. David Ross - Oh really?

Dr. Wilma Bergfeld - You realize that most of the plant is a grass.

Dr. David Cohen - Most of the plant is grass or is a grass?

Dr. Wilma Bergfeld - No, is grass ingredient. At Rosebud's, Rose Flowers recognized as safe grass for use in foods and human consumption.

Dr. David Ross - Yeah.

Dr. Wilma Bergfeld - Also, we determined our grass for use in foods, drugs related products for animal consumption. And then they.

Dr. David Ross - I don't think we're asking. I don't think they ask was for any oral like Wilma, which just ask derm?

Dr. Wilma Bergfeld - Sometimes we don't ask for the oral if we have the grass.

Dr. David Ross -. No, as I'm saying it, we didn't ask for oral (*inaudible). I will dermal still OK to ask for. Looks.

Dr. David Cohen - Well, so we know that the intrinsically it has sensitizers. Right. And has geraniol and eugenol on farnesol and citronella. I mean it had it has sensitizers, so in the dermal tox, what are we looking for? If, if it's being

eaten and we know it's a sensitizer? Right. So if we rub it on and we get it absorbed, do we have that not covered by it being eaten? And we know that when we rub it on, it may be a sensitizer.

Dr. David Ross - I think there was the exact same discussion in the transcript section

Dr. David Cohen - Well, at least we're consistent.

Dr. David Ross - Trying to find.

Dr. David Cohen - I remember the discussion that you brought up, David, that I asked for and I don't remember if it was Rosetta Folia, but Don said, but we already know that this is a sensitizer somehow that's burned in my head so. Can we, can we just relook at it for a moment? And see where our real data needs are and can we start clearing some of these? Well, all the flour components are eaten and what level of grass is this? Remember, we had that grass conversation. Is this sort of FDA grass is this?
Do we know Regina? What kind of clearance this has as a as food?

Dr. Wilma Bergfeld - FDA has determined FDA.

Dr. David Cohen - FDA has determined, OK, so the flower, which is the flower components.
Are our orally the flowers are eaten?

Dr. Tom Slaga - Right.

Dr. David Cohen - Right. I don't think we eat the stems. Right. But can we not clear all the flour components?

Dr. Tom Slaga - I thought we already did that. With some reason.

Dr. David Cohen - Regina, I don't think we cleared anything last time, right? Or did we?

Regina Tucker (CIR) - No. No, we didn't.

Dr. David Cohen - It is the team, OK? What? No, go ahead. I'm sorry.

Carol Eisenmann (PCPC) - I thought you cleared flower and bud last time based on the it being grass and some dermal sensitization data, but because and because you didn't have specifically ask for any information on flower and bud, as far as I know.

Dr. David Cohen - So in the memorandum. We, the memorandum says, the 12 components we had data needs on the 12 components. It I you know what it this is what we have it as, but we're moving this forward anyway, so shall we not? And we need it. I need a team consensus on there. Are we going safe as used formulated not to be sensitizing on the flower components?

Dr. Tom Slaga - Right.

Dr. David Cohen - Right.

Dr. Tom Slaga - I can go with that.

Dr. David Cohen - And what about bud extract? I know we had some. We've had conversations about buds, but. You know, bugs are like baby flowers.

Dr. Wilma Bergfeld - OK.

Dr. David Cohen - Of the flower buds eaten.

Dr. David Ross - No idea.

Dr. David Cohen - So we're left with stem. What we have information. I'm sorry to belabor this, I just want to make sure we're not just asking for information we don't need.

Dr. Tom Slaga - We didn't have information on STEM and something else I.

Dr. David Cohen - We got stem composition and impurities.

Dr. Tom Slaga - Right.

Dr. David Cohen - Right. And it has.

Dr. Wilma Bergfeld - Believe.

Dr. David Cohen - Very small amounts of Limonene and benzyl alcohol. We have the and we have its method of manufacturing. So is anything I'm looking at it in the composition and impurities? Is there anything in there that would change?

Dr. Tom Slaga - In this step, we don't.

Dr. David Cohen - Our capacity to clear it. What Tom?

Dr. Tom Slaga - What the whole plant includes the stem, which it probably does. Then it's all safe, right?

Dr. David Cohen - Well.

Dr. Tom Slaga - Formulated to be non sensitizing.

Dr. David Cohen - Right now.

Dr. Wilma Bergfeld - Was irritating in the rabbits though. Once the oil flower oil.

Dr. Tom Slaga - Umm.

Dr. David Ross - Well. Yeah.

Dr. David Cohen - Right. So the question is if we put it as formulated to, not the sensitizing. Do we ever use formulated to not be irritating and sensitizing?

Dr. Wilma Bergfeld - I never saw that.

Dr. David Cohen - I think sensitization would you know, once you have a sensitized person, it's a low bar.

Dr. Tom Slaga - Yeah. No, we have had both those together. Yeah, we have had them both together.

Dr. David Ross - I think, David, the problem with you know saying the whole extract you know you that's say it's everything else that said is there all made in slightly different ways and so you're going to have maybe different

things but certainly different concentrations of the sensitizers in each individual product. So. You know, I think. That would be some of that by steam distillation, right, so.

Dr. David Cohen - Do you so not. You're not talking about the flower anymore? We're talking about basically stems, leaves roots, stems and leaves.

Dr. Tom Slaga - Whole plant.

Dr. Wilma Bergfeld - I don't think there are any roots.

Dr. David Cohen - Right. Well, it says the whole plant extract in under extract in method of manufacturing but we don't have we don't have compensation and impurities of the extract. So I don't think we clear that. Right. So we don't clear extract. Right because we don't have composition and impurities. Is that fair so far?

Dr. David Ross – Fair enough.

Dr. Susan Tilton - Full plant extract.

Dr. David Ross - Yeah.

Dr. David Cohen - Yeah, they're calling it. Ohh yeah, yeah, we're where's whole plant.

Dr. Susan Tilton - Not somewhere. Right.

Dr. David Cohen - It's just called extract. It's the third row.

Dr. Susan Tilton - OK.

Dr. David Cohen - Stem extract. We actually got composition and method of manufacturing on.

Dr. Tom Slaga - Yeah, with the new data, yeah.

Dr. David Cohen - Right. So the question is and it's the wrong term, can we read across you know, I mean that figuratively. That we know there's the composition. Already has some. It's already built in, with the provisos that we have, but are there any toxicology issues? That we worry about with the stem?

Dr. David Ross - With this Stem specific?

Dr. David Cohen - Yeah, the stem.

Dr. Tom Slaga - Well does stem should be part of the whole plant, right? Don't we have the whole plant extract?

Dr. David Cohen - We don't have a lot of data on it. We only have method of manufacturing on the plant extract, right?

Dr. Tom Slaga - OK.

Dr. David Ross - I don't think.

Dr. David Cohen - And the dermal tox is on the flower materials, the oral is on the flower. Short term tox is on flour. We do have genotox on the stem.

Dr. Tom Slaga - Well, I my recollection, when was the last time Ron was on that he wanted the, on the stem, he wanted a 28 day dermal. Or is that?

Dr. David Cohen - Well, we asked for it on everything. We got genotoxic on it. We have composition and impurities. So I guess the I'm pushing on is we know what's in it.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - It's not genotoxic. It has low levels of sensitizers in it already. We know that.

Dr. Tom Slaga - Right.

Dr. David Cohen - And we know method of manufacturing, what would we?

Dr. Tom Slaga - We have dermal irritation. I can't.

Dr. David Cohen - Not on the stem.

Dr. Tom Slaga - Not on a stem, right?

Dr. David Cohen - No, but we know that there's some sensitizers in that and would it not be covered under formulated?

Dr. Tom Slaga - Right.

Dr. David Cohen - It's not to be sensitizing.

Dr. Tom Slaga - To be. Yeah.

Dr. David Cohen - Another way? Well, let's let me rephrase it. To clear STEM for the team, what do you need or what do you want? Susan. David, I mean, is there anything like cause if we're not going to clear it, we need to ask for what we want.

Dr. Susan Tilton - I mean, I think we've already requested what we would have primarily wanted, which was 28, you know a 28 day dermal. We do have.

Dr. David Cohen - OK.

Dr. Susan Tilton C - Irritation and sensitization studies for the flower. Certain formulations of it.

Dr. David Cohen - Yeah. So dermal tox on the stem.

Dr. Susan Tilton C - But it I guess we're not getting that. So we've already requested it, but it it's not available. Is that?

Dr. David Ross - Correct.

Dr. David Cohen - OK. That's right.

Dr. Susan Tilton - Other requests work.

Dr. David Cohen - So dermal tox on the stem. And the extract. And what do we have that cell culture?

Regina Tucker (CIR) - Yes. So it would, I think it would be the cell culture and the Leafs and the leaf cell extract that you would still need.

Dr. Tom Slaga - Right.

Dr. David Cohen - A dermal tox on the on which Regina?

Regina Tucker (CIR) - So. To clear the stem and the extract you would need this you would need the cell culture and the leaf cell and the leaf cell extract. It would be those 2.

Dr. David Cohen - And stem?

Regina Tucker (CIR) - And in the stem? Yes.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - And stem and stem. OK.

Dr. Wilma Bergfeld - What about the leaves?

Regina Tucker (CIR) - Yes, in the leaf. So you would need the to, you would need the cell culture, the leaf cell and the stem.

Dr. Tom Slaga - Right.

Dr. David Cohen - And callous culture. We have leaf cell extract stem extract. Extract. Callous culture. Do we don't have method of manufacturing on the calls culture, right? And we don't have composition impurities on it, so those are additional data needs?

Dr. Tom Slaga - Yeah.

Dr. David Cohen - OK. I think I have it.

Dr. David Ross - So David, you're not asking for any repeat dose on dermal (*inaudible) on anything, right? So you were going to ask for 28 day, or will you not going to ask for 28 day?

Dr. David Cohen - I was going to ask for 28 day. On STEM, leaf cell extract. Right? The parts that weren't going to be eaten. The butok, the callus culture, the extract, the leaf cell culture and the stem extract.

Dr. Tom Slaga – Yeah.

Dr. David Ross - If you have, you're having a local effects at the level of the skin. Does it really matter if they have grass status or not? I mean, that's my question, I guess. I think that was the discussion last time. I just looking at it in the Belsito group, whether or not then dermal versus, you know, versus the grants that ISON. I think they came down to still needing it, which was you request for the 28 day dermal. I think that's why I don't right now that's fine.

Dr. David Cohen - Yeah, I think we asked for 28 day dermal because we don't have systemic toxicity on it because it's not being eaten. Is that reasonable?

Dr. David Ross - I think if it's grass, I'm not sure you need that systemic tox, right?

Dr. David Cohen - Right. But I don't know that the callous, the extract which is the whole plant, the leaf cell and the stem, they're not eating. Are they eating?

Dr. Wilma Bergfeld - The flower and the bud?

Regina Tucker (CIR) - We have the flower in the bud are generally recognized as safe and use in foods, drugs and related products for animal consumption.

Dr. Wilma Bergfeld - And just above that.

Regina Tucker (CIR) - So it's just the buds and the flowers.

Dr. Wilma Bergfeld - Just above that, it says for human too.

Regina Tucker (CIR) - Yes. And for human, yes.

Dr. David Cohen - Yeah. Yeah. So what that left was the callusest culture. The extract, which is the whole plant, those leaf cell culture and the stem extract. We don't have as grass. So. Do we not ask for the 28 day dermal tox on that?

Dr. Tom Slaga - Right.

Dr. David Cohen - And if positive. You know the all the follow up rolled up stuff after that.

Dr. Tom Slaga - All that extra, yeah. Yeah.

Dr. David Cohen - But we can clear the lion share of what's in here.

Dr. Tom Slaga - Right.

Dr. Wilma Bergfeld - While we're in the bud.

Dr. Susan Tilton - I agree with that.

Dr. David Cohen - Yeah. Yeah, there's a number of them. I mean it's all, but it's eight of the 12.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - Are we in agreement with that?

Dr. Wilma Bergfeld - I guess like to ask that Monice do you can you redefine the callus? I just wonder how close it was to the bud.

Monice Fiume (CIR) - So the definition for the callous culture extract is the extract of a culture of the callous. So if I remember correctly, it's not. They culture the cells. It's not the plant itself, it's a cell culture from the plant.

Dr. Wilma Bergfeld - What part of the plant?

Monice Fiume (CIR) - It's it, says the callous. I don't. Let me see if I can Google the definition of a callous.

Carol Eisenmann (PCPC) - I think it can be any part of the from any part of the plant. It's the part of the plant that's growing is where they take it from. So I think it can be a leaf, it can be you know it's the cells that are growing they take.

Monice Fiume (CIR) - OK.

Carol Eisenmann (PCPC) - Isn't it was? If I remember correctly from that presentation we had once.

Dr. David Cohen - That's vague.

Dr. Tom Slaga - Well, the cell culture we always had trouble with it because once you put something in culture, it changes because the cells have to adapt to plastic and becomes a whole new world. We don't have any data to support anything in.

Monice Fiume (CIR) - That's why many times that the information isn't available directly on the callous culture of the cell cultures, they cannot typically be grouped under the information from the other parts.

Dr. Tom Slaga - Yeah.

Dr. Wilma Bergfeld - OK.

Dr. David Ross - Can we do we have just getting back to that one time I have lost it and all.
Definition of different thoughts about the. There's no ocular. And right above the ocular irritation studies in the document there's an eye serum. Which is highlighted which contains the extract that's new data. But what was your sense of ocular? We didn't need it? I mean, if things are being used around the eye and the use tables. Looked like there might be.

Dr. David Cohen - Let me let me look back. I seem a point 1%. Where did you are? Are you looking in the dermal irritation and sensitization studies verbiage?

Dr. David Ross - Yeah, that was that was a verbiage, David, yeah.

Monice Fiume (CIR) - PDF page 40.

Dr. David Ross - I'm just going back to the use table so you know where we are, see.

Monice Fiume (CIR) - Dr. David Ross If I coule provide just a little historical as to why ocular is missing a lot of times that is something that would not typically have been requested by the panel because of it was always an animal study and it wasn't always viewed as humane so.

Dr. David Ross - Yeah.

Monice Fiume (CIR) - Now there are more instances of in vitro ocular irritation, but not always. So that's why that seems to be lacking in a lot of the reports.

Dr. David Ross - Yeah. Well, I'm looking at this. The flower extract, which is by far the most used 174 uses. It only has five uses around the eye. So it's pretty minimal.

Monice Fiume (CIR) - And part of the not that this is ever a reason to discount it, but intended use is what is viewed, so it's not meant to be placed in the eye, although we know it can happen. So sometimes there's a fine line when reviewing it of intended use versus incidental exposure.

Dr. David Ross - But we do have this quotation of an eye serum.

Monice Fiume (CIR) - What's that?

Dr. David Ross - You have this notion of an eye serum, that being.

Dr. David Cohen - Well, first the Max use around the eye. The Max concentration is .002% which is 5 times no. 02. Yeah, it's about five times lower than the Max use elsewhere. And two, one thing that I noted early on when I joined the panel is we'll see sensitization and irritation data on products that contain a higher concentration than the Max use. And what we were told is that many of those products aren't in use anymore, but they were used for the original, tolerability trials so. The eye areas got a lower concentration of use than the Max use elsewhere. And the eye serum discussion relates to irritation and sensitization.

Dr. David Ross - Correct. Yeah.

Dr. David Cohen - Right.

Dr. Wilma Bergfeld – Skin not eye.

Dr. David Cohen - Yeah, you know, but they talk about testing and eye serum, that's what they're talking about testing an eye serum.

Dr. Wilma Bergfeld -Yeah.

Dr. David Cohen - OK.

Dr. David Ross - I'm OK with that. You don't want to bring it up. I mean, that's fine.

Dr. Tom Slaga - OK.

Full Panel - September 27, 2022

Dr. Don Belsito - Yeah. Rosa Centifolia. I hope you all saw the article in New Yorker magazine on it. It's a very interesting article. I sent it to Bart and Monice. I think last night to distribute. Read it. It's a fun, fun thing to read. Anyway, Rosa Centifolia at the March 2022 meeting, we issued an insufficient data announcement for the 12 ingredients for method of manufacturing composition, impurities data for all except the flower and bud ingredients. Dermal toxicity which could be a 28 day dermal toxin if positive other toxicologic endpoints might be needed are we did receive a large amount of data. Particularly on stem extract, looking at this and knowing that the flower and bud ingredients are grass and looking at the additional data we got on the stem extract as well as the composition of the stem extract which was very similar to the flower and bud, we felt that we could go safe as used for the flower bud and stem. extract ingredients and insufficient. For the whole plant, callus culture extract and leaves out extract and the insufficiencies were manufacturing impurities 28 day dermal tox and if evidence of absorption, other endpoints and sensitization and their irritation at concentration of use. So essentially they flower bud and stem extract flower and bud ingredients and stem extract safe as used the others insufficient.

Dr. Wilma Bergfeld - Doctor Cohen.

Dr. David Cohen - So Don, we came to the same conclusions that you did. We literally went back and forth on the stem and we teetered on it. We put it in our insufficient data, but I the logic that you just went through was basically, you we know the stem constituents and there was nothing new or concerning in there that you didn't feel you needed further tox on. It was that how I read it?

Dr. Don Belsito - Yes, we felt that we could use the flower and bud to read across to the stem for other endpoint.

Dr. David Cohen - I'm inclined to agree with that I'll just ask for if there's any comments from Susan, Dave or Tom on the second thing, Don's motion, we had this extensive discussion about this on the stem.

Dr. Tom Slaga - I could go with that too would, would Don said.

Dr. Susan Tilton - Yeah, I think that aligns with our discussion that we had. So I would support that.

Dr. David Ross - Yeah. I agree.

Dr. David Cohen - OK. So we second the Belsito motion.

Dr. Wilma Bergfeld - So any other discussion or edits that need to be spoken about at this point? If not, then I'll do you have. I heard somebody.

Monice Fiume (CIR) - This is Monice. I have a question. Can I just get clarification for the conclusion? Is it safe as used or safe when formulated to be non sensitizing?

Dr. Don Belsito No. Sorry, Monice. Thank you. Safe when formulated to be nonsense.

Monice Fiume (CIR) - Thank you.

Dr. David Cohen - Second, yes.

Dr. Wilma Bergfeld - Thank you. All right, I'll call the question those opposing? Abstaining? Approved. It's safe, so moving on to the next ingredient, the polyhydroxy stearic acid, Doctor Cohen.

Safety Assessment of *Rosa centifolia*-Derived Ingredients as Used in Cosmetics

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel members involved in this assessment: Daniel C. Liebler, Ph.D. and Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., former Senior Scientific Analyst/Writer, and Regina Tucker, M.S., Scientific Analyst/Writer, CIR.

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651
CIRINFO@CIR-SAFETY.ORG

ABBREVIATIONS

CFR	Code of Federal Regulations
CFU	colony forming units
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPA	cyclophosphamide
CPSC	Consumer Product Safety Commission
EC	European Commission
EU	European Union
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
GRAS	generally recognized as safe
HRIPT	human repeated insult patch test
LA	Luria agar
LD_{50}	median lethal dose
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
Rif^R	rifampicin-resistant
Rif^S	rifampicin-sensitive
*rpo*B	RNA polymerase B
RIFM	Research Institute for Fragrance Materials
s.c.	subcutaneous
SLS	sodium lauryl sulfate
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program
wINCI; *Dictionary*	web-based *International Cosmetic Ingredient Dictionary and Handbook*

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 12 *Rosa centifolia*-derived ingredients as used in cosmetic formulations. The majority of these ingredients are reported to function in cosmetics as skin conditioning agents. Because final product formulations may contain multiple botanicals, each 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; with *Rosa centifolia*-derived ingredients, the Panel was concerned about the presence of citronellol and geraniol as potential sensitizers in cosmetics. Industry should use good manufacturing practices to minimize impurities. The Panel considered the available data and concluded that 9 *Rosa centifolia*-derived ingredients (i.e., the flower-, bud-, and stem-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. Additionally, the Panel also concluded that the available data are insufficient to make a determination that the remaining 3 *Rosa centifolia*-derived ingredients are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of the following 12 *Rosa centifolia*-derived ingredients as used in cosmetics is reviewed in this safety assessment.

Rosa Centifolia Bud Extract	Rosa Centifolia Flower Extract	Rosa Centifolia Flower Water
Rosa Centifolia Callus Culture Extract	Rosa Centifolia Flower Juice	Rosa Centifolia Flower Wax
Rosa Centifolia Extract	Rosa Centifolia Flower Oil	Rosa Centifolia Leaf Cell Extract
Rosa Centifolia Flower	Rosa Centifolia Flower Powder	Rosa Centifolia Stem Extract

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), most *Rosa centifolia*-derived ingredients are reported to function as skin conditioning agents in cosmetic products (Table 1).[1] Other functions associated with ingredients in this group include abrasives, antioxidants, fragrance ingredients, and skin protectants. Additionally, Rosa Centifolia Flower Oil is reported to function as a fragrance ingredient (only) in cosmetics. The Expert Panel for Cosmetic Ingredient Safety (Panel) does not review ingredients that function only as fragrance ingredients because, as fragrances, the safety of these ingredients is evaluated by the Research Institute for Fragrance Materials (RIFM). However, this ingredient is not currently scheduled for review by RIFM; thus, the Panel is reviewing the safety of this ingredient.

The Panel has previously reviewed the safety of one of the main volatile components of *Rosa centifolia*. In 1990, the Panel published a safety assessment of phenethyl alcohol, with the conclusion that phenethyl alcohol is safe in cosmetic products in the present practices of use at concentrations of up to 1%;[2] the Panel reaffirmed this conclusion, as published in 2008.[3] The full report and re-review summary on this ingredient can be accessed on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list 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 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 may be provided by the cosmetics industry, as well as by other interested parties. A published RIFM monograph was available for "Rose Oil Moroccan,"[4] and unpublished studies were provided by RIFM to the CIR on Rosa Centifolia Flower Oil.[5-13] The unpublished studies were ascribed, typically, to an "absolute" or a "concrete;" these names are provided with the data.

Botanicals, such as *Rosa centifolia*-derived ingredients, may contain numerous constituents, some of which may have the potential to cause toxic effects; for example, citronellol and geraniol are potential sensitizers. In this assessment, the Panel is evaluating the potential toxicity of each of the *Rosa centifolia*-derived ingredients as a whole, complex mixture; toxicity from single components may not predict the potential toxicity of botanical ingredients.

The names of the ingredients in this report are written in accordance with the INCI naming conventions, i.e., capitalized without italics or abbreviations. When referring to the genus and species from which the ingredients are derived, the standard taxonomic practice of using italics is followed (e.g., *Rosa centifolia*). It is often not known how the substance being tested in a study compares to the cosmetic ingredient. In the report text, if it is known that the material being tested is a cosmetic ingredient, the INCI naming convention will be used (e.g., Rosa Centifolia Extract). However, if it is not known that the test substance is the same as the cosmetic ingredient, the taxonomic naming conventions (e.g., a *Rosa centifolia* extract) will be used.

CHEMISTRY

Definition and Plant Identification

Botanicals are cosmetic ingredients directly derived from plants.[1] Generally, these ingredients have not undergone chemical modification and some are classified as follows: extracts, juices, waters, powders, oils, and waxes. Definitions of the *Rosa centifolia*-derived ingredients reviewed in this safety assessment are presented in Table 1.

Cabbage rose is a common name for *Rosa centifolia*.[14] *Rosa centifolia* L. (Rosaceae), a perennial plant that is also commonly known as hundred-leaved rose or shatapatri or taruni, is available throughout India.[15] It is a complex hybrid that is bred from *Rosa gallica* L., *Rosa moschata* Herm., *Rosa canina* L., and *Rosa damascene* Mill.

According to another source, *Rosa centifolia* grows as a plant, shrub, bush, or thicket.[16] This plant is of Asiatic origin, and the countries where it is extensively cultivated for extractive purposes include: Bulgaria, Turkey, Morocco, France, and Italy. The parts used are the flowers, buds, leaves, and fruit (hips).

Chemical Properties

Rosa Centifolia Extract is a light-brown, viscous liquid, and Rosa Centifolia Flower Wax is a solid that is insoluble in water.[16,17] According to another source, Rosa Centifolia Bud Extract, Rosa Centifolia Callus Culture Extract, or Rosa Centifolia Flower Extract may be a solid or liquid, depending upon the components of the extract.[18-20] Also, the water solubility of the extract is related to components of the extract and the solvent that is used for extraction. Rosa Centifolia Flower Oil is miscible with chloroform.[21] UV absorption data indicate an absorption peak at 320 nm (shoulder) for Rosa Centifolia Flower Extract (rose absolute).[5] A flash point of ≥ 100ºC has been reported for a Rosa Centifolia Flower Extract trade name mixture.[22] Chemical properties data on *Rosa centifolia*-derived ingredients are presented in Table 2.

Method of Manufacture

Some of the following methods of manufacturing described below are general to the production of some of the *Rosa centifolia*-derived ingredients, and it is unknown whether these methods are used in the manufacture of these ingredients for use in cosmetics. Additionally, in some cases, the definition of the ingredients, as given in the *Dictionary*, provides insight as to the method of manufacture.[1]

Rosa Centifolia Extract

A whole plant extract of *Rosa centifolia* is prepared by extraction with volatile solvents, which are subsequently removed (usually under vacuum).[16] The removal of solvents is followed by redissolution in alcohol, chilling, filtration, and removal of the alcohol.

Rosa Centifolia Flower Extract

According to a supplier of Rosa Centifolia Flower Extract, a fraction of the petals of rose of Morocco (*Rosa centifolia*) is extracted by a mixture of propylene glycol + water.[23] This process is followed by filtration, yielding a Rosa Centifolia Flower Extract trade name mixture.

The production method for another Rosa Centifolia Flower Extract trade name mixture has also been described.[24] Dried raw material is extracted with hot water, and this step is followed by filtration and then concentration. The concentrated filtrate is dissolved in 1,3-butylene glycol (50 vol%) solution. The resulting solution is subjected to sedimentation and filtration, and the production sequence ends with adjustment, and packaging.

Rosa Centifolia Flower Juice

According to a supplier of Rosa Centifolia Flower Juice, petals of *Rosa centifolia* are rehydrated and then pressed.[25] This process is followed by stabilization with vegetal glycerin and then filtration, yielding a Rosa Centifolia Flower Juice trade name mixture. The supplier also stated that, in the method of manufacture of this trade name mixture, the *Rosa centifolia* petals are cold pressed without using any solvents.[26]

Rosa Centifolia Flower Oil

Rosa centifolia flower oil is produced by the steam distillation of the flowers of *Rosa centifolia*.[4,21]

Rosa Centifolia Flower Powder

Rosa Centifolia Flower Powder is obtained from the dried, ground flowers of *Rosa centifolia*.[1]

Rosa Centifolia Flower Water

Rosa Centifolia Flower Water is an aqueous extract obtained by steam distillation of rose petals from *Rosa centifolia*.[27] Another source states Rosa Centifolia Flower Water is manufactured by subjecting dried raw material to steam distillation, yielding a water-soluble fraction.[24] Ethanol (15 vol%) is then added to this fraction, and the production sequence ends with filtration and packaging.

According to another source, the distillation of *Rosa centifolia* (rose) yields the following 3 products: rose water, rose oil, and rose waste biomass.[28,29] The method of manufacture of a Rosa Centifolia Flower Water trade name material involves the steam distillation of *Rosa centifolia* petals, and this process is followed by filtration.[30]

Rosa Centifolia Flower Wax

The extraction process that is used to produce rose absolutes (aromatic oils) from *Rosa centifolia* also yields an intermediary product that contains resins, waxes, and other lipids.[31] After the volatile oils have been removed, the waxy components can be used to produce floral wax, also referred to as a concrete.

Rosa Centifolia Stem Extract

A production method for a Rosa Centifolia Stem Extract was provided by a supplier.[32] An extract was harvested using the epicormic, new, and old shoots of Rosa Centifolia through direct thermomechanical extraction in a water/ethanol solution. Following a series of 3 solid-liquid separations first to remove coarser solid fraction, second via centrifugation to remove fine particles, and third via filtration to remove the finest particles), the extract is then concentrated by vacuum distillation and spray-dried (both steps remove the solvent) to form a powder.

Composition/Impurities

The main volatile constituents of *Rosa centifolia* have been identified as citronellol, geraniol, and phenethyl alcohol.[16] Composition data relating to the essential oil, flower and leaf parts, stem, and whole plant of *Rosa centifolia* are presented in Table 3.[14,16,26,27,33-35]

Composition data on *Rosa centifolia* hydrosol were also found in the published literature.[36] Hydrosols are products of the hydro-distillation of aromatic herbs and plants and are basically saturated solutions of essential oils (volatile fraction) in water. Rose hydrosols (e.g., *Rosa centifolia*) contain 103 ± 4.1 mg/l of total volatile compounds. The major volatile compounds in *Rosa centifolia* hydrosol have been identified as: phenethyl alcohol (42 ± 2 mg/l), citronellol (22 ± 1 mg/l), geraniol (14 ± 1 mg/l).

Rosa Centifolia Flower Extract

A Rosa Centifolia Flower Extract trade mixture of propylene glycol, water, and Rosa Centifolia Flower Extract contains 2.8% to 3.8% dry extract.[37] The total aerobic microbial count is ≤ 100 colony forming units (CFU)/g. Additional data on composition indicate that another Rosa Centifolia Flower Extract trade name mixture contains flavonoid and tannin.[24]

Rosa Centifolia Flower Juice

A Rosa Centifolia Flower Juice trade name mixture consisting of glycerin and Rosa Centifolia Flower Juice is preserved with 0.2% potassium sorbate.[38] Additional data on this Rosa Centifolia Flower Juice trade name mixture indicate that the total aerobic microbial count is ≤ 100 CFU/g.[26]

Rosa Centifolia Flower Water

Rosa Centifolia Flower Water (aqueous extract of *Rosa centifolia* petals) is preserved with 1.5% phenoxyethanol.[27] The total aerobic mesophilic microorganisms count is ≤ 100 CFU/g. A bibliographical study on realized *Rosa centifolia* revealed the potential presence of citral (< 8 ppm), citronellol (< 100 ppm), eugenol (< 6 ppm), geraniol (< 150 ppm) and farnesol (< 4 ppm) in the plant. Composition data on another Rosa Centifolia Flower Water trade name material indicate that it contains β-phenylethyl alcohol and geraniol.[24]

Rosa Centifolia Stem Extract

According to a supplier, a Rosa Centifolia Stem Extract contains 2 - 6 % water, < 20% ash (determined by sulfuric ashes), ≤ 1 % lipids, and ≥ 20 % polyphenols (typical concentration ≤ 40 %).[35] Of the allergens listed in Annex III of European Union (EU) Regulation 1223/2009, ≤ 1 ppm limonene and ≤ 4ppm benzyl alcohol were present; the remaining 24 allergens, including geraniol and citronellol, were not detected.

USE

Cosmetic

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

According to 2022 VCRP data, Rosa Centifolia Flower Extract has the greatest frequency of use; it is reported to be used in 174 cosmetic products, 150 of which are leave-on formulations (Table 4).[39] The results of a concentration of use survey conducted by the Council in 2021 indicate that Rosa Centifolia Flower Water has the highest concentration of use; it is used at maximum use concentrations up to 0.096%, specifically in face and neck products (not spray), body and hand products (not spray), and moisturizing products (not spray).[40] According to both VCRP and Council survey data, 5 of the 12 *Rosa centifolia*-

derived ingredients reviewed in this safety assessment are not currently in use in cosmetic products. These ingredients are listed in Table 5.[39]

Cosmetic products containing *Rosa centifolia*-derived ingredients may incidentally come in contact with the eyes (e.g., Rosa Centifolia Flower Extract is used in mascaras at up to 0.02%).[39] *Rosa centifolia*-derived ingredients are also being used in cosmetic products that may be incidentally ingested (e.g., Rosa Centifolia Flower Extract is used at up to 0.002% in lipstick formulations).

Additionally, some of these ingredients are reported to be used in cosmetic products that could possibly be inhaled; for example, Rosa Centifolia Flower Extract is reported to be used at up to 0.025% in fragrance preparations and at up to 0.0001% in face powders.[39,40] In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

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

The *Rosa centifolia*-derived ingredients are not restricted from use in any way under the rules governing cosmetic products in the EU.[41] However, it should be noted that 2 of the main volatile components of *Rosa centifolia*, citronellol and geraniol, are included in Annex III of the Cosmetics Regulation European Commission (EC) No. 1223/2009 (list of substances which cosmetic products must not contain except subject to the restrictions laid down) as fragrance allergens. These ingredients must be on the label if they exceed 0.001% in leave-on and 0.01% in rinse-off products.

Non-Cosmetic

According to the US FDA, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of rose absolute (*Rosa alba* L., *Rosa centifolia* L., *Rosa damascena* Mill., *Rosa gallica* L., and vars. of these spp.), rose buds, and rose flowers are generally recognized as safe (GRAS) for use in foods for human consumption (21 CFR 182.20). The FDA has also determined that these are GRAS for use in foods, drugs, and related products for animal consumption (21 CFR 582.20).

Rosa centifolia is famous among oil-producing species of roses.[42] Additionally, it is used in the traditional systems of medicine for the management of inflammatory conditions, including arthritis, cough, asthma, bronchitis, wounds, and ulcers.[15,43] Specifically, therapeutic uses (as astringent) of the dried petals of rose flower (e.g., from *Rosa centifolia*) include treatment of mild inflammations of the oral and pharyngeal mucosa (dosage = 1 to 2 g of drug per cup (200 ml) of water, for tea).[44]

TOXICOKINETIC STUDIES

Toxicokinetics studies of the *Rosa centifolia*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data 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

Dermal

Rosa Centifolia Flower Extract

Rosa Centifolia Flower Extract (rose absolute; (a product of extraction of a concrete with ethanol[34]) was evaluated for acute dermal toxicity using 7 rabbits (strain not stated).[6] The test substance was administered (protocol not included) at single dermal doses of 0.8 g/kg (2 animals) and 5 g/kg (5 animals). Dosing was followed by a 14-d observation period. There were no mortalities at the 0.8 g/kg dose; moderate redness (2 rabbits) and slight edema (1 rabbit) were observed. All 5 animals dosed with 5 g/kg died on observation day 2; ataxia was reported. Moderate redness (5 rabbits), slight edema (2 rabbits), and moderate edema (3 rabbits) were also observed in the 5 g/kg dose group. An acute dermal LD_{50} of > 0.8 g/kg was reported.

Rosa Centifolia Flower Oil

An acute dermal LD_{50} of > 2.5 g/kg for Rosa Centifolia Flower Oil was reported in a study involving rabbits (number and strain not stated).[4] Details relating to the test protocol and study results were not included.

Oral

Rosa Centifolia Flower Extract

The acute oral toxicity of a *Rosa centifolia* flower extract (ethanol extract) was evaluated according to Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 425.[15] A limit test on a *Rosa centifolia* flower extract (ethanol extract; dose = 2 g/kg body weight; administered as an oral dose by gavage) was performed using 5 male Wistar albino rats. Dosing was followed by a 14-d observation period. None of the animals died during the observation period, and the LD_{50} was established at > 2 g/kg body weight.

The acute oral toxicity of Rosa Centifolia Flower Extract (rose absolute) was evaluated using 10 rats (strain not stated).[6] The test substance was administered as a single oral dose of 5 g/kg. Dosing was followed by a 14-d observation period. Three of 10 animals died on day 2 of the observation period; piloerection and lethargy were observed. An LD_{50} of > 5 g/kg was reported.

Short-Term Toxicity Studies

Oral

Rosa Centifolia Flower Extract

The short-term oral toxicity of *Rosa centifolia* flower extract (ethanol extract) was evaluated according to OECD TG 407.[15] Two groups of 8 male Wistar rats were used. *Rosa centifolia* flower extract was administered orally (method of oral administration was not stated; dose of 640 mg/kg) to one of the groups once daily for 28 d. The control group was dosed orally with normal saline (1 ml/kg). After day 28, the animals were killed, and the heart and liver were examined histologically. Repeated dosing resulted in a statistically significant decrease in hepatic transaminases and an increase in white blood cells. However, it was noted that these changes were within the physiological limits for the rat and not toxicologically relevant. When compared to the control group, no other physiological, biochemical, or histopathological changes were observed in the animals dosed with *Rosa centifolia* flower extract.

Subchronic Toxicity Studies

Data on the subchronic toxicity of the *Rosa centifolia*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

Chronic Toxicity Studies

Data on the chronic toxicity of *Rosa centifolia*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of *Rosa centifolia*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

The genotoxicity studies summarized below are presented in Table 6.

The genotoxic potential of Rosa Centifolia Stem Extract was evaluated in an Ames test and in 2 in vitro micronucleus assays. Rosa Centifolia Stem Extract (at doses of 5 – 5000 µg/plate) was not mutagenic to *Salmonella typhimurium*, tested with and without metabolic activation.[45] Additionally, it was not genotoxic in a micronucleus assay using cultured human peripheral blood lymphocytes (at concentrations of 200 - 5000 µg/ml),[46] or in an EpiSkin™ micronucleus assay (at concentrations of 25 – 100 mg/ml),[47] with or without metabolic activation.

ANTI-MUTAGENICITY STUDIES

Rosa Centifolia Flower Extract

The anti-mutagenicity of aqueous extracts of petals from different cultivars ("passion," "pink noblesse," and "sphinx") of *Rosa centifolia* was studied using the *Escherichia coli* RNA polymerase B (*rpo*B)-based $Rif^S \rightarrow Rif^R$ (rifampicin sensitive to resistant) forward mutation assay against ethyl methanesulfonate-induced mutagenesis.[48] *E. coli* MG1655 cells were used. The cell suspension was mixed with a *Rosa centifolia* flower extract (aqueous extract) and ethyl methanesulfonate (133 mM) and the mixture was incubated. Later, the culture was serially diluted and spread-plated on Luria agar (LA)-rifampicin (100 µg/ml) plates for scoring Rif^R mutants and LA plates for enumerating viable cells. Mutation frequency was calculated as ratio of total number of Rif^R mutants per ml to the total number of viable cells in same culture volume. Spontaneous mutation frequency was determined by incubating the cell suspension in the absence of mutagen. The Rif^R mutation frequency in *E. coli* cells exposed to ethyl methanesulfonate was approximately $1500/10^8$ cells, whereas the spontaneous mutation frequency was approximately $1/10^8$ cells. Aqueous extracts of rose petals of the 3 cultivars, "passion," "pink noblesse," and "sphinx" (1.5 mg/ml), resulted in reduction in the mutation frequency by 55, 19, and 4%, respectively. Thus, the "passion," cultivar was the most antimutagenic among the rose cultivars that were evaluated. The analysis of antimutagenicity indicated that the blue-

colored anthocyanin(s) (for which concentration was maximum in the passion cultivar) was the major contributing bioactive constituent.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of *Rosa centifolia*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

OTHER RELEVANT STUDIES

Anti-Inflammatory Activity

Because skin irritation is a sign of dermatitis (skin inflammation), data on anti-inflammatory activity may be useful in evaluating the safety of Rosa Centifolia Flower Extract in the absence of skin irritation data.

Rosa Centifolia Flower Extract

The anti-inflammatory activity of a *Rosa centifolia* flower extract (ethanol extract; doses of 32, 64, and 128 mg/kg) was evaluated using the carrageenan-induced paw edema and Freund's complete adjuvant (FCA)-induced arthritis model.[15] The study involved the following 5 groups of 6 male Wistar albino rats, dosed by gavage: group 1 (2 ml/kg of 1% gum acacia suspension; vehicle control), group 2 (3 mg/kg of indomethacin), group 3 (32 mg/kg of *Rosa centifolia* flower extract), group 4 (64 mg/kg of *Rosa centifolia* flower extract), and group 5 (128 mg/kg of *Rosa centifolia* flower extract). At 30 min post-administration, paw inflammation was induced by subcutaneous (s.c.) administration of 0.1 ml of 1% λ-carrageenan in saline into the subplantar surface of the left hind paw. Paw volume was measured at 1 , 3 , and 6 h after s.c. λ-carrageenan injection. The *Rosa centifolia* flower extract (64 and 128 mg/kg) statistically significantly ($p < 0.01$) inhibited carrageenan-induced paw edema at 1 , 3 , and 6 h post-carrageenan challenge and demonstrated statistically significant ($p < 0.01$) antiarthritic activity on days 3, 7, 14, and 21 after complete FCA immunization. Treatment with the *Rosa centifolia* flower extract (128 mg/kg) also caused a statistically significant decrease in circulating pro-inflammatory cytokine levels when compared to the control.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below are presented in Table 7.

Undiluted Rosa Centifolia Flower Oil was classified as moderately irritating to the skin when applied for 24 h to intact or abraded skin of rabbits (number and strain not stated) using occlusive patches.[4] In a study involving hairless mice (number and strain not stated), undiluted Rosa Centifolia Flower Oil was applied to the back for an unspecified duration; skin irritation was not observed. In human clinical studies, a face mask containing 0.8% Rosa Centifolia Flower (undiluted) was not irritating in a 24-h single insult occlusive patch test involving 20 subjects.[49] Rosa Centifolia Flower Oil (2% in petrolatum) was not irritating in a 48-h closed patch test (number of subjects not stated).[4]

A face mask containing 0.8% Rosa Centifolia Flower was not a sensitizer in a maximization study with sodium lauryl sulfate (SLS) pretreatment in 25 subjects.[50] In human repeated insult patch tests (HRIPT), an eye serum containing 0.1% Rosa Centifolia Flower Extract (49 subjects) [51] and a Rosa Centifolia Flower Extract trade name mixture (tested at 20% in 55 subjects) were not sensitizers.[24,52] Multiple maximization studies with SLS pretreatment were performed with Rosa Centifolia Flower Extract (test concentration not stated).[7,8,10-13] In 6 studies, involving 22 – 33 subjects per study, the only reaction reported was an incidence of contact sensitization in 1 subject (out of 25).[7] In a maximization test of Rosa Centifolia Flower Oil (2% in petrolatum) involving 24 subjects, no evidence of skin sensitization was found.[4]

OCULAR IRRITATION STUDIES

Data on the ocular irritation potential of *Rosa centifolia*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

CLINICAL STUDIES

Case Report

Rosa Centifolia Flower Extract and Rosa Centifolia Extract

A non-atopic female patient with a history of polymorphic light eruption presented with a 2-wk history of a rash after use of a *Rosa centifolia* flower extract (rose absolute eau de parfum) and a non-scented body lotion containing a *Rosa centifolia* extract.[53] Erythema, papules, and edematous plaques were observed on the neck (only perfume application site), upper chest, arms, shoulders, abdomen, and upper thighs. Patch testing (protocol not stated) was performed using van der Bend chambers, and *Rosa centifolia* extract (5% in alcohol) and the body lotion induced the following positive reactions: + (on day 2), ++ (on day 4), and + (on day 7). Testing with the *Rosa centifolia* flower extract (rose absolute eau de parfum) did not cause a positive reaction on day 2 but did cause positive reactions on days 4 (+ reaction) and 7 (+ reaction).

Other Clinical Reports

Rosa Centifolia Flower Extract

A clinical evaluation (double-blind study) of a shampoo for seborrheic dermatitis was performed using 3 groups of up to 25 patients with this scalp condition.[54] The composition of the shampoo was as follows: 0.01% *Rosa centifolia* flower extract, 0.005% epigallocatechin gallate, 0.3% zinc pyrithione, and 0.45% climbazole. The study was classified as double-blind, and one group of 24 patients was treated with the *Rosa centifolia* flower extract shampoo. The other 2 groups were treated with a 2% ketoconazole shampoo (25 patients) and a 1% zinc pyrithione shampoo (23 patients), respectively. All patients in each group were instructed to massage their scalps for at least 5 min with the assigned shampoo. This was followed by rinsing with water 3 times per wk for 4 wk. A clinical severity score was determined at 2 and 4 wk after shampoo use. Irritation was assessed using a questionnaire, and photographs were taken using a folliscope. In all groups, the clinical severity score improved statistically significantly ($p < 0.05$) relative to baseline at weeks 2 and 4. However, the changes in the clinical severity score at weeks 2 and 4 did not differ statistically significantly between the 3 groups ($p = 0.39$ and $p = 0.63$, respectively). The changes in clinical severity sub-scores (i.e., for erythema, dandruff, and lesion extent) at weeks 2 and 4 did not differ statistically significantly between the 3 groups. Irritation did not differ statistically significantly between the 3 groups ($p = 0.63$). Of the 11 patients who complained of irritation, 9 reported pruritus and 4 reported erythema. These reactions were identified as mild, and the distribution of reactions among the groups was not stated.

Rosa Centifolia Flower Oil

A randomized, placebo-controlled aromatherapy trial was performed.[55] In the experimental group of 25 female subjects, treatment involved massage into abdominal skin (for 15 min after topical application) of a botanical mixture consisting of *Lavandula officinalis* (lavender, 2 drops), *Salvia sclarea* (clary sage, 1 drop), and a *Rosa centifolia* flower oil (rose, 1 drop) in 5 ml of almond oil. The subjects reported no treatment-related side effects.

SUMMARY

The safety of 12 *Rosa centifolia*-derived ingredients as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, most *Rosa centifolia*-derived ingredients are reported to function as skin conditioning agents in cosmetic products. Other functions associated with ingredients in this group include abrasives, antioxidants, fragrance ingredients, and skin protectants.

The main volatile constituents of *Rosa centifolia* have been identified as citronellol, geraniol, and phenethyl alcohol. UV absorption data indicate an absorption peak at 320 nm (shoulder) for Rosa Centifolia Flower Extract (rose absolute).

According to 2022 VCRP data, Rosa Centifolia Flower Extract has the greatest frequency of use; it is reported to be used in 174 cosmetic products (150 leave-on, 23 rinse-off, and 1 diluted for bath use). The results of a concentration of use survey conducted by the Council in 2021 indicate that Rosa Centifolia Flower Water has the highest concentration of use; it is used at maximum use concentrations up to 0.096%.

Two of the main volatile components of *Rosa centifolia*, citronellol and geraniol, are included in Annex III of Cosmetics Regulation European Commission (EC) No. 1223/2009 (list of substances which cosmetic products must not contain except subject to the restrictions laid down) as fragrance allergens. These ingredients must be on the label if they exceed 0.001% in leave-on and 0.01% in rinse-off products.

According to the US FDA, essential oil, oleoresins (solvent-free), and natural extractives (including distillates) of rose absolute (including *Rosa centifolia* L.), rose buds, and rose flowers are GRAS for use in foods for human consumption and for use in foods, drugs, and related products for animal consumption.

Rosa Centifolia Flower Extract (rose absolute) was evaluated for acute dermal toxicity using 7 rabbits (strain not stated). Single dermal doses of 0.8 g/kg (2 animals) and 5 g/kg (5 animals) were administered. At a dose of 0.8 g/kg, moderate erythema (2 rabbits) and slight edema (1 rabbit) were observed. At 5 g/kg, moderate erythema (5 rabbits), slight edema (2 rabbits), and moderate edema (3 rabbits) were observed. An acute dermal LD_{50} of > 0.8 g/kg was reported. An acute dermal LD_{50} of > 2.5 g/kg for Rosa Centifolia Flower Oil was reported in a study involving rabbits (number and strain not stated).

The acute oral toxicity of a *Rosa centifolia* flower extract (ethanol extract) was evaluated using 5 male Wistar rats. None of the animals died during the 14-d observation period, and the LD_{50} was > 2 g/kg body weight. An acute oral LD_{50} of > 5 g/kg was reported for Rosa Centifolia Flower Oil in a study involving rats (number and strain not stated). The acute oral toxicity of Rosa Centifolia Flower extract (rose absolute) was evaluated using 10 rats (strain not stated). Three of 10 rats died, and piloerection and lethargy were observed. An LD_{50} of > 5 g/kg was reported.

The short-term (28-d) oral toxicity of Rosa Centifolia Flower Extract (ethanol extract) was evaluated using groups of 8 male Wistar rats (method of oral administration not stated; dose of 640 mg/kg). When compared to the saline control group, no toxicologically relevant findings were observed after dosing with Rosa Centifolia Flower Extract.

The genotoxic potential of Rosa Centifolia Stem Extract was evaluated in an Ames test and in 2 in vitro micronucleus assays. Rosa Centifolia Stem Extract (at doses of 5-5000 μg/plat) was not mutagenic to Salmonella typhimurium, tested with

and without metabolic activation. Additionally, it was not genotoxic in a micronucleus assay using cultured human peripheral blood lymphocytes (at concentrations of 200 - 5000 µg/ml), or in an EpiSkin™ micronucleus assay (at concentrations of 25-100 mg/ml), with or without metabolic activation.

The anti-mutagenicity of aqueous extracts of petals from different cultivars ("passion," "pink noblesse," and "sphinx") of *Rosa centifolia* was studied using the *E. coli rpo* B-based $Rif^S \rightarrow Rif^R$ forward mutation assay against ethyl methanesulfonate-induced mutagenesis. The cell suspension was mixed with *Rosa centifolia* flower extract (aqueous extract) and ethyl methanesulfonate (133 mM). Aqueous extracts of rose petals of the 3 cultivars, "passion," "pink noblesse," and "sphinx" (1.5 mg/ml), resulted in reduction in the ethyl methanesulfonate mutation frequency by 55, 19, and 4%, respectively. An anthocyanin, peonidin 3-glucoside, was identified as the major bioactive contributing to rose antimutagenicity.

The anti-inflammatory activity of a *Rosa centifolia* flower extract (ethanol extract; doses of 32, 64, and 128 mg/kg) was evaluated using the carrageenan-induced paw edema and FCA- induced arthritis model. *Rosa centifolia* flower extract (64 and 128 mg/kg) statistically significantly ($p < 0.01$) inhibited carrageenan-induced paw edema at 1, 3, and 6 h post-carrageenan challenge and demonstrated statistically significant ($p < 0.01$) antiarthritic activity on days 3, 7, 14, and 21 after complete FCA immunization.

Undiluted Rosa Centifolia Flower Oil was classified as moderately irritating to the skin when applied for 24 h to intact or abraded skin of rabbits (number and strain not stated) using occlusive patches. In a study involving hairless mice (number and strain not stated), undiluted Rosa Centifolia Flower Oil was applied to the back for an unspecified duration; skin irritation was not observed. In human clinical studies, a face mask containing 0.8% Rosa Centifolia Flower (undiluted) was not irritating in a 24-h single insult occlusive patch test involving 20 subjects. Rosa Centifolia Flower Oil (2% in petrolatum) was not irritating in a 48-h closed patch test (number of subjects not stated).

A face mask containing 0.8% Rosa Centifolia Flower was not a sensitizer in a maximization study with SLS pretreatment in 25 subjects. In HRIPTs, an eye serum containing 0.1% Rosa Centifolia Flower Extract (49 subjects) and a Rosa Centifolia Flower Extract trade name mixture (tested at 20% in 55 subjects) were not sensitizers. Multiple maximization studies with SLS pretreatment were performed with Rosa Centifolia Flower Extract (test concentration not stated). In 6 studies, involving 22 – 33 subjects per study, the only reaction reported was an incidence of contact sensitization in 1 subject (out of 25). In a maximization test of Rosa Centifolia Flower Oil (2% in petrolatum) involving 24 subjects, no evidence of skin sensitization was found.

A non-atopic female patient presented with a rash after use of a *Rosa centifolia* flower extract (rose absolute eau de parfum) and a non-scented body lotion containing *Rosa centifolia.* Patch testing with *Rosa centifolia* extract (5% in alcohol) and the body lotion induced the following positive reactions: + (on day 2), ++ (on day 4), and + (on day 7). Testing with the *Rosa centifolia* flower extract (rose absolute eau de parfum) did not cause a positive reaction on day 2 but did cause positive reactions on days 4 (+ reaction) and 7 (+ reaction).

A 4-wk clinical evaluation of a shampoo for seborrheic dermatitis containing 0.01% *Rosa centifolia* flower extract was performed using 3 groups of up to 25 patients with this scalp condition; each group used a different shampoo. Of the 11 patients who complained of irritation, 9 reported pruritus and 4 reported erythema. These reactions were identified as mild, and the distribution of reactions among the groups was not stated. Irritation did not differ statistically significantly between the 3 groups.

No treatment-related side effects were observed in an aromatherapy trial involving 25 female subjects. A botanical mixture consisting of Lavandula *officinalis* (lavender, 2 drops), *Salvia sclarea* (clary sage, 1 drop), and *Rosa centifolia* (rose, 1 drop) in 5 ml of almond oil was massaged into abdominal skin for 15 min.

DISCUSSION

This assessment reviews the safety of *12 Rosa centifolia*-derived ingredients. The Panel concluded that the available data are sufficient for determining the safety of 9 ingredients, i.e., those derived from the flower, bud, and stem, for use in cosmetic products when formulated to be non-sensitizing, but that the data are insufficient for determining safety of the remaining 3 ingredients. The Panel noted that the flower- and bud-derived ingredients that are reviewed in this safety assessment are found in foods that are generally recognized as safe (GRAS). Composition and other data on the stem extract denote similarities to both the flower and the bud and obviate the need for additional toxicological data.

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 *Rosa centifolia*-derived ingredients, the Panel was concerned about the presence of citronellol and geraniol in cosmetics, which could result in sensitization reactions. 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 in cosmetic formulations.

For the 3 *Rosa centifolia*- derived ingredients for which the Panel determined the data were insufficient, the Panel felt that there may be differences in the methods of manufacturing, compositions and impurities, and other data points, as compared to the ingredients that had sufficient data. Thus, it was unclear if inferences from the flower, bud and stem could be applied to the callus culture, leaf cell, and whole plant extract. Accordingly, the additional data needed to determine the safety of these ingredients in cosmetics are:

- Method of manufacture
- Composition and impurities data
- 28-day dermal toxicity data
- if positive additional toxicological endpoints may be needed
- Dermal irritation and sensitization data at expected maximum concentration of use

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (for example, Rosa Centifolia Flower Extract is reported to be used at up to 0.025% in spray fragrance preparations and at up to 0.0001% in face powders). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

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

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 9 *Rosa centifolia*-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:

Rosa Centifolia Bud Extract*
Rosa Centifolia Flower
Rosa Centifolia Flower Extract
Rosa Centifolia Flower Juice
Rosa Centifolia Flower Oil
Rosa Centifolia Flower Powder
Rosa Centifolia Flower Water
Rosa Centifolia Flower Wax
Rosa Centifolia Stem Extract*

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

Additionally, the Panel also concluded the available data are insufficient to make a determination that the following 3 *Rosa centifolia*-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Rosa Centifolia Callus Culture Extract**
Rosa Centifolia Extract**
Rosa Centifolia Leaf Cell Extract **

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

TABLES

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

Ingredient/CAS No.	Definition & Structures	Function(s)
Rosa Centifolia Bud Extract	Rosa Centifolia Bud Extract is the extract of the buds of *Rosa centifolia*.	Skin-Conditioning Agents - Emollient
Rosa Centifolia Callus Culture Extract	Rosa Centifolia Callus Culture Extract is the extract of a culture of the callus of *Rosa centifolia*.	Skin Protectants
Rosa Centifolia Extract	Rosa Centifolia Extract is the extract of the whole plant, *Rosa centifolia*.	Skin-Conditioning Agents - Miscellaneous
Rosa Centifolia Flower	Rosa Centifolia Flower are the flowers of *Rosa centifolia*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Rosa Centifolia Flower Extract 84604-12-6	Rosa Centifolia Flower Extract is the extract of the flowers of *Rosa centifolia*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Rosa Centifolia Flower Juice	Rosa Centifolia Flower Juice is the juice expressed from the flower of *Rosa centifolia*.	Skin-Conditioning Agents - Miscellaneous
Rosa Centifolia Flower Oil	Rosa Centifolia Flower Oil is the volatile oil obtained from the flowers of *Rosa centifolia*.	Fragrance Ingredients
Rosa Centifolia Flower Powder	Rosa Centifolia Flower Powder is the powder obtained from the dried, ground flowers of *Rosa centifolia*.	Abrasives
Rosa Centifolia Flower Water	Rosa Centifolia Flower Water is an aqueous solution of the steam distillate obtained from the flowers of the rose, *Rosa centifolia*.	Skin-Conditioning Agents - Miscellaneous
Rosa Centifolia Flower Wax	Rosa Centifolia Flower Wax is a wax obtained from the flower of *Rosa centifolia*.	Skin-Conditioning Agents - Miscellaneous
Rosa Centifolia Leaf Cell Extract	Rosa Centifolia Leaf Cell Extract is the extract of a culture of the leaf cells of *Rosa centifolia*.	Antioxidants; Skin Protectants
Rosa Centifolia Stem Extract	Rosa Centifolia Stem Extract is the extract of the stems of *Rosa centifolia*.	Skin-Conditioning Agents - Emollient

Table 2. Chemical properties

Property	Value/Results	Reference
Rosa Centifolia Bud Extract		
Form	Solid or liquid; appearance is related to components of the extract	18
Solubility	Solubility is related to components of extract and solvent used for extraction	18
Rosa Centifolia Callus Culture Extract		
Form	Solid or liquid; appearance is related to components of the extract	19
Solubility	Solubility is related to components of extract and solvent used for extraction	19
Rosa Centifolia Extract		
Form	Yellowish to light-brown viscous liquid	16
Rosa Centifolia Flower Extract		
Form	Solid or liquid; appearance is related to components of the extract	20
Solubility	Solubility is related to components of extract and solvent used for extraction	20
Rosa Centifolia Flower Extract (trade mixture)		
Form (at 20°C)	translucent solution with possibly a slight precipitate (brown, orange color)	37
Density (at 20°C)	1.053 – 1.065	37
Refractive index (at 20°C)	1.412 – 1.423	37
Solubility	Miscible in water and alcohol (50% v/v); immiscible in mineral oils and vegetable oils	37
Flash point	≥ 100°C	22
Rosa Centifolia Flower Juice (trade mixture)		
Form (20°C)	liquid to opalescent liquid with an orange to brown color	26
Density (at 20°C)	1.130 – 1.150	26
Refractive index (at 20°C)	1.390 – 1.410	26
Solubility	Miscible in water and alcohol (50% v/v); immiscible in mineral oils and vegetable oils	26
Rosa Centifolia Flower Oil		
Form	Colorless or yellow liquid	21
Solubility	Miscible with chloroform	21
Specific gravity (at 30º C/15º C)	0.848 – 0.863	21
Refractive index (at 30º C)	1.457 – 1.463	21
Rosa Centifolia Flower Extract (rose absolute)		
UV absorption peak (nm)	320 (shoulder)	5
Rosa Centifolia Flower Water (trade name material)		
Form (at 20°C)	Colorless, transparent liquid.	27
Density (at 20°C)	0.999 – 1.002	27
Refractive index (at 20°C)	1.332 – 1.339	27
Solubility	Miscible in water and alcohol (50% v/v) and immiscible in mineral oils and vegetable oils; soluble in propylene glycol	27,56
Rosa Centifolia Flower Wax		
Form	Solid	17
Solubility	Insoluble in water	17

Table 3. Constituents of *Rosa centifolia*

Constituents	Concentration
Essential Oil	
α-pinene	not stated.[14]
β-phenethyl alcohol	0.09%.[34]
β-pinene	not stated.[14]
cis-rose oxide	0.07%.[34]
citral	not stated.[14]
citronellol	1200 ppm.[14]
citronellol	9.22%.[34]
n-eicosane C_{20}	0.55%.[34]
eugenol	0.74%.[34]
farnesol	3.48%.[34]
geranic acid	not stated.[14]
geraniol	17.60%.[34]
geraniol aldehyde	not stated.[14]
n-heneicosane C_{21}	6.31%.[34]
n-heptacosane C_{27}	1.79%.[34]
n-heptadecane	1.07%.[34]
limonene	0.05%.[34]
linalool	1.03%.[34]
methyl eugenol	0.56%.[34]
myrcene	not stated.[14]
nerol	4.36%.[34]
n-nonadecane C_{19}	8.10%.[34]
nonadecene $C_{19:1}$	2.28%.[34]
n-pentacosane C_{25}	2.86%.[34]
trans-rose oxide	0.04%.[34]
n-tricosane C_{23}	5.90%.[34]
Flower	
cyanin	not stated.[14]
EO (undefined)	2000 ppm.[14]
eusupinin A	not stated.[33]
gallic acid	not stated.[14]
malic acid	not stated.[14]
methionine sulfoxide	not stated.[14]
pectin	not stated.[14]
quercitrin	not stated.[14]
resin	not stated.[14]
rugosin A	not stated.[33]
rugosin B	not stated.[33]
rugosin D	not stated.[33]
saponin	13,000 ppm.[14]
shisonin-A	not stated.[14]
sugar	not stated.[14]
tannins	100,000 to 240,000 ppm.[14]
tartaric acid	not stated.[14]
tellimagrandin I	not stated.[33]
wax	not stated.[14]
Leaf	
saponin (in leaf)	85,000 ppm[14]
Stem	
ash content	< 20%[35]
benzyl alcohol	< 4 ppm[35]
limonene	< 1 ppm[35]
lipid content	< 1%[35]
polyphenols	> 20%[35]
water content	2 - 6 %[35]
Whole plant (main volatile constituents)	
citronellol	not stated[16]
geraniol	not stated[16]
phenethyl alcohol	not stated[16]
Whole plant (constituent levels potentially present)	
citral	< 8 ppm.[27]
citronellol	< 250 ppm.[26]
citronellol	< 100 ppm.[27]
eugenol	< 6 ppm.[27]
geraniol	< 250 ppm.[26]
geraniol	< 150 ppm.[27]
farnesol	< 4 ppm.[27]

Table 4. Frequency (2022)[39] and concentration (2021)[40] of use according to likely duration and exposure and by product category.

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Rosa Centifolia Flower		Rosa Centifolia Flower Extract		Rosa Centifolia Flower Juice	
Totals	**14**	**NR**	**174**	**0.0001-0.025**	**1**	**NR**
summarized by likely duration and exposure*						
Duration of Use						
Leave-On	*6*	*NR*	*150*	*0.0001-0.025*	*1*	*NR*
Rinse-Off	*2*	*NR*	*23*	*0.0001-0.002*	*NR*	*NR*
Diluted for (Bath) Use	*6*	*NR*	*1*	*0.0001-0.002*	*NR*	*NR*
Exposure Type*						
Eye Area	NR	NR	5	0.0005-0.02	NR	NR
Incidental Ingestion	NR	NR	7	0.002	NR	NR
Incidental Inhalation-Spray	4[a]; 2[b]	NR	5; 50[a]; 71[b]	0.0005-0.025; 0.01[b]	1[a]	NR
Incidental Inhalation-Powder	4[a]	NR	50[a]; 1[c]	0.0001; 0.00013-0.002[c]	1[a]	NR
Dermal Contact	13	NR	158	0.0001-0.025	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	9	0.001-0.002	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	NR	11	0.0001-0.002	NR	NR
Baby Products	NR	NR	1	NR	NR	NR
as reported by product category						
Baby Products						
Baby Lotions/Oils/Powders/Creams			1	NR		
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts	4	NR				
Bubble Baths			1	0.0001		
Other Bath Preparations	2	NR	NR	0.002		
Eye Makeup Preparations						
Eye Lotion			2	0.0005		
Eye Makeup Remover			1	NR		
Mascara			NR	0.02		
Other Eye Makeup Preparations			2	NR		
Fragrance Preparations						
Cologne and Toilet Water			NR	0.0005-0.025		
Perfumes			1	NR		
Other Fragrance Preparation			4	0.025		
Hair Preparations (non-coloring)						
Hair Conditioner			4	0.001		
Hair Spray (aerosol fixatives)						
Rinses (non-coloring)						
Shampoos (non-coloring)			3	0.001-0.002		
Tonics, Dressings, and Other Hair Grooming Aids			1	NR		
Other Hair Preparations			1	NR		
Hair Coloring Preparations						
Hair Dyes/Colors (all types requiring caution statements and patch tests)						
Makeup Preparations						
Face Powders			NR	0.0001		
Foundations			NR	0.0001		
Lipstick			7	0.002		
Makeup Bases			2	NR		
Other Makeup Preparations			1	NR		
Personal Cleanliness Products						
Bath Soaps and Detergents			3	0.0001-0.001		
Douches	1	NR				
Other Personal Cleanliness Products			NR	0.0001		
Skin Care Preparations						
Cleansing			8	0.002		
Face and Neck (exc shave)	4	NR	35	0.00013-0.002	1	NR
Body and Hand (exc shave)			15	0.001-0.002		
Moisturizing	2	NR	65	0.001		
Night						
Paste Masks (mud packs)	1	NR	4	NR		
Skin Fresheners			5	0.01		
Other Skin Care Preparations			8	0.001		

Table 4. Frequency (2022)[39] and concentration (2021)[40] of use according to likely duration and exposure and by product category.

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Rosa Centifolia Flower Oil		Rosa Centifolia Flower Powder		Rosa Centifolia Flower Water	
Totals	**25**	**0.001-0.002**	**5**	**NR**	**99**	**0.0000096-0.096**
summarized by likely duration and exposure*						
Duration of Use						
Leave-On	*17*	*0.001-0.002*	*3*	*NR*	78	*0.000096-0.096*
Rinse-Off	*6*	*NR*	*1*	*NR*	21	*0.0000096-0.023*
Diluted for (Bath) Use	*2*	*NR*	*1*	*NR*	NR	*0.0048*
Exposure Type*						
Eye Area	NR	NR	NR	NR	10	NR
Incidental Ingestion	1	0.001	NR	NR	3	NR
Incidental Inhalation-Spray	4[a]; 8[b]	NR	2[a];1[b]	NR	1; 30[a]; 33[b]	0.00096; 0.00096[b]
Incidental Inhalation-Powder	4[a]	0.001-0.002[c]	2[a]	NR	30[a]	0.096[c]
Dermal Contact	20	0.001-0.002	5	NR	93	0.0000096-0.096
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	NR	NR	NR	2	0.00096-0.023
Hair-Coloring	NR	NR	NR	NR	NR	0.0096
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	5	0.001	1	NR	10	0.0048
Baby Products	NR	NR	NR	NR	NR	NR
as reported by product category						
Baby Products						
Baby Lotions/Oils/Powders/Creams						
Bath Preparations (diluted for use)						
Bath Oil, Tablets, and Salts	2	NR	1	NR	NR	0.0048
Bubble Baths						
Other Bath Preparations						
Eye Makeup Preparations						
Eye Lotion					1	NR
Eye Makeup Remover					4	NR
Mascara						
Other Eye Makeup Preparations					5	NR
Fragrance Preparations						
Cologne and Toilet Water						
Perfumes						
Other Fragrance Preparation					1	NR
Hair Preparations (non-coloring)						
Hair Conditioner	1	NR			1	0.023
Hair Spray (aerosol fixatives)					NR	0.00096
Rinses (non-coloring)	1	NR				
Shampoos (non-coloring)	1	NR			1	0.0096
Tonics, Dressings, and Other Hair Grooming Aids					NR	0.00096
Other Hair Preparations						
Hair Coloring Preparations						
Hair Dyes/Colors (all types requiring caution statements and patch tests)					NR	0.0096
Makeup Preparations						
Face Powders						
Foundations						
Lipstick	1	0.001			3	NR
Makeup Bases						
Other Makeup Preparations						
Personal Cleanliness Products						
Bath Soaps and Detergents	1	NR			5	NR
Douches	1	NR			1	NR
Other Personal Cleanliness Products					1	NR
Skin Care Preparations						
Cleansing	1	NR			7	0.0000096
Face and Neck (exc shave)	2	0.002	1	NR	25	0.096
Body and Hand (exc shave)	2	0.001	1	NR	5	0.096
Moisturizing	7	0.002	1	NR	23	0.096
Night					3	0.000096
Paste Masks (mud packs)	1	NR	1	NR	1	NR
Skin Fresheners					7	NR
Other Skin Care Preparations	4	0.001			5	0.02%

Table 4. Frequency (2022)[39] and concentration (2021)[40] of use according to likely duration and exposure and by product category.

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Rosa Centifolia Flower Wax					
Totals	**10**	**NR**				
summarized by likely duration and exposure*						
Duration of Use						
Leave-On	*9*	*NR*				
Rinse-Off	*1*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*				
Exposure Type*						
Eye Area	1	NR				
Incidental Ingestion	3	NR				
Incidental Inhalation-Spray	3[a]; 1[b]	NR				
Incidental Inhalation-Powder	3[a]	NR				
Dermal Contact	6	NR				
Deodorant (underarm)	NR	NR				
Hair - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Mucous Membrane	4	NR				
Baby Products	NR	NR				
as reported by product category						
Baby Products						
Baby Lotions/Oils/Powders/Creams						
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts						
Bubble Baths						
Other Bath Preparations						
Eye Makeup Preparations						
Eye Lotion						
Eye Makeup Remover						
Mascara	1	NR				
Other Eye Makeup Preparations						
Fragrance Preparations						
Cologne and Toilet Water						
Perfumes						
Other Fragrance Preparation						
Hair Preparations (non-coloring)						
Hair Conditioner						
Hair Spray (aerosol fixatives)						
Rinses (non-coloring)						
Shampoos (non-coloring)						
Tonics, Dressings, and Other Hair Grooming Aids						
Other Hair Preparations						
Hair Coloring Preparations						
Hair Dyes/Colors (all types requiring caution statements and patch tests)						
Makeup Preparations						
Face Powders						
Foundations						
Lipstick	3	NR				
Makeup Bases						
Other Makeup Preparations						
Personal Cleanliness Products						
Bath Soaps and Detergents	1	NR				
Douches						
Other Personal Cleanliness Products						
Skin Care Preparations						
Cleansing						
Face and Neck (exc shave)	1	NR				
Body and Hand (exc shave)	2	NR				
Moisturizing	1	NR				
Night						
Paste Masks (mud packs)						
Skin Fresheners						
Other Skin Care Preparations	1	NR				

NR – not reported

*likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

**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] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] 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

Table 5. *Rosa centifolia*-derived ingredients with no reported uses.[39]

Rosa Centifolia Bud Extract
Rosa Centifolia Callus Culture Extract
Rosa Centifolia Extract
Rosa Centifolia Leaf Cell Extract
Rosa Centifolia Stem Extract

Table 6. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle/Solvent	Test System	Procedure	Results	Reference
			IN VITRO			
Rosa Centifolia Stem Extract	5 – 5000 200 ug/plate	Vehicle – water	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA102)	OECD TG 471; Ames test, with and without metabolic activation. Vehicle and appropriate positive controls were used.	not mutagenic Positive control caused statistically significant increase	[45]
Rosa Centifolia Stem Extract	1000 – 5000 µg/ml (3 h exposure) and 200 – 800 µg/ml (24 h exposure) without activation 2000 – 5000 µg/ml with activation (3 h)	Vehicle – water	cultured human peripheral blood lymphocytes	In vitro mammalian cell micronucleus test: cells were exposed to the test article for 3 or 24 hand for 3 h without metabolic activation	not genotoxic Positive control induced statistically significant increases	[46]
Rosa Centifolia Stem Extract	25 – 100 mg/ml	normal saline	12 reconstructed epidermal units	EpiSkin™ micronucleus assay Mitomycin was used as the positive control	not genotoxic Positive control caused statistically significant increase	[47]

Table 7. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION					
ANIMAL					
Rosa Centifolia Flower Oil	Undiluted	Hairless mice (number and strain not stated)	Applied to the back for an unspecified duration. Additional study details not included	No evidence of skin irritation	[4]
Rosa Centifolia Flower Oil	Undiluted	Rabbits (number and strain not stated)	Applied for 24 h to intact or abraded skin using occlusive patches. Additional study details not included	Test substance classified as moderately irritating to the skin	[4]
HUMAN					
Face mask containing 0.8% Rosa Centifolia Flower	Undiluted	20 subjects	Single-insult occlusive patch test; 24 h patch. Irritation scores determined at time of patch removal	No evidence of skin irritation	[49]
Rosa Centifolia Flower Oil	2% in petrolatum	number of subjects not stated	48-h closed patch test	No evidence of skin irritation	[4]
SENSITIZATION					
HUMAN					
Face mask containing 0.8% Rosa Centifolia Flower	tested neat (0.05 ml)	25 subjects (20 females, 5 males)	Maximization test. Test article (0.05 ml) applied under 15 mm occlusive patch to SLS (0.25%) pretreated site on upper outer arm or back. Procedure involved five 48-h induction patches (72 h on weekends). After a 10 - 14 d non-treatment period, a -h occlusive patch with 5% aq. SLS was applied to a previously untreated site, and an occlusive patch with the test substance was applied for 48 h. Challenge site evaluated for reactions at time of patch removal and 24 h later.	No adverse or unexpected reactions during induction phase. No evidence of contact allergy at time of challenge patch removal or 24 later. Concluded that the test article does not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions.	[50]
Eye serum containing 0.1% Rosa Centifolia Flower Extract	tested neat (0.1 – 0.15 g) approximately 25 – 38 mg/cm^2 test material	49 subjects	HRIPT. Occlusive patches were applied 3x/wk for 3 wk, for a total of 9 induction applications. (The test material was volatilized for 30 – 90 min on the patch prior to application.) After a 2-wk non-treatment period, a challenge patch was applied to a new site, and 24 to 72 h after, the site was scored.	No reactions were observed during induction or challenge and the researchers concluded that the test article was not associated with skin irritation or allergic contact dermatitis.	[51]
Rosa Centifolia Flower Extract trade name mixture	20%	55 subjects (45 females, 10 males)	HRIPT (modified Shelanski method). Total of 9 induction patches (occlusive patches) applied over 3-wk period. Induction phase followed by 10- to 21-d non-treatment period. Occlusive challenge patch applied to new site on lower back.	No dermal reactions observed during induction or challenge phase. Test substance did not induce delayed contact sensitization.	[24,52]
Rosa Centifolia Flower Extract (concrete rose)	Undiluted	28 subjects	Maximization test. Test substance applied, under occlusion, to volar aspect of forearm for 5 alternate-day 48-h periods. Test site pretreated for 24 h with 5% aqueous SLS (under occlusion). After 10- to 14-d non-treatment period, challenge phase. Single challenge application preceded by 30-min application of SLS (under occlusion). Another challenge application (different site, no pretreatment) also made	Moderate degree of irritation observed at SLS-treated site. No other significant or allergic reactions observed.	[8]
Rosa Centifolia Flower Extract (concrete rose)	Undiluted	25 subjects	Modified maximization test procedure. Test substance applied, under occlusion, to volar aspect of forearm for 5 alternate 48-h periods. Initial patch test site pretreated for 24 h with 5% aqueous SLS (under occlusion). After 10- to 14-d non-treatment period, test substance (under occlusive challenge patch) applied for 48 h to new test site. Challenge applications preceded by 30-min application of 5% aqueous SLS (under occlusion). Additional challenge site not pretreated with SLS.	Approximately 1/3 of subjects tested developed irritation at SLS-treated site. No other significant irritation or allergic reactions observed. Test substance produced no reactions that were considered significantly irritating or allergic in nature	[10]

Table 7. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Rosa Centifolia Flower Extract (concrete rose)	Undiluted	22 subjects	Modified maximization test procedure, as described above	Test substance produced no reactions that were considered significantly irritating or allergic in nature	[11]
Rosa Centifolia Flower Extract (rose centifolia concrete)	Undiluted	33 subjects	Modified maximization test procedure, as described above.	Sweat retention response observed in 1 subject. Test substance produced no reactions that were considered significantly irritating or allergic in nature	[12]
Rosa Centifolia Flower Extract (rose absolute)	Undiluted	24 subjects	Modified maximization test procedure, as described above, except, challenge applications preceded by 30-min application of 2% aqueous SLS (under occlusion). Additional challenge site not pretreated with SLS.	A 3+ reaction observed in 1 subject after initial patch application. Retesting of subject did not yield positive reaction. Test substance did not induce skin sensitization	[13]
Rosa Centifolia Flower Extract (rose absolute)	Undiluted	25 subjects	Maximization test. Test substance applied, under occlusion, to volar forearm for 5 alternate-day 48-h periods. Patch test sites pretreated for 24 h with 5% aqueous SLS (under occlusion). After 10-d non-treatment period, test substance, under occlusive challenge patch, applied for 48 h to new test site. Challenge applications preceded by 1-h application of 10% aqueous SLS (under occlusion). Challenge sites evaluated at time of patch removal and 24 h later.	Test substance induced contact sensitization (mild reaction) in 1 subject; therefore, the researcher concluded the test material is a mild sensitizer	[7]
Rosa Centifolia Flower Oil	2% in petrolatum	24 subjects	Maximization test. Protocol details not included	No evidence of skin sensitization	[4]

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