Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 16, 2025
Panel Meeting Date:	June 9 -10, 2025

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.; Cohen, M. Samuel, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Thomas J. Slaga, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Preethi Raj, M.Sc., former Senior Scientific Analyst/Writer, CIR, and Thushara Diyabalanage, Ph.D., Scientific Analyst/Writer, CIR.

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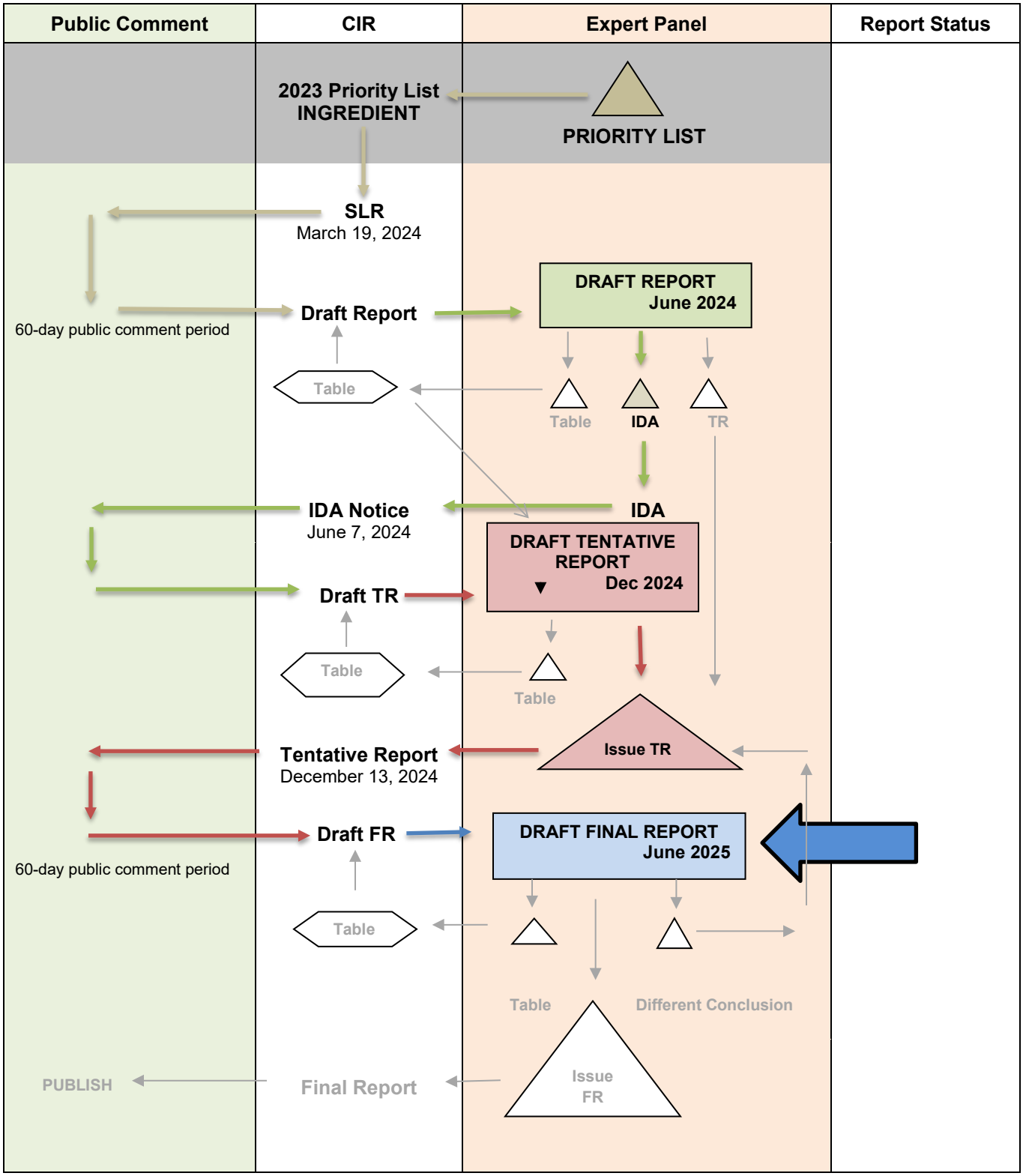
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Paeonia suffruticosa*-Derived Ingredients

MEETING June 2025



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage, Ph.D., Scientific Analyst/Writer, CIR
Date: May 16, 2025
Subject: Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Final Report on the Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics. (It is identified as *report_PaeoniaSuffruticosa_062025* in the pdf document.) At the December 2024 meeting, the Panel concluded that Paeonia Suffruticosa Seed Oil is safe as used in cosmetics. However, The Panel also concluded that the available data are insufficient to make a determination of safety for Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, Paeonia Suffruticosa Root Extract and Paeonia Suffruticosa (Tree Peony) Root Bark Extract under the intended conditions of use in cosmetic formulations.

For these 4 ingredients, the Panel determined that the following data are needed to determine safety:

- For Paeonia Suffruticosa Root Bark Extract
  - Clarification on the definition, methods of manufacture, and composition as applicable to cosmetic use
  - Clarification as to whether Paeonia Suffruticosa Root Extract includes the root bark of the plant
- For Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, and Paeonia Suffruticosa Root Extract
  - Maximum concentration of use
  - Ocular irritation data (in vitro) at the maximum reported concentration of use for near the eye.
- For all 4 ingredients
  - 28-d dermal toxicity assay
    - If positive, data on systemic toxicity endpoints (e.g. developmental and reproductive toxicity) may be needed
  - Genotoxicity data
- For Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, and Paeonia Suffruticosa (Tree Peony) Root Bark Extract
  - Dermal irritation and sensitization data

The following data were received in response to the insufficient data conclusion. This information has been included in this report, as indicated by highlighted text.

- Safety data of Paeonia Suffruticosa Root Extract (ocular irritation and genotoxicity data) of a test sample containing 1.5% Paeonia Suffruticosa Root Extract (*data1_PaeoniaSuffruticosa_062025*)
- Updated use information (*data2_PaeoniaSuffruticosa_062025*)

The Council also submitted The Japanese Standards of Quasi-Drug Ingredients for Paeonia suffruticosa (2021; ChatGPT English translation provided) and a toxicology study on Moutan bark (Japanese article with an English translation). In that these are published documents, they are not included with the report package.

A table is included at the end of this memo to provide an overview of the information needed/received for each ingredient.

Council comments received prior to the December 2024 meeting on the draft Tentative Report (*PCPCcomments1_PaeoniaSuffruticosa_062025*) and those received on the Tentative Report

(*PCPCcomments2_PaeoniaSuffruticosa_062025*) have mostly been addressed (*response-PCPCcomments1_PaeoniaSuffruticosa_062025; response-PCPCcomments2_PaeoniaSuffruticosa_062025*). However, one comment on the Tentative Report stated: "*With the lack of data on the cosmetic ingredients, it may be helpful to include some information on one of the main components paeonol, to add to a weight of evidence assessment for these ingredients*." (Some abstracts were included with the comment.)

The Panel should provide guidance about such an approach as it is a clear deviation from the Panel's current strategy to evaluate a naturally complex substance as one whole substance. The Introduction of each botanical report states*: the Panel is evaluating the safety of each of the [natural complex substances] as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical ingredients*.

Additional supporting documents for this report package include the following:

- flow chart (*flow_PaeoniaSuffruticosa_062025)*
- report history (*history_PaeoniaSuffruticosa_062025*)
- a search strategy (*search_PaeoniaSuffruticosa_062025*)
- a data profile (*dataprofile_PaeoniaSuffruticosa_062025*)
- transcripts from the previous meeting (*transcripts_PaeoniaSuffruticosa_062025*)

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

Ingredient	**Data insufficiency**	**Data received**
Paeonia Suffruticosa Bark Extract	maximum concentration of use	N
	ocular irritation data (in vitro) at the maximum reported concentration of use for near the eye	N
	28-d dermal toxicity assay; if positive, data on systemic toxicity endpoints (e.g., DART)	N
	genotoxicity data	N
	dermal irritation and sensitization data	N
Paeonia Suffruticosa Extract	maximum concentration of use	N
	ocular irritation data (in vitro) at the maximum reported concentration of use for near the eye	N
	28-d dermal toxicity assay; if positive, data on systemic toxicity endpoints (e.g., DART)	N
	genotoxicity data	N
	dermal irritation and sensitization data	N
Paeonia Suffruticosa Root Extract	maximum concentration of use	Y
	ocular irritation data (in vitro) at the maximum reported concentration of use for near the eye	Y
	28-d dermal toxicity assay; if positive, data on systemic toxicity endpoints (e.g., DART)	N
	genotoxicity data	Y
Paeonia Suffruticosa (Tree Peony) Root Bark Extract	clarification on the definition, method of manufacture, and composition, as applicable to cosmetic use	Y(?)
	clarification as to whether Paeonia Suffruticosa Root Extract includes the root bark of the plant	N
	28-d dermal toxicity assay; if positive, data on systemic toxicity endpoints (e.g., DART)	N
	genotoxicity data	N
	dermal irritation and sensitization data	N

Personal Care Products Council
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Memorandum

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

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

DATE: November 26, 2024

SUBJECT: Draft Tentative Report: Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics (December 2-3, 2024 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the Draft Tentative Report, Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics.

Method of Manufacture, Paeonia Suffruticosa Extract – The personal communication citation needs a reference in the reference section that includes to whom and when the communication occurred.

Cosmetic Use - The Cosmetic Use section should note that small businesses are exempt from MoCRA reporting for most cosmetic product categories. MoCRA defines a small business as average gross annual sales of cosmetic products in the United States for the previous 3 years of <$1,000,000 adjusted for inflation and the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 hours (see section 612 of MoCRA).

It should be noted that FDA is collecting data for airbrush use of four makeup product categories (foundations, leg and body paints, makeup bases, other makeup preparations), and indoor tanning products. The PCPC surveys also request that airbrush uses be identified.

Developmental and Reproductive Toxicity, Animal, Paeonia Suffruticosa Seed Oil – Please clarify the species used. For the sperm abnormality study, it says rats were used, but the next sentence says: “Sexually mature male mice were administered….”. For the developmental study, it says that pregnant rats were treated, but then it says, “live fetal mouse development”.

Summary – The species used in the developmental study of the seed oil should be stated. It currently states “pregnant dams”.

Table 2 – As there is only one study summarized in this table, it would be helpful to include a footnote as to how the study was completed. Were all plant parts in the table analyzed for all the components in the table? Please explain what the blank cells mean. Do they mean the component was not analyzed in that plant part, or the component was not detected in that plant part?

***Paeonia suffruticosa*-derived ingredients - June 2025 meeting – Thushara Diyabalanage, Ph.D.**	
Comment Submitter: Alexandra Kowcz, Personal Care Products Council **Date of Submission: November 26, 2024 (comments on draft Tentative Report; December 2024 meeting)**	
Comment	**Response/Action**
Method of Manufacture, Paeonia Suffruticosa Extract – The personal communication citation needs a reference in the reference section that includes to whom and when the communication occurred.	Since it was personal communication it was not cited as a reference as we follow AMA style.
Cosmetic Use - The Cosmetic Use section should note that small businesses are exempt from MoCRA reporting for most cosmetic product categories. MoCRA defines a small business as average gross annual sales of cosmetic products in the United States for the previous 3 years of <$1,000,000 adjusted for inflation and the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 hours (see section 612 of MoCRA).	Addressed
It should be noted that FDA is collecting data for airbrush use of four makeup product categories (foundations, leg and body paints, makeup bases, other makeup preparations), and indoor tanning products. The PCPC surveys also request that airbrush uses be identified.	Addressed
Developmental and Reproductive Toxicity, Animal, Paeonia Suffruticosa Seed Oil – Please clarify the species used. For the sperm abnormality study, it says rats were used, but the next sentence says: “Sexually mature male mice were administered….”. For the developmental study, it says that pregnant rats were treated, but then it says, “live fetal mouse development”.	The species used was not mentioned in the article. Addressed Addressed
Summary – The species used in the developmental study of the seed oil should be stated. It currently states “pregnant dams”	It was corrected as pregnant rats. The species is not stated in the review article. The original publication is in Chinese
Table 2 – As there is only one study summarized in this table, it would be helpful to include a footnote as to how the study was completed. Were all plant parts in the table analyzed for all the components in the table? Please explain what the blank cells mean. Do they mean the component was not analyzed in that plant part, or the component was not detected in that plant part	Addressed. Table 2 was created by combining information from 4 publications that include many phytochemical investigations to provide a general idea about the secondary metabolite profile of the plant. The methodologies used for extraction, separation and identification of them differ from one study to another. A blank cell means that a particular compound was not reported from that plant part in these investigations.

Personal Care Products Council
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Memorandum

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

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

DATE: January 2, 2025

SUBJECT: Tentative Report: Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics (release date December 13, 2024)

The Personal Care Products Council respectfully submits the following comments on the Tentative Report, Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics.

Key Issue
With the lack of data on the cosmetic ingredients, it may be helpful to include some information on one of the main components paeonol, to add to a weight of evidence assessment for these ingredients. A few abstracts of papers that may be helpful are provided below.

J Ethnopharmacol. 1987 Sep-Oct;21(1):37-44.
doi: 10.1016/0378-8741(87)90092-4.

Biopharmaceutical studies on crude drug preparations. I: Permeation of paeonol in a decoction and dry extract of Paeonia suffruticosa root cortex using an absorption simulator

T Tani [1], K Inoue, S Arichi, T Ohno

PMID: 3695554
DOI: 10.1016/0378-8741(87)90092-4

Abstract
The permeation behavior of paeonol, one active constituent of a crude Chinese drug called Moutan Cortex, through an artificial gastric lipid barrier was examined in vitro using an absorption simulator in order to clarify how the administered form influenced the bioavailability of paeonol from a crude preparation. Paeonol concentrations were determined by a high-performance liquid chromatographic method developed during this study. Paeonol showed greater permeation from artificial gastric juice into artificial plasma when it was applied as a decoction or freeze-dried extract of Moutan Cortex than when applied as purified paeonol alone.

Int J Mol Sci 2010;11(12):4882-90.
doi: 10.3390/ijms11124882. Epub 2010 Nov 26.

In situ and in vivo study of nasal absorption of paeonol in rats

Xiaolan Chen [1], Yang Lu, Shouying Du, Bing Xu, Shan Wang, Yongsong Zhai, Xiao Song, Pengyue Li

PMID: 21614179
PMCID: PMC3100845
DOI: 10.3390/ijms11124882

Abstract

The objective of this work was to study the in situ and in vivo nasal absorption of paeonol. A novel single pass in situ nasal perfusion technique was applied to examine the rate and extent of nasal absorption of paeonol by rats. Various experimental conditions, such as perfusion rate, pH, osmotic pressure and drug concentration, were investigated. The in situ experiments showed that the nasal absorption of paeonol was not dependent on drug concentration, and fitted a first order process. The absorption rate constant, Ka, increased with an increase in perfusion speed. Paeonol was better absorbed in acidic solutions than in neutral or alkaline solutions. The value of Ka was higher in a hypertonic environment than under isotonic or hypotonic conditions. In vivo studies of paeonol absorption were carried out in rats and the pharmacokinetics parameters of intranasal (i.n.) and intragastric (i.g.) administration were compared with intravenous (i.v.) administration. The bioavailabilities of paeonol were 52.37% and 15.81% for i.n. and i.g, respectively, while T(max) values were 3.05 ± 1.46 min and 6.30 ± 0.70 min. MRT (Mean Residence Time) were 23.19 ± 6.46 min, 41.49 ± 2.96 min and 23.09 ± 5.88 min for i.n., i.g. and i.v. methods, respectively. The results demonstrate that paeonol could be absorbed promptly and thoroughly by i.n. administration in rats.

Radioisotopes 1983 Jan;32(1):7-12.
doi: 10.3769/radioisotopes.32.7.

Studies on the percutaneous absorption of paeonol in experimental animals by a radioactive tracer technique

K Mimura, S Baba

PMID: 6856883
DOI: 10.3769/radioisotopes.32.7

Abstract

Studies on in vivo percutaneous absorption of paeonol (2-hydroxy-4-methoxyacetophenone: I) in rabbits, guinea pigs, and rats were carried out by a radioactive tracer technique. Hydrophilic ointment (specific activity: 376 Bq (0.01016 microCi)/mg) containing I[carbonyl-14C] was applied for 24 h by occlusive dressing treatment on the shaven back of experimental animals. Then, the 14C-activity in urine, which is the dominant excretion route, was determined for 8 days. Percentage excreted within 24 h after application to rabbits, guinea pigs, and rats were 42.8%, 46.5% and 52.0%, respectively. Urinary metabolites were identified as 2,5-dihydroxy-4-methoxyacetophenone, resacetophenone, and substrate I in all the case.

Chem Biodivers 2020 Oct;17(10):e2000422.
doi: 10.1002/cbdv.202000422. Epub 2020 Sep 21.

In Silico and In Vivo Toxicological Evaluation of Paeonol

Kaveri M Adki [1], S Murugesan [2], Yogesh A Kulkarni [1]

Affiliations

PMID: 32955165

DOI: 10.1002/cbdv.202000422

Abstract

Paeonol is a phenolic compound reported for its various pharmacological activities such as antioxidant, anti-inflammatory and antidiabetic activity. There are no systematic scientific reports on the in vivo toxicity of paeonol. So, the present work was designed to study in silico and in vivo toxicity of paeonol. In silico toxicity predictions were carried out using pkCSM, ProTox-II, pre-ADMET server and OSIRIS property explorer. Acute oral toxicity study of paeonol was carried out in female Sprague Dawley rats at a single dose of 300 mg/kg, 2000 mg/kg and 5000 mg/kg. Animals were observed for toxicity signs and mortality for 14 days. Repeated dose oral toxicity study of paeonol was carried out in female and male Sprague Dawley rats at a dose of 50, 100 and 200 mg/kg body weight for 28 days. At the end of the study, hematological, biochemical and urine parameters were assessed. Histopathology of vital organs was also carried out. In silico toxicity study predicted that paeonol is non-toxic. The maximally tolerated dose of paeonol was found to be 5000 mg/kg in acute toxicity study in female rats. Paeonol was found to be safe at a dose of 50, 100 and 200 mg/kg in repeated dose toxicity study in male and female rats.

Review

Life Sci 2020 Jun 1:250:117544.

doi: 10.1016/j.lfs.2020.117544. Epub 2020 Mar 13.

Chemistry, pharmacokinetics, pharmacology and recent novel drug delivery systems of paeonol

Kaveri M Adki [1], Yogesh A Kulkarni [2]

PMID: 32179072

DOI: 10.1016/j.lfs.2020.117544

Abstract

Paeonol is a bioactive phenol present in Dioscorea japonica, Paeonia suffruticosa and Paeonia lactiflora. It is reported for various pharmacological activities.

Aim: To review chemistry, pharmacokinetics, pharmacological activities as well as various formulations of paeonol.

Materials and methods: A literature search was done using different search terms for paeonol by using different scientific databases like PubMed, Scopus and ProQuest. Scientific papers published during the period 1969 to 2019 were comprehensively reviewed.

Key findings: Researchers have synthesized methoxy, ethoxy, piperazine, chromonylthiazolidine, phenol-phenylsulfonyl, alkyl ether, aminothiazole, tryptamine hybrids and paeononlsilatie derivatives to enhance the stability of paeonol. These derivatives were synthesized and evaluated for in vitro series of biological activities like anti-inflammatory, tyrosinase inhibitory, neuroprotective, anticancer and antiviral activity. Regardless of valuable therapeutic potential, the clinical use of paeonol is restricted due to poor water solubility, low oral bioavailability, low stability and high volatility at room temperature. To enhance the

bioavailability of paeonol various formulations are prepared and evaluated for its activity. Paeonol formulations can be categorized as conventional-tablets, topical gel and hydrogel; polymeric delivery system-microparticles, microsponges, dendrimers, nanocapsules, polymeric nanoparticles, nanospheres; lipid-based delivery systems-microemulsion, self-micro-emulsifying drug delivery, liposome, transethosomes, ethosomes, niosomes, proniosomes, lipid-based nanoparticles and nanoemulsion of paeonol.
Significance: Paeonol has a potential to be developed as a techno-commercial product with respect to its multi-faceted pharmacological properties. Even though in vitro and in vivo studies have been reported the important activities of paeonol, its commercial utilization requires extensive safety and efficacy data.

Additional Considerations
Method of Manufacture, Paeonia Suffruticosa Extract – A reference needs to be added to the reference section to provide some information about the personal communication, e.g., communication to CIR staff member in November 2024.

Method of Manufacture, Paeonia Suffruticosa – The end parenthesis is missing from "(24 MPs at a rate of 21 l/h, at 46 ºC for 124 min…"

Composition and Impurities – Please correct: "pewnta" (delete "w")

Cosmetic Use – If more details about the limits to mandatory reporting, e.g., small company exemption, are not added to the CIR report, please provide a reference to the regulation.

If the Cosmetic Use section does not describe which FDA product categories ask for information on airbrush use, a reference to list of new FDA product categories should also be provided in the CIR report.

Toxicological Studies; Summary – For the studies on the herbal mixture containing 14.29% moutan cortex, it would be helpful to also state the doses of moutan cortex in addition to the doses of the mixture. In the Summary, it would be helpful to state the dose of moutan cortex in addition to the herbal mixture for the NOAEL of the 90-day study.

Inhibition of Tumor Growth – It does not seem appropriate to call reference 14 a "tumor promotion study" as it looked at the inhibition of tumor growth.

Paeonia suffruticosa-derived ingredients - June 2025 meeting – Thushara Diyabalanage Ph.D.	
Comment Submitter: Alexandra Kowcz, Personal Care Products Council **Date of Submission: January 2, 2025 (comments on Tentative Report)**	
Comment	**Response/Action**
With the lack of data on the cosmetic ingredients, it may be helpful to include some information on one of the main components paeonol, to add to a weight of evidence assessment for these ingredients. s. A few abstracts of papers that may be helpful are provided below. 1. J Ethnopharmacol. 1987 Sep-Oct;21(1):37-44. doi: 10.1016/0378-8741(87)90092-4. Biopharmaceutical studies on crude drug preparations. I: Permeation of paeonol in a decoction and dry extract of Paeonia suffruticosa root cortex using an absorption simulator T Tani 1 , K Inoue, S Arichi, T Ohno PMID: 3695554 DOI: 10.1016/0378-8741(87)90092-4 2. In situ and in vivo study of nasal absorption of paeonol in rats Xiaolan Chen 1 , Yang Lu, Shouying Du, Bing Xu, Shan Wang, Yongsong Zhai, Xiao Song, Pengyue Li PMID: 21614179 PMCID: PMC3100845 DOI: 10.3390/ijms1112488 3. Studies on the percutaneous absorption of paeonol in experimental animals by a radioactive tracer technique K Mimura, S Baba PMID: 6856883 DOI: 10.3769/radioisotopes.32.7 4. In Silico and In Vivo Toxicological Evaluation of Paeonol Kaveri M Adki 1 , S Murugesan 2 , Yogesh A Kulkarni 1 Affiliations PMID: 32955165 DOI: 10.1002/cbdv.202000422 5. Chemistry, pharmacokinetics, pharmacology and recent novel drug delivery systems of paeonol Kaveri M Adki 1 , Yogesh A Kulkarni 2 PMID: 32179072 DOI: 10.1016/j.lfs.2020.117544	**Panel input needed** Based on CIR protocols and the Panel's previous comments regarding including safety information on individua components, naturally-complex substances such as *Paeonia suffruticosa*-derived ingredients are evaluated as a whole substance, not based on the individual components.
Method of Manufacture, Paeonia Suffruticosa Extract – A reference needs to be added to the reference section to provide some information about the personal communication, e.g., communication to CIR staff member in November 2024.	This was a personal communication and such communications are not cited in the reference section according to the AMA style we follow.
Method of Manufacture, Paeonia Suffruticosa – The end parenthesis is missing from "(24 MPs at a rate of 21 l/h, at 46 º C for 124 min…"	Addressed
Composition and Impurities – Please correct: "pewnta" (delete "w"	Addressed
Cosmetic Use – If more details about the limits to mandatory reporting, e.g., small company exemption, are not added to the CIR report, please provide a reference to the regulation.	Addressed
If the Cosmetic Use section does not describe which FDA product categories ask for information on airbrush use, a reference to list of new FDA product categories should also be provided in the CIR report.	Addressed
Toxicological Studies; Summary – For the studies on the herbal mixture containing 14.29% moutan cortex, it would be helpful to also state the doses of moutan cortex in addition to the doses of the mixture. In the Summary, it would be helpful to state the dose of moutan cortex in addition to the herbal mixture for the NOAEL of the 90-day study.	Addressed
Inhibition of Tumor Growth – It does not seem appropriate to call reference 14 a "tumor promotion study" as it looked at the inhibition of tumor growth	Addressed

CIR History of:

***Paeonia suffruticosa*-derived Ingredients**

July 2022

-Concentration of use data submitted by Council

January 2023

-Frequency of use data obtained

March 2024

-Scientific Literature Review was posted

Data received:

March 29, 2024:

- Updated concentration of use data submitted by the Council
- Anonymous. 2020. Repeated insult patch test (face mask containing 0.5% Paeonia Suffruticosa Root Extract).

April 11, 2024:

- Anonymous. 2024. Summary Information - Paeonia Suffruticosa Root Extract.
    - Method of manufacture
    - Impurities
    - 24-h closed patch dermal irritation test (20 subjects)

June 2024

A draft report was submitted to the Panel. The Panel issued an insufficient data announcement

December 2024

A draft tentative report was submitted. The panel concluded that Paeonia Suffruticosa Seed Oil is as safe as used as a cosmetic. An insufficient data announcement was issues for the other 4 ingredients.

Data received:

March 7, 2025

- Anonymous. 2025. Safety data of Paeonia Suffruticosa Root Extract.
    - Ocular irritation data, Short Time Exposure Test.
    - Genotoxicity data, Ames test
    - Genotoxicity data, In vitro micronucleus test

April 11, 2025

- Updated concentration of use data.

June 2025

A draft final report is being submitted.

***Paeonia suffruticosa*-Derived Ingredients Data Profile* – June 9-10, 2025 – Thushara Diyabalanage**																														
				Toxicokinetics			**Acute Tox**			**Repeated Dose Tox**			**DART**			**Genotox**		**Tumer growth Inhibition**			**Dermal Irritation**			**Dermal Sensitization**			**Photo toxicity**	**Ocular Irritation**		**Clinical Studies**	
	Reported Use	**Method of Mfg**	**Impurities/ Composition**	**log P/log K_{ow}**	**Dermal Penetration**	**ADME**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**Inhalation**	**In Vitro**	**Dermal**	**Oral**	**In Vitro**	**In Vivo**	**In Vitro**	**Dermal**	**Oral**	**In Vitro**	**Animal**	**Human**	**In Vitro**	**Animal**	**Human**		**In Vitro**	**Animal**	**Retrospective/ Multicenter**	**Case Reports**
Paeonia Suffruticosa Bark Extract	X	X	X										X								X									
Paeonia Suffruticosa Extract	X	X	X															X												
Paeonia Suffruticosa Root Extract	X	X	X													X							X			X				
Paeonia Suffruticosa Seed Oil	X	X	X					X			X				X															
Paeonia Suffruticosa (Tree Peony) Root Bark Extract	X	X	X					X			X							X												

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

[*Peonia suffruticosa* – derived Ingredients

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Paeonia Suffruticosa Root Extract	223747-88-4		NR	NR	NR	NR	✓*	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	
Paeonia Suffruticosa Extract	223747-88-4	✓	NR	NR	NR	NR	✓*	NR	✓*	✓*	NR	NR	NR	NR	NR	✓*	
Paeonia Suffruticosa Bark Extract	223747-88-4		NR	NR	NR	NR	✓*	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	
Paeonia Suffruticosa Seed Oil	223747-88-4	✓	NR	NR	NR	NR	✓*	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	
Paeonia Suffruticosa (Tree Peony) Root Bark Extract		✓	✓	NR	NR	NR	✓*	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	

NR – not reported; ✓ - data are available; ✓* - mentioned in database, but data not relevant

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	AGRICOLA	IFRA	RIFM
Paeonia Suffruticosa Root Extract	223747-88-4	√	√	√	√	√	√		
Paeonia Suffruticosa Extract	223747-88-4	√	√	√	√	√	√		
Paeonia Suffruticosa Bark Extract	223747-88-4	√	√	√	√	√	√		
Paeonia Suffruticosa Seed Oil	223747-88-4	√	√	√	√	√	√		
Paeonia Suffruticosa (Tree Peony) Root Bark Extract									

Search Strategy

PubMed – performed as of 04/18/2024, last search 04/10/2025
((Paeonia Suffruticosa Bark Extract) OR (Paeonia Suffruticosa (Tree Peony) Bark Extract)) OR (223747-88-4)) OR (OriStar Paeonol)) OR (MyeongAn YunGo)) OR (Paeonia Suffruticosa Extract)) OR (Paeonia Suffruticosa (Tree Peony) Extract)) OR (Paeonia Suffruticosa Root Extract)) OR (Paeonia Suffruticosa (Tree Peony) Root Extract)) OR (OriStract PSRE)) OR (ActivOil Spotless)) OR (Activoil Spotless ZRO)) OR (Alprotector)) OR (Biocleanact Paeonia Extract (MSK-NE 150))) OR (Bio-Complex)) OR (Biyeonmongnandan)) OR (BMB-CF)) OR (BMB-CFG)) OR (BMB-CFM)) OR (BMC-CME)) OR (Botanpi Liquid B)) OR (Botanpi Liquid E)) OR (Cellule Blanc)) OR (Chem-Free)) OR (Chem-Free S)) OR (ENS Real Cactus Vinegar)) OR (ENS Real Kelp Vinegar)) OR (ENS Real Rose Vinegar)) OR (Extract of Paeonia Suffruticosa)) OR (Extract of Paeonia Suffruticosa I)) OR (Germall Free M)) OR (Germall-Free)) OR (Hair Growth Complex)) OR (Harmowhite)) OR (Moutan Bark Extract)) OR (Multi Flavonoid Extract)) OR (Naturo STEM EX)) OR (NaturoComplex)) OR (Paeonia Extract)) OR (Phyto Desensitizer)) OR (Phytoblend TIPS)) OR (RoSphere 3.0))) OR (Paeonia Suffruticosa Seed Oil)) OR (Paeonia Suffruticosa (Tree Peony) Seed Oil)) OR (Peony Seed Oil)) AND (toxicity) - 581, 231 hits/8 useful

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (2nd Edition; 2013) - http://abc.herbalgram.org/site/DocServer/AHPABotanicalSafety_FMexcerpt.pdf?docID=4601
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

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

JUNE 2024 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team Meeting – June 3, 2024

DR. BELSITO: Okay. So, we also got a Wave 2 on this one before we start. I agreed with all PCPC comments on Wave 2.

DR. SNYDER: Same with me. Same with me.

MS. RAJ: Just to clarify, the calculation in the PCPC comments is actually 258.33 micrograms per centimeter square. I (inaudible).

DR. EISENMANN: I made a mistake in the calculation?

DR. BELSITO: I'm sorry. What are you referring to --

MS. RAJ: One of the PCPC comments wanted us to include the dose per area (inaudible). And, yeah, the actual number for that is 258.33 micrograms per centimeter squared.

DR. BELSITO: Okay.

MS. RAJ: This is what was provided in the comments.

DR. BELSITO: Okay. Rather than 0.64.

MS. RAJ: Yes.

DR. BELSITO: Okay. So, you've corrected that.

MS. RAJ: (Inaudible).

DR. BELSITO: Okay, great. Thank you. Curt, we just said that we agreed with the PCPC comments on Paeonia from Wave 2 is where we're at.

DR. KLAASSEN: Okay.

DR. BELSITO: So, this is the first time we're looking at the safety assessment of five cosmetic ingredients. The SLR was the issue in March 19, 2024. There is a material root bark extract. It's not included in the web-based dictionary, but it's reported to be used. My comment on this is I think it's fine to add it into the report if we're finding uses for it. Would we expect this bark -- which is essentially at the surface of a plant. Because when I first saw it, I said, how can a root have bark? But actually, there is such a thing as root bark, and it's the part of the root just as it comes up to the service where the bark forms for the first time. I'm not sure that's going to be terribly different from the bark that's further out, but it's not my area of specialty. But that was my assumption as we looked at this.

I think in terms of looking at all of the data we need additional composition on the extract, the root extract, the bark extract, and the root bark extract. We need an impurities data for all except the root extract. And then we need the botanical boilerplate for metals and pesticides in the discussion when we get to that, just to make a note. But those were my data needs for this group. Paul, Curt, Allan?

DR. RETTIE: I had a note that there's nine uses near the eye. Do we need ocular irritation?

MS. RAJ: I don’t believe there's ocular irritation data.

DR. RETTIE: I didn't find any. So, maybe consider that as an additional need.

DR. BELSITO: We're throwing it out. I didn't note that as a data need, but we can certainly put that out. Typically, when we ask for it, we ask for ocular irritation if available. But we've now heard about these in vitro methods, so we certainly can ask for that since I think hopefully we all know what they mean.

DR. SNYDER: Don, we also have incidental inhalation, airbrush use.

DR. BELSITO: Oh, yeah.

DR. SNYDER: And then the root extract is actually at a higher concentration of use, 0.5 percent compared to the other ingredients. So, we need to take that into consideration.

DR. BELSITO: In terms of?

DR. SNYDER: What data will be sufficient.

DR. BELSITO: Oh, okay.

DR. RETTIE: We have dermal irritation and sensitization for the most common ingredient.

DR. BELSITO: We usually ask for the one with the highest concentration of use.

DR. RETTIE: Yeah. And that would be -- five percent -- the root extract.

DR. SNYDER: I believe the root extract, 2.5 percent.

DR. RETTIE: Root extract.

DR. SNYDER: Yeah.

DR. RETTIE: But we have it for --

MS. RAJ: Yes.

DR. RETTIE: We do. So, we're covered for the one with the most uses, highest concentration.

DR. KLAASSEN: We don't have genotoxicity.

DR. RETTIE: Do we typically ask for that for botanicals?

DR. KLAASSEN: Probably not.

DR. BELSITO: Yeah, we have 13 weeks of chronic. I thought the DART was insufficient as well, 28-day dermal or additional data on root extract is what I have. Sorry, my computer's acting up while my comments are just popping up now. Also, we had some data here on the flower, but it's not even an ingredient we're being asked to use. So, I don't understand why.

DR. EISENMANN: I think I included that because I (inaudible).

DR. BELSITO: Okay. But I think that title is misleading because it looks like it's going to be data on the extract.

DR. EISENMANN: Could you kindly point out where --

DR. BELSITO: PDF Page 13.

DR. EISENMANN: Are you looking under Composition and Impurities? Okay. So, on the bottom.

DR. BELSITO: Hold on.

DR. EISENMANN: I see it under Extract.

DR. BELSITO: Yeah, it's under the Extract. It's the last paragraph. It should just say flower because it's not the extract, right. It's just the data on the flower.

DR. EISENMANN: Well, are you saying you'd rather have it removed?

DR. BELSITO: No, I don't think we need to remove it if you think it might give us some information when we get to the whole extract, but it's not the whole extract. It's the flower. So, the title of that is misleading because, when one looks at it, one would think that you're going to see data on the flower, and that's not what we're seeing.

DR. EISENMANN: Sure. Okay.

DR. BELSITO: Yeah. The root extract is 0.5 percent. Did you say five percent, Paul?

DR. SNYDER: No, 0.5. I said 0.5 percent. Yeah.

DR. BELSITO: Okay.

DR. SNYDER: The tox data that we had is very high oral LD50s. I don't anticipate there's going to be any issues with this stuff. But it's just a matter of we need to have the data. I think the composition, the impurities data is important to have.

DR. BELSITO: Yeah. And under this PDF Page 16, the Paeonia Suffruticosa Root Bark Extract, the 13-week oral study, I just want to point out that a lot of these, at least as written, don't seem to have a dose response; things we're seeing at 760 but not higher, or 750 and 3000, not at 1500. Is this correct? Because throughout, it looks like there's a whole bunch of 13 weeks of chronic studies without a dose response.

MS. RAJ: (Inaudible) as to why the numbers were (inaudible).

DR. BELSITO: Could you check it because, again, it doesn't make sense? It says, for instance, if you look at PDF Page 16 under the Root Bark Extract, "A statistically significant increase in white blood cell values was observed in both male and female in the 750 and 3000 milligram per kilogram dose group," and these animals were dosed with 750, 1500, and 3000. So, it wasn't seen in 3000. Then there's another where, again, you're seeing changes at 750 but not at higher doses. It just makes no sense.

DR. SNYDER: Unless there was cytotoxicity, Don. Unless at those higher levels you couldn't see the shift in the cell tox because of something like cytotoxicity. You have to look at those a little more carefully.

DR. BELSITO: So, you just think that the effect occurred at 750, so above 750 nothing else was seen? Is that how you interpreted it, Paul?

DR. SNYDER: That's one possibility. Have to go back and look at those individual reports.

DR. BELSITO: Yeah. Just check it, Preethi, because that whole paragraph on the 13-week oral, which may become important as we look at this further, doesn't make any sense to me.

DR. ZHU: (Inaudible) were there other references or places you wanted me to check?

DR. BELSITO: No, it was all in the 13-week oral tox study. Just make sure that all of those endpoints and the values where you said there were increases or decreases are absolutely correct because then it goes on to say, "The no-observed-adverse-effect-level of the herbal mixture was determined to be 3000 milligrams per kilogram per day." But when you're seeing effects at 750, that makes no sense. The DART is insufficient. Everyone would agree with that? We need a 28-day dermal or additional data on this product.

DR. SNYDER: At this stage, yes.

DR. BELSITO: Okay. Genotox is insufficient. We need bacterial and mammalian genotox. On PDF Page 18, Tumor Promotion, that should be Tumor Inhibition. It also appears to have a potential -- PDF Page 18 -- potential effect on melanogenesis because of this tyrosinase inhibition. So, that would, again, need to be in our discussion as we dealt, I think, before with these materials that have this effect. That this would not occur with a cosmetic I think is how we've generally approached it. Is that correct, Carol?

DR. EISENMANN: If you have language like that.

DR. BELSITO: Yeah, I mean, I don't think we've ever asked, give a NOAEL for that. Simply, we've pointed that it could have this effect. I think the sensitization is okay. They did a human repeat in-cell patch testing on Point 5, so I think that's okay. And therefore by default, the irritation has to be because you would've seen irritation after applying something three times a week for three weeks on the back. I think the ocular irritation we need, as Allan previously pointed out. And I think at this point we can request, if available, in vivo, but otherwise in vitro.

So, to summarize, composition of all except the seed oil; impurities for all except the root extract; 28-day dermal, and if absorbed, additional DART genotox data; and discussion of respiratory boilerplate, botanical boilerplate, and effect on tyrosinase. Did I capture everything? Sorry that I'm having such computer issues?

DR. SNYDER: That's everything I had, Don.

DR. KLAASSEN: Sounds good.

DR. BELSITO: Okey-doke. Preethi, you're on page and then clarification of 13-week subchronic.

MS. RAJ: Yeah.

Cohen Team Meeting – June 3, 2024

DR. COHEN: Okay. So, Paeonia suffruticosa. This is a draft report.

MS. BURNETT: Sorry.

DR. COHEN: No, no. It's okay. This is the first time we're looking at this safety assessment of these five cosmetic ingredients. One ingredient reviewed in this report tree peony root bark extract is not listed in the dictionary. However, its use is reported in the VCRP in 2023 and thus is part of this review. The root bark ingredients commonly used in Chinese medicine, however there's ambiguity with regards to specificity of the genus and species and plant part used as well as the extraction methodology.

The 2023 VCRP survey data has the root extract in 213 formulations of which 173 are leave on. The other ingredients have 18 or fewer reported uses. The results of a concentration of use survey conducted by the Council in 2024 indicated its highest maximum reported concentration of use of 0.5 percent in pastes, masks, and mud packs. So, we have the five cosmetic ingredients. These are reported to be skin conditioning agents.

The seed oil is reported to function as a hair conditioning agent and skin protectant. We have method of manufacturing and impurities. We have HRIPT for root extract at maximum use. So, we can run the room now and see what your thoughts are.

DR. TILTON: Can we, I guess, first talk about the plant parts and components and overlaps mostly related to the root the bark extract, root extract, and root bark? I saw that there's this great table of the composition, but is the -- when we talk about the root, does that also include the root bark?

DR. COHEN: I go to method of manufacturing for that, and I don't know if it helped.

DR. TILTON: It was the whole root. Does that contain the bark?

DR. COHEN: Is the extract of the roots.

DR. TILTON: The roots.

DR. BERGFELD: I assumed it did, then.

DR. COHEN: I did, too.

DR. TILTON: Okay.

DR. COHEN: And that might not be true, but the --

DR. ROSS: Doesn't necessarily mean it's the same thing.

DR. TILTON: Not that they're the same thing, but that because we have so much data -- so most of the uses and formulations are for the root but we have a lot of data for the bark and root bark. So, I was just trying to figure out how applicable that was to the root itself.

DR. ROSS: But the data we have is the tree peony root bark extract, right?

DR. COHEN: We have irritation and sensitization for the root extract.

DR. ROSS: We do. Which is important with respect to the number of uses.

DR. BERGFELD: Is that the whole plant?

DR. ROSS: No, just the root extract.

DR. COHEN: Just the root extract.

DR. BERGFELD: I was letting the whole plant carry the whole thing.

DR. COHEN: But we don't have it on the whole plant. I was hoping the whole plant would carry -- would allow us to drag across the rest of them. But all we have is root extract.

DR. BERGFELD: And bark extract.

DR. TILTON: Yeah, it's quite a bit of data in some areas just on the seed oil and the root bark extract. For the root bark extract, you know, if I would assume that's part of the root.

DR. ROSS: Was that the -- was not --

MS. FIUME: The root bark extract?

DR. ROSS: Yeah. Was not --

MS. RAJ: It's not in the VCRP.

DR. ROSS: Thank you for that.

DR. TILTON: Or if it is --

DR. COHEN: You're talking about the tree peony root bark extract.

MS. RAJ: It is in the VCRP but not in the dictionary.

DR. COHEN: Not in the dictionary, yeah. I felt like we had enough for root extract.

DR. ROSS: I would just point out that when I looked at this on any of the ingredients, we had no dermal toxicity at all. Acute or 28 days. We had no ocular toxicity at all and a few of them are used around the eye. And we had no genotoxicity at all -- any of the products. And I have a whole list of specific needs.

DR. COHEN: Why don't you run them because we're obviously going to an IDA on this.

DR. ROSS: Yeah, okay. I had dermal irritation/sensitization on seed oil.

DR. COHEN: Wait. So dermal irritation and sensitization --

DR. ROSS: On seed oil.

DR. COHEN: Why wouldn't we have it on everything but the root extract?

DR. ROSS: Let me see here. I think I went to the seed oil because it --

DR. TILTON: It's the most different.

DR. ROSS: It's most likely the components to produce irritation and sensitization. But I mean, there's no reason not, David, to include the other components as well.

DR. COHEN: You know, when I look at these tables, number one, it harkens me to other ones that we've done where the (inaudible), the location of growing markedly changes the constituents here. Number two, it assumes that this constituent table has everything in there. It's just what they've tested. We actually don't know what it doesn't have. Right? So, I look at these, you know, the terpenoids. I didn't see a lot in here but when you look at the flower, if you look at this table, you know the flower has these flavonoids and that's all there is in there in the flower. Obviously not.

DR. ROSS: Yeah, let's go to all of them.

DR. COHEN: Except --

DR. ROSS: The root extract. Except the root extract.

DR. COHEN: Okay. You want dermal tox on everything?

DR. ROSS: Yeah.

DR. TILTON: Yes.

DR. COHEN: Dermal to- -- 28 day -- if it's absorbed, right? Oh, wait, no.

MS. FIUME: Contaminants are generally consumed.

DR. BERGFELD: Just a question, David. Under your sub tox studies, several of these ingredients are included and they have summary remarks, you know, basically benign response. You can't use any of that information to support safety? Under --

DR. COHEN: You're talking about under oral tox?

DR. BERGFELD: Yeah, it's oral. Sub chronic.

DR. ROSS: Isn't that the --

DR. COHEN: That's the seed oil.

DR. BERGFELD: Then other development -- the DART studies, again, they said the bark. It's okay and the animal seed oil studies, again, pretty benign in their summaries.

DR. COHEN: The DART seed oil is oral. Is the in vitro enough for the bark extract for DART?

DR. TILTON: Well, I guess -- I mean, what we were initially focusing on which was dermal tox.

DR. ROSS: Yeah.

DR. COHEN: Thank you. Get us back on track.

DR. TILTON: Dermal tox and dermal sensitization.

DR. ROSS: And if there is tox then we may need additional data such as DART. I think, isn't that how we usually phrase it?

DR. BERGFELD: There's absorption, 28 day, then --

DR. ROSS: Twenty-eight-day toxicity, we may need additional data such as DART.

DR. COHEN: So, give me the --

DR. TILTON: And ocular. I guess dermal and ocular. The two variants.

DR. ROSS: Okay, yeah.

DR. COHEN: So, we want dermal tox, acute tox, 28-day.

DR. ROSS: Yeah.

DR. BERGFELD: If absorbed.

DR. COHEN: If absorbed.

MS. FIUME: So generally, we have a statement in here saying we're not expected because it's a botanical and it's a mixture, so you don't know what you're looking for. So, is it 28-day dermal tox regardless or --

DR. COHEN: No. I'm getting a little caught up in that myself right now.

DR. ROSS: I would say 28-day dermal tox with these agents is preferred and not particularly acute. If not, it would need the bare minimum of acute dermal toxicity. Because right now you know nothing about the toxicity of these things on the skin. At least, the way I read it.

DR. COHEN: So, we're asking for 28-day dermal tox. And you're saying that we haven't been doing that?

MS. FIUME: No, no, I was clarifying that that's --

DR. COHEN: With the absorption statement.

MS. FIUME: -- (inaudible) someone said if absorbed because it's not -- if it's absorbed you not knowing what you're looking for because it's a complex issue.

DR. COHEN: We don't know; we're looking in the syrup for. Twenty-eight-day dermal tox. Irritation and sensitization on everything except the root extract. And then what other tox because Wilma brought up the oral tox for the seed oil and the root bark extract, but we don't know what this tree peony root bark extract is, right?

MS. RAJ: There is a little bit of ambiguity in the literature, but it has been referred to the root bark extract, though.

DR. COHEN: Root bark extract is prepared --

MS. RAJ: Or I should say the root bark.

DR. COHEN: Well, there's a bark extract which is going to be different than the root bark extract I would assume.

DR. ROSS: The other thing I bring up here on the oral toxicity/acute toxicity we'd be discussing is that you look at the root extract, for example, there's very few other uses where there's potential for incidental -- easy for you to say -- incidental ingestion and I think there was two of 213 may be incidentally ingested and those two uses didn't have any reported concentrations. Maybe that's enough. Maybe we need oral toxicity there. Maybe we don't.

But right now, certainly, we need some dermal tox data.

DR. COHEN: We're asking for that across the board, no?

DR. ROSS: Yeah.

DR. COHEN: Although --

DR. BERGFELD: We have that, we have the animal study in there --

DR. COHEN: We have --

DR. BERGFELD: -- and they have limited human, I think. One of them, I think it's on the bark. Yeah. A root extract for human. Twenty subjects for --

DR. COHEN: Are we talking about irritation.

DR. BERGFELD: Irritation.

DR. COHEN: Yeah, we have irritation/sensitization in humans.

DR. BERGFELD: And then humans is 0.5 percent on the root.

DR. COHEN: Which is at max use.

DR. BERGFELD: Yes. And no adverse reactions. I'm not seeing the number of patients -- 106 patients.

DR. COHEN: So, are we -- probably okay not needing that, right?

DR. BERGFELD: That's right.

DR. COHEN: So, I'll go except root extract.

DR. ROSS: Except root extract. Correct.

DR. BERGFELD: Yep.

DR. ROSS: Is anyone comfortable with the new genotoxicity at all in any of these compounds?

DR. BERGFELD: Did they have carcinogenicity? I'm just taking a look at it again.

DR. ROSS: They had some in vitro according to this.

DR. BERGFELD: In vitro, no geno, and they had DART, I think.

DR. ROSS: Seed oil DART.

DR. BERGFELD: And they had some DART.

DR. ROSS: Seed oil.

DR. BERGFELD: Seed oil.

DR. COHEN: Seed oil's going to be very --

DR. BERGFELD: And bark.

DR. COHEN: -- different than the rest of this.

DR. ROSS: Seed oil's probably the outlier, isn't it?

DR. COHEN: So, do we want the --

DR. TILTON: Yeah. I mean, I guess I had made note of potential in vitro genotox.

DR. ROSS: Yeah. I think you should have it.

DR. TILTON: Yeah.

DR. BERGFELD: On all of them?

DR. TILTON: Oral is available, especially as we start to learn more about the relationship between the --

DR. COHEN: Just because it's not causing -- well, we don't know if it's absorbed. We don't know what's absorbed.

DR. ROSS: You won't get absorption.

DR. COHEN: No. So how is this going to be genotoxic?

DR. ROSS: Well, it's got lots of phenolics and all oxidizable.

DR. COHEN: So, you want genotox on this?

DR. ROSS: I think it would be advisable to have but --

DR. COHEN: Okay.

DR. ROSS: I mean. The other thing I think we do need is an ocular tox endpoint. Some ocular tox endpoint whether it be (inaudible) some of the things we heard about this morning for all the substances used around the eye at max concentrations. Plus, we need the ocular concentrations of use, I think, from my read of it and correct me if I'm wrong, I don't think we had ocular concentrations of use. Which is not unusual at least. No, we didn't.

DR. BERGFELD: No, we didn't.

DR. COHEN: Okay.

DR. ROSS: So, we need some new in vitro method to look at ocular toxicity and also ocular concentrations of use for all products used around the eye.

DR. COHEN: I put that down. I'm just looking back at the use table.

MS. RAJ: So, will it still be listed as ocular irritation if available? That's what was done in the past or will that change?

DR. ROSS: I think it should change, I mean, given what we heard this morning. I mean, these tests take (inaudible) than 72 hours.

DR. COHEN: Yeah, we'll take something.

DR. TILTON: I guess we can make it clear that it doesn't have to be in vivo.

DR. ROSS: That sort of terminology relegates ocular concerns, though.

MS. FIUME: Irritation?

DR. ROSS: Yeah, but that ocular if available, you know, it relegates ocular concerns to sort of (inaudible).

DR. COHEN: Yeah, but --

MS. FIUME: It wasn't that. It was that you want (inaudible) had only animal ocular tests so that's why it was if available. We're asking people to go out and do tests on animals for ocular irritation.

DR. ROSS: I see.

DR. COHEN: Yeah, I don't think we should -- if you want something we shouldn't say if available --

MS. FIUME: It was only the ocular --

DR. COHEN: -- because -- I understand, this was a Draize test.

DR. ROSS: So, now we have NAMs.

MS. FIUME: So, you did say ocular irritation? Okay. I just wanted to make the clarification --

DR. COHEN: That's a good point.

MS. FIUME: -- that is what we normally do versus what --

DR. ROSS: Well, thank you. That helps me.

DR. COHEN: It's a complete legit point.

DR. ROSS: It wasn't that. Okay.

MS. FIUME: It wasn't that it wasn't necessary, it was because of the severity of the test.

DR. ROSS: That helps me a lot. Thank you.

DR. COHEN: Any other IDA points for paeonia?

MS. FIUME: So, David, I think you were talking about the root bark extract, not being sure what it is and it's not in the dictionary, so if you want, the Panel can request for clarification of our definition as to what it is and why or how it's manufactured. You know, whatever information you need about it as a cosmetic since you don't have it. The Panel's done that in the past.

DR. TILTON: Yeah. Some clarification would be good so that we can interpret the data that we have.

DR. COHEN: I don't know what cortex moutan powder is.

DR. BERGFELD: It must not be the bark. Cortex is the inner part of the root stem.

MS. RAJ: In some studies, it actually says that's the root bark and, in some studies, it may not state it explicitly so that's why we have this.

DR. COHEN: I'm trying to figure out how to ask the question. What I'd like to know is root extract -- does root extract include the root bark?

MS. FIUME: So, do you want definition, composition, and method of manufacture for that?

DR. COHEN: But we have method of manufacturing in here for it.

MS. FIUME: But non-cosmetic specific, though, right? So, it's in the studies. It wasn't specific to a cosmetic. That was for a study.

DR. COHEN: Are all the other ones for cosmetics?

MS. FIUME: Generally, not. That's why we always sate their -- it's unknown how they're applied to cosmetic ingredient manufacturing, but I just didn't know for this one because the moutan extracts sometimes it's not the genus species that is included in this report and since there's no definition of it either, I didn't know if that's important for --

DR. COHEN: No, it's important for us to sort of help clear it for the future reports. So, help me with the question.

MS. FIUME: So, do you want to say this definition, composition, and method of manufacture of this ingredient as used in cosmetic formulations?

DR. COHEN: For the root bark extract?

MS. FIUME: Mm-hmm.

DR. ROSS: You want to know specifically, David, whether the root extract and the root bark extract -- this tree peony material -- whether they contain similar constituents, or one comes from the other or one can be included in the other?

DR. COHEN: Yeah. Right. So, the definition, method of manufacturing, composition for the root bark extract for cosmetic use, right, that's one part because it's not in the dictionary. And two, does root extract include the root bark?

DR. TILTON: And that's my question.

DR. ROSS: The other issue, even if we get answers to all these questions, we have no reported concentrations of use for, you know, apart from the root extract which is the one that has the most uses and the seed oil. So, we have no reported concentrations of use for the bark extract. The suffruticosa extract itself.

DR. COHEN: That's the whole plant.

DR. ROSS: Yeah. So, we've got nothing. So even if we got a definition of what these things contain, there's really no way to assess the toxicity because you don't have the concentration.

DR. COHEN: So, we need concentration of use.

DR. ROSS: Yes.

DR. COHEN: That's another.

DR. ROSS: Yeah.

MS. FIUME: The survey was just conducted in 2024 and there was no reported concentrations for those ingredients where it says NR at the table.

DR. COHEN: Yeah, there's uses.

DR. ROSS: So, meaning that we're unlikely to get --

MS. FIUME: Because they just --

DR. ROSS: Just did it.

MS. FIUME: -- did that survey and none were reported.

DR. COHEN: Right. Remember the email we sent two weeks ago. Can you send the concentrations of use --

MS. FIUME: Yeah, because I think it's actually that says collected in 2022. Preethi, did we receive more current -- am I misreading the use section?

MS. RAJ: No. I mean, I think this is the most up to date. It may have been -- oh, it was updated in 2024. See at the bottom, there's a footnote.

DR. COHEN: Concentration of use survey conducted in 2024.

MS. RAJ: Yeah, because they updated the maximum concentration of use.

MS. FIUME: Okay.

MS. RAJ: Yeah.

MS. FIUME: So, the true complete study was done in 2022. In 2024 someone updated a concentration. So, it is two years old because it was prepared in July of 2022.

DR. COHEN: So, we can ask for it.

MS. FIUME: Mm-hmm.

DR. BERGFELD: You do have some -- I'm not sure where you would find this -- after the references, you do have some concentrations presented to us from the FDA on the root extract and it's really quite low; 0.00009 percent -- 0.002.

DR. COHEN: The root extract we have, and we have sensitization at max use, right? The issue is the root extract is going to be very different than the bark extract, the plant extract, the seed oil, and the root bark extract. So, with that concentration of use we may not be able to clear these at all.

DR. BERGFELD: Right. So, you're going to ask for those specifically. The seed and the bark, and the whole plant, I think.

DR. COHEN: We have seed oil.

DR. ROSS: I wanted a clarification of the seed oil constituents. (Inaudible) came from PCPC, I think. I think there's one study where very high fatty acid content. Whereas the other one only mentioned flavonoids, phenolics, stilbenoids, terpenes.

DR. COHEN: So, what else did you need?

DR. ROSS: All the usual suspects. I wanted to know -- those things seem contradictory, those studies. Maybe you can help.

MS. RAJ: Yeah. There may be an opportunity to clarify that now that we have Thushara on board because he's an expert in these kind of things so he said he might help me clarify some things.

DR. ROSS: That'd be great if you could help me out with that.

MS. RAJ: Sure.

DR. ROSS: That'd be good.

DR. COHEN: So, what are we going to ask for though?

DR. ROSS: Well, a clarification, okay, where it comes from, of what's in this seed oil extract.

MS. FIUME: Yeah, because these are from general published papers, not -- sometimes we get it from a supplier, but the only supplier information seems to be for the root extract.

DR. ROSS: I mean, it might be that these two studies are not contradictory, and they actually agree with each other. But it's not clear from what we've got in there that that's the case.

DR. COHEN: Because the constituent verbiage is different than the table, right, or it seems different.

MS. RAJ: Well, if I recall, that comment was talking about seed oil being a fixed oil, right, Dr. Ross?

DR. ROSS: Right. Yeah. But I think it's on PDF 14 --

DR. COHEN: In composition and impurities, right?

DR. ROSS: Yeah. Paragraph which says the plant polyphenols identified. That's how the paragraph starts.

DR. COHEN: Yeah.

DR. ROSS: Well, actually, it's probably not contradictory. The plant polyphenols identified in seed oil were phenolics, flavonoids stilbenoids, monoterpenes, and phenol and steroids. In another composition analysis seed oil is seed oil, fatty acids accounted for 98 percent of the total weight. And I think PCPC made this comment that maybe the rest of the stuff was in the 1.6 percent that was left.

DR. COHEN: You mean, those are the stilbenoids?

DR. ROSS: Yeah. Flavonoid stilbenoids, terpenes. So, most of it is possible. So maybe it's not contradictory, we just need a clarification.

DR. COHEN: We can ask. We can ask for clarification.

DR. ROSS: Yeah.

MS. RAJ: So, is this clarification on a specific composition?

DR. COHEN: Clarification on constituents of the seed oil.

MS. RAJ: Okay.

DR. ROSS: Yeah.

DR. COHEN: I got a lot in this IDA.

DR. ROSS: You can read those back.

DR. COHEN: Okay, you ready?

DR. ROSS: Yeah.

DR. COHEN: All right. Dermal tox --

DR. BERGFELD: On everything.

DR. COHEN: -- on everything. I have irritation and sensitization on all except the root extract. Genotox on everything. Ocular tox at max use but we need the ocular concentration. Definition, method of manufacturing, and composition of root bark extract for cosmetic use. Clarification does the root extract include root bark.

DR. BERGFELD: Did you have concentrations of use anywhere?

DR. COHEN: Next is concentrations of use for all but seed oil and root bark. And seven, clarification of constituents of the seed oil.

MS. FIUME: David, can I clarify, you said ocular tox? It's generally ocular irritation.

DR. COHEN: It's kind of in my head was the same thing but, yes, you're right.

MS. RAJ: And for genotox did you ask for in vitro?

DR. ROSS: It'd be in vitro, yeah.

DR. COHEN: I didn't, but I can ask for that.

DR. ROSS: I mean, in vivo is always better, but in vitro is a lot simpler.

DR. COHEN: I was just going to leave it as genotox and see what we get.

DR. ROSS: Can I just ask for my edification here, is this correct that the incidental ingestion of these things would be minimal, right? If you look at the root extract which has got 213 uses in Table 3. The incidental ingestion is only two uses, so.

MS. FIUME: For the?

DR. ROSS: The PS root extract. That's the third column across. The one with the majority of uses.

MS. FIUME: Yeah. So it would be, I'm guessing (inaudible).

DR. ROSS: Where do those come from?

MS. FIUME: With the categories or the VCRP?

DR. ROSS: I was hung up on that. With all those uses there's only two out of 213 where you could possibly ingest it.

MS. FIUME: So, the ingestion would be if it's a mouthwash, if it's a lipstick, if it's --

DR. ROSS: Yeah.

DR. COHEN: It's apparently used as a fragrance. I wonder if RIFM --

DR. BERGFELD: It's also used as a medication in China.

DR. COHEN: Yeah. I wonder if RIFM looked at it.

DR. BERGFELD: What?

DR. COHEN: I wonder if RIFM looked at it.

DR. BERGFELD: Interesting.

MS. RAJ: Meaning the other oral hygiene? Other oral hygiene. I see two.

MS. FIUME: Oh, okay. Yeah, it would be the other oral hygiene. Yep.

DR. ROSS: So, what does that mean?

MS. FIUME: That it might be --

DR. ROSS: Mouthwash?

MS. FIUME: -- used in something that could be mouth spray. Yeah, could be something. But the focus was on the oral part so trying to (inaudible) under there.

DR. ROSS: So, the fact that it's only two of 213, that -- obvious the need for a lot of the acute oral toxicity and that's --

DR. COHEN: We can't buy this stuff. It seems to me a want to eat.

DR. ROSS: Oh, really.

DR. COHEN: We just don't know exactly what it is but there's a large number of available --

DR. ROSS: In that case --

DR. BERGFELD: Chinese medicine. People do buy that.

DR. ROSS: -- do you need oral toxicity as well? We haven't asked for that.

DR. BERGFELD: There is oral for some of them.

DR. ROSS: That's what I was trying to get at.

DR. TILTON: Yeah, I mean, I was, I guess, concerned about oral. We have some of that data. There's some --

DR. ROSS: I wasn't that concerned. It was minimal number of uses.

DR. BERGFELD: So, I did the safe.

DR. TILTON: That's right.

DR. BERGFELD: Sort of sponged it.

MS. FIUME: Add to the composition, it says according to the Chinese government, there's a greater than 30 percent in α-linolenic acid in the single roll.

DR. ROSS: Yeah, I saw that. Yeah. That's a long laundry list, Dr. Cohen.

DR. COHEN: It is.

DR. TILTON: And were you all okay with the PCPC comments?

DR. COHEN: Wait a minute.

DR. ROSS: Which one specifically?

MS. RAJ: I have one correction for the dose per area calculation. It's actually 258.33 micrograms of that (inaudible) per centimeter squared as opposed to the 0.64 that was quoted in the comments. I confirmed this with Carol, so.

DR. ROSS: This one's for cytotoxicity, no? Or --

MS. FIUME: This was in the Wave 2 comments.

DR. COHEN: Is this for the sensitization?

MS. RAJ: No. This was for a dose per area calculations.

MS. FIUME: For sensitization.

DR. COHEN: Yeah. For the pa- -- yeah. Oh, boy.

MS. FIUME: They would like that for us when all the information's available to calculate the dose per unit area.

DR. COHEN: I know they like that.

DR. BERGFELD: Why us? Why us?

DR. COHEN: What's that?

DR. BERGFELD: Why us? Why don't they do it?

DR. COHEN: Well, and the other thing is unless you know for sure. So, since there's enough information to calculate but let me just look back on that. Hold on.

DR. ROSS: I'm just looking -- it's in the Wave 2.

DR. COHEN: Where's the report on how they did it?

MS. RAJ: Well, I can provide the calculation.

DR. COHEN: It's here, right? This?

MS. RAJ: Yes, I think that's the one.

DR. ROSS: Which page is it, David? Supplement data?

DR. COHEN: It's at the end. It's the patch test report.

DR. ROSS: Oh.

DR. COHEN: And I went right to the graph with the numbers. I'm looking at a lot of zeros which is good. But the methodology has it -- should be in here somewhere.

DR. TILTON: Well, you won't find the calculations there if we just used information to do it.

DR. COHEN: It says approximately 0.2 grams of test material. Now having put hundreds of these on a week, we approximately put this amount on with probably an error range of this much. You know what I mean? Here's your means and here's your standard error. You're putting -- you're not weighing it. You're just putting a bit on. So, I don't know if there's enough data on here to create that calculation, right. This is boilerplate methodology. So, I don't think so.

We can talk about it with Don tomorrow maybe, if you remember to bring it up. But this, to me, is an approximate amount that's going in a chamber on visual inspection. You're going like this or you're scooping a little in.

MS. RAJ: Thank you. I'll definitely bring it up because I believe this is something Council has been kind of asking for.

DR. COHEN: If it said 0.2 microliters were pipeted in, that's a whole other story. But doing these tests on a regular basis, it's very rough. I don't know if I'd go ahead and do that calculation. We'll see. Sometimes we pipet things in. Okay, are we done with peonies? That'll be a nice discussion.

Full Panel – June 4, 2024

DR. BELSITO: Okay, so this is another ingredient that it's the first time the Panel is seeing the safety assessment on five cosmetic ingredients. Scientific literature was announced in -- review was announced in March 19, 2024. We are told that there is a material that has uses that is the Root Bark Extract that's not in the INCI Dictionary that we will be bringing into this report.

We looked at all of the information that we did receive here, which was a good amount, but we felt that it was still insufficient for composition of all except the Seed Oil; impurities for all except the Root Extract; 28-day dermal and if absorbed additional DART, genotox, Ames and mammalian would be needed. And at this point the respiratory boilerplate would be the botanical boilerplate in terms of pesticides and heavy metals. There is no evidence that we need a sensitization component to that botanical boilerplate. And just the discussion of the effect on tyrosinase and the fact we'd expect not to have an effect on skin pigmentation from a cosmetic, but still insufficient.

DR. COHEN: Yeah, before I seconded it we can go through some of our IDA; I think they're lining up. And, just as a matter of question. You don't want a sensitization because we're going to go out with a botanical boilerplate for sensitization?

DR. BELSITO: No, we're not.

DR. COHEN: So, why don't you want irritation and sensitization? I thought I heard you say you didn't want that.

DR. SNYDER: We got irritation data.

DR. BELSITO: I don't want the irritation sensitization boilerplate because there are no components of it at this point that seem to be sensitizers. We have a facemask formulation 0.5 percent with an HRIPT in 106 subjects that was negative.

DR. COHEN: That's just from the Root Extract. That's not whole plant, Seed Oil. So why don't we go through our IDA.

DR. BELSITO: Okay.

DR. COHEN: You mentioned the dermal tox already. We had irritation sensitization on all of them except Root Extract. Of course if we have the whole plant that would do the job for us. Genotox, we had ocular irritation at max use, but we need ocular concentrations, definition, method of manufacturing and composition for the Root Bark Extract for cosmetic use. It looked like we didn't have that last one for cosmetic use. We had a question. Does the Root Extract include Root Bark, so we can put them together? We needed concentration of use for all but the Seed and the Root Bark. We need clarification of the constituents of the Seed Oil. And, it was a question to you, Don. I saw somewhere this may be used as a fragrance. Do you know if RIFM has looked at this?

DR. BELSITO: We have not.

DR. COHEN: Okay. So, those are our additional IDAs; it's early in the course.

DR. BELSITO: Fine.

DR. COHEN: Okay. You want me to -- so, you already covered dermal tox. We wanted irritation and sensitization for everything except the Root Extract, genotox, ocular irritation and we needed the ocular concentration of use. We needed further definition, method of manufacturing, composition for the Root Bark Extract for cosmetic use because I don't think we have that. Does the Root Extract include Root Bark? We need concentration of use for all but Seed Oil and Root Bark, and clarification of the constituents of the Seed Oil. That's it.

DR. BELSITO: Well, we're not going to -- I mean, we have the definition of Root Extract, and it doesn't include Bark. It says the extract of the roots.

DR. COHEN: I know. I think when you read it, but -- you're right.

DR. BELSITO: So how are we going to get any further clarification than the dictionary?

DR. COHEN: Maybe one of the manufacturers can clarify that when they're using the root it's not de-barked. You know, is the root peeled, or --

DR. BELSITO: I mean, it's early, we can ask. But I think that you're probably not going to get it. I think we should assume that the Root Extract is the extract of the root without any bark on it.

DR. COHEN: Without any bark on it. Right, but the root, by the term root, might have bark on it.

DR. BELSITO: There is a new category, Root Bark.

DR. COHEN: Extract. Well, it's the same idea, Don, when we're saying if we have a whole plant we can sweep along the rest with a whole plant. So, can we sweep along Root Bark Extract -- although we have the -- can we bring Root in with the Root Bark Extract? I'm not sure; I think I just messed that up when I said it.

DR. BELSITO: I think Root Bark Extract is the extract of the bark. And Root Bark is that bark that develops just as the root is coming out of the ground. Probably is very similar to the rest of the bark on the plant.

DR. COHEN: I think we could just ask does Root Extract include bark or not. And if we don't get an answer, we don't get an answer, but if we do it might make it a little easier.

DR. BELSITO: Okay.

DR. BERGFELD: Okay, so have you seconded it?

DR. COHEN: I seconded it and added to it.

DR. BELSITO: Added to my IDA.

DR. COHEN: And, you're okay with it?

DR. BELSITO: Yeah.

DR. COHEN: Don was okay with the amended.

MS. RAJ: To clarify. Did you want the like 28-day dermal tox on everything, and (inaudible), or?

DR. BELSITO: How much composition do we have here?

DR. COHEN: Dermal tox.

DR. ROSS: I don't think we had any dermal tox at all on any of these ingredients. I think we said we preferred 28-day dermal tox, but if there was some acute dermal tox, but we prefer 28-day dermal.

DR. COHEN: Yes.

DR. BERGFELD: Do you have the expand on what we need then?

MS. RAJ: Want me to read it?

DR. BERGFELD: Sure.

MS. RAJ: So, clarification on the Root Bark Extract completed; include the definition at the manufacturer and composition of this ingredient as used in cosmetics. Additional question, does the Root Extract includes the Root Bark? Clarification on constituents of Seed Oil, concentrations of use for the Bark Extract, the (inaudible) and the Root Extract, 28-day dermal tox on everything based on whether they're absorbed we need DART, dermal irritation and sensitization on all ingredients except the Root Extract, genotox for all ingredients, and ocular irritation at maximum, composition of use for all ingredients used in the eye as well as concentration use data.

DR. BERGFELD: All right, agreeable?

DR. BELSITO: So the composition you want just on the Seed Oil? Because we thought we wanted composition on all except the Seed Oil.

DR. ROSS: I'm fine they're getting composition on all of them. The only issue with the Seed Oil, and it may be explained in the document. I think it was raised by PCPC. There were a couple of studies; one said it was very, very high in fatty acids 90 percent or so. And then the other studies said it was (inaudible), flavanols, etcetera, etcetera. So, may be that comes from the residual 10 percent. So maybe it is self-explanatory in that, but we just wanted some clarification that that was the case. You know, one study it was all fatty acid, the other study was just referring to the potential sensitizing compounds.

DR. COHEN: It's the verbiage and then there's the table.

DR. EISENMANN: The dictionary defines it as a fixed oil, not an essential oil. So, I just wasn't sure the -- if somebody is making essential oil; I don't know. But the dictionary it is a fixed oil. So, I wasn't sure what the other data, if it was the little bit left in the fixed oil or if somebody was actually making an essential oil. And if that's the case, it's not the ingredient that is in the dictionary.

DR. ROSS: Yeah, so we just wanted some clarification of that.

DR. BELSITO: So then essentially all.

DR. COHEN: Okay.

DR. BERGFELD: Okay. Go ahead.

MS. RAJ: I have one question for the -- one of the PCPC comments on including the dose per area calculation. I had a correction on the number from Carol, but there were some discrepancies with (inaudible).

DR. COHEN: Yeah, so my concern was when you look at that HRIPT report, it's a boilerplate description of the patch test. And it says approximately 0.2 grams are applied to the chamber. Having done this a million times, and Don two million times, it's very rough estimate. I got no impression from this report that they're weighing out this material. But rather they're putting an amount that fills the chamber adequately and that's it. And so you have a mean here, and you have a standard area this big on it, unless they're aliquoting with a pipette or they're weighing the materials these tests, the way they're described, I don't think give you that much comfort that you get certitude on the dose per unit area in these patch tests. That's just my take on it from the street.

DR. RETTIE: What's the volume of the container?

DR. COHEN: It depends if they're using an eight millimeter chamber or a larger one. But they said they used approximately 0.2 grams. If you're not weighing it, what is -- the 0.2 grams you're going to have a lot of leeway on putting that into a chamber. If you really want dose per unit area, you have to either weigh it or aliquot the liquid.

DR. RETTIE: I don't disagree. I was just trying to get a sense of how that was done since I don't do it.

DR. COHEN: I think what it's doing is it's creating the sensation or the feeling of having controlled information, but the source is not that controlled.

DR. BELSITO: It is actually, I mean, this was an HRIPT on epiderm skin.

DR. COHEN: Yup.

DR. BELSITO: It was performed according to OECD test guidelines 439. These would be measured out. It's very different from what you and I do in a patch test clinic where our MA or assistant puts a little ribbon across an eight millimeter fin chamber.

DR. COHEN: But, it says approximately 0.2 grams of the test material or an amount sufficient to cover the contact surface was applied to the 0.6 square inch absorbent pad portion of the adhesive dressing. Like, to me, that's like what we do in the clinic. There are going to be reports we see where there weighed in aliquot. When you have 0.2, or amount sufficient to cover, that's it.

DR. EISENMANN: And frequently they just use the same language from HIRPT.

DR. COHEN: I know.

DR. EISENMANN: So, it may not actually reflect what they did. We'd like to see the dosage at -- I mean, we understand it's not -- no dose is ever. And even Allan said it, those dosages aren't exact. And that's why Dr. Klaassen always is concerned about rounding. He rather see fewer significant digits because you're not measuring anything exact. We'd also like to see some measure of dose per unit area in the report.

DR. COHEN: I agree.

DR. EISENMANN: Having Paul's information, plus the calculation, we think is helpful. And we understand that it's more of a ballpark area of a dose rather than exact.

DR. COHEN: This could be off by two and three times. I think, if you want that, and I don't disagree we should have that, then the methodology needs to be described in greater detail. But I don't think you can go back and look at these and have any sense of certitude on how much material went in there. It's just 0.2, or amount sufficient to cover contact surface, which could be twice as much or half as much. Depending on the viscosity of the product, depending on if it's waxy, if it's liquid; it's just going to go all over the place. So, I appreciate it. I don't think this report is the one to dig our flagpole in. That's all. That's just my take on filling fin chambers.

DR. BERGFELD: So what is the consensus, the amount per unit? You can't do it on this one.

DR. COHEN: You just can't do it on this one. I think if we want to go forward, it's just like the evolution of the tools we're using here, going forward we need to have industry discuss with their testing groups can you be more precise on how much goes in the chamber. And then from then on we could start measuring a dose per unit area.

DR. BERGFELD: Okay. Don?

MR. BJERKE: I Think, you're right, or to cover the patch just really kind of catch all. For (inaudible) you need certain tasks for something's not easily (inaudible). I'd say the vast majority of the HIRPTs that I've seen and they actually (inaudible), it's a liquid. It's, you know --

DR. COHEN: Perfect.

MR. BJERKE: There's variability to everything (inaudible). So it gives a good estimate of the dose per unit area. I think if you have something that's (inaudible) are not easily (inaudible), then usually there's a comment in the report that they did something different because of those (inaudible) properties.

But I think, in a case like this you may want to look and say what was the composition of the test material that was being administered, and if it's something that you've got confidence in for liquid it's probably (inaudible). I think that's the standard.

DR. COHEN: And feedback, the methodology shouldn't be a cut and paste to every report. You know what I mean? I'm not saying -- that was a strong suggesting that that occurs all the time.

MR. BJERKE: Yeah.

DR. COHEN: But, this seemed boilerplate this methodology.

MR. BJERKE: The protocols are kind of written in boilerplate.

DR. COHEN: Yeah.

MR. BJERKE: I agree completely. I can understand and appreciate your perspective.

DR. BERGFELD: So, anything else to discuss? I'm going to call the question.

DR. COHEN: Yeah.

DR. BERGFELD: I'm going to call the question. All those in favor please raise your hand.

DR. SNYDER: I concur.

DR. BERGFELD: Thank you, unanimous.

DECEMBER 2024 PANEL MEETING – SECOND REVIEW, DRAFT TENTATIVE REPORT

Belsito Team Meeting - December 2, 2024

DR. BELSITO: Paeonia suffruticosa. This was another we got a Wave 2 from PCPC that I agreed with. Okay. So, at the June 2024 meeting we determined the data were insufficient to support safety of the ingredients. The additional data for the root bark extract clarification on definition, on method of manufacture, composition, as applicable to cosmetic use. Clarification to whether the root extract included root bark of the plant.

For the seed oil, clarification of the ingredient constituents. For the bark extract, the extract of the whole plant, the root extract concentration of use, ocular irritation and reported maximum use concentration around the eye. For all ingredients, 28-day dermal tox, if positive, data on systemic tox endpoints such as DART.

Also, genotoxicity is a separate requirement for all ingredients and all ingredients except the root extract dermal irritation and sensitization and concentration of use. We did receive a human repeat-insult patch test on a lotion containing 0.0015 percent of the root extract but that was not one of our data needs.

And none of the other information that we asked for did we get back, so I was of the opinion that we're insufficient with the same data needs as previously described.

DR. SNYDER: I agree.

DR. RETTIE: Did we conclude that the root extract is okay? I had a note that that was okay.

DR. BELSITO: But we wanted a 28-day dermal tox for all ingredients.

DR. RETTIE: Oh, including that. Okay.

DR. BELSITO: And even for the root extract, we wanted concentration of use and ocular irritation at maximum concentration of use. So, we got none of that.

DR. RETTIE: Yep.

DR. EISENMANN: What I want you to consider though is the data on the seed oil. It's a fixed oil and it's 98.46 percent fatty acids, 89 percent which are unsaturated, and there are 30 day and 90 day oral studies on it. I admit there's no dermal studies but based on composition you might consider that one or at least changing the data needs because I'm not sure why -- with an oral study I'm not sure -- negative oral studies why you need additional systemic toxicity data.

DR. BELSITO: Well, we had for the seed oil clarification of ingredient constituents. And now I don't recall what specifically that was.

DR. SNYDER: I think, at this stage, we can just ask for all of this. Continue to ask for this because it's, yeah. I'm still fine with insufficient for all the data needs.

DR. BELSITO: Yeah, I think what that was about, you know, clarification of constituents. It says a nutritional study in Paeonia seeds indicated the presence of crude oil at 34.35 percent. So, I guess we maybe we misinterpreted this. So, reading this again, the Paeonia seed -- about a third of the seed is crude oil, right, and compositional analysis of the seed oil, fatty acids were 98.5 percent of the total weight. Interestingly, 89.3 of this was composed of unsaturated fatty acids.

And we have -- and you're right, we have this oral stuff, and we've reviewed the safety of fatty acids and the seed oil. What is the concentration of use of the seed oil? Root extract. Root extract.

DR. HELDRETH: 0.0025 percent.

DR. BELSITO: Yeah. I mean, I think given the composition of the oral studies and the concentration of use, we probably can go safe with the seed oil. Paul, Curt, Allan?

DR. KLAASSEN: I agree.

DR. SNYDER: Yeah, at that level -- I didn't realize it was that low of level of use. I'm okay with that.

DR. RETTIE: I agree.

DR. BELSITO: So, in the discussion for the seed oil we can point out that negative 90-day oral composition, low volume of use, supports the safety. Okay, so the seed oil is fine but all the others we're continuing with our list. We don't have dermal irritation/sensitization data, but again I don't think we need it given the concentration of use and the composition. Okay. Anything else on this ingredient group? Okay.

Cohen Team Meeting - December 2, 2024

DR. COHEN: We're going to lead off with two botanicals so we'll need each other's help on this. So we're ready, Paeonia Suffruticosa. This is a draft-tentative report. The 2023, VCRP survey data for root extract reported 213 uses, 173 were leave-on, the RLD showed 736 formulations, something I think we're going to get used to seeing, big differences.

In June, we had an insufficient -- an IDA with a number of requests. We had for root bark, clarification on the definition, method of manufacturing, composition as applicable for cosmetic use, clarification if the root extract included root bark. For the seed oil, clarification of the ingredient constituents. For the bark extract, extract and root extract, max use concentration, ocular irritation. And for all ingredients, 28-day dermal tox and, if positive, further information as well as for all ingredients, except root extract, irritation and sensitization. Since the IDA, we received HRIPT on .0015 for root extract.

So, we've had that additional data. Just wanted to make one comment. We've been going back and forth, I think with the Council, on the detailed nature of the HRIPTs. And that perhaps they're not like clinical patch testing, but they rise to a level of much higher scientific rigor regarding the measuring of product. And I just wanted to point out in this one where we're specifically indicating how much went into these HRIPTS. And I personally think there's a little bit of a push back of this conversation where it says, "Patches contained approximately 25 to 38 milligrams per centimeter squared of test material. That's a 50 plus percent range. That is not specific. That is not scientifically rigorous, right?
So I'm pushing back again that unless I see specificity of what goes in there, I hardly think these HRIPTs are any -- I hardly think they're very different than a lot of the patch tests that are being put on. Unless it was a very specific -- that's a giant range.

So, why don't we open it up to the group and just reevaluate the needs on this because it didn't seem like we got a lot. David, thoughts?

DR. ROSS: Yeah, my thoughts on this, David -- that's two Davids and two Cohens. Yeah, this is really going to be interesting.

DR. COHEN: Makes it easy -- we're going to need, like, nickname from Brooklyn, like, you know, Lefty and Stretch.

DR. ROSS: Classic. Classic stuff. Yeah, well on this one, getting back to business, we did get something but it didn't really add anything to what we already had.

For me, I didn't see any change in the IDA requests for me. So it would be exactly the same for me. I thought it was incomplete, same deficiencies as last time, and that's where I left it.

DR. COHEN: Because the additional material was on the root, and it was the one thing we didn't need additional material on.

DR. ROSS: Exactly. Exactly.

DR. BERGFELD: Could I ask a question? I was confused about the discussion about bark and root. And in and some of the minutes, it stated that they were the same. Is that correct?

DR. COHEN: I think the conversation went, in the root extract, did that include the bark of the root or was it peeled or debarked? Right? Because could we bring in bark if we have root material?

DR. BERGFELD: That's the question, if that's true.

DR. COHEN: Yeah, we didn't know.

DR. TILTON: We didn't know and it's not specifically listed in the constituents table.

DR. DIYABALANAGE: Actually, I can add a few things into this because I took over this project from Priya and went over all the correspondence and then the background of all the history.

I think the issue is that I'm a plant natural products chemist, so I've done it many times in my career. So usually, peeling off bark is very rare, if you are doing a root extract. So, I actually talked to Joanne Nikitakis about the information, whether they have any information about the collection and then the method of manufacture, they don't have anything specific, so it's unclear.
My assumption is, pretty much, when they do the root extraction, it's they extracted the whole thing. They did not peel off the mark.

DR. COHEN: We just don't have -- we don't have it documented though, right? I mean, I know -- yeah.

DR. DIYABALANAGE: No, no, they don't have any documentation.

DR. ROSS: Yeah, yeah, that the point.

DR. TILTON: And even if we were to group them together, we are still missing the 28-day dermal or ocular, so.

DR. ROSS: And genotox, nothing.

DR. COHEN: Yeah, this is a little concerning to me because we're moving this report downfield, and it has a lot of uses, right?

DR. ROSS: Yeah.

DR. COHEN: And so, Monice, what do you think here? I know this one seems to concern me a bit more than some others, where, you know, there's six things, 700 reported uses and we have nothing.

DR. ROSS: Yeah.

MS. FIUME: It's definitely unusual. Because even if we look at the VCRP, which is what you would have been looking at before saying we still didn't get information. It was over 200.

DR. COHEN: Yeah.

MS. FIUME: And I don't. I don't know who's using this ingredient, that if they're not members or why we're not receiving the information. I don't of industry is online and could impart any information as to why they think we're not getting the information. I mean, unfortunately, it's going to have to go forward as an insufficient data conclusion. But that's insufficient data for a good number of uses and a lot of them are dermal contact.

I can't recall not receiving information on something that had this many uses in the past. I'm really not sure why we didn't receive any information.

DR. BERGFELD: There's no one from PCPC to answer that on our team?

MS. FIUME: Kathy, are you online and can you provide any information, or Kim?

MS. STANTON: I am online. Because of the way that things are being reported, I don't know if we can extract any more information than what is already reported.

MS. FIUME: It goes beyond concentration of use, there was also a lot of data needs for these. Nothing like -- you know, irritation and sensitization, genotox, things like that. And we nothing was received.

MS. STANTON: Nothing is received. Yeah.

MS. FIUME: Yeah.

DR. COHEN: This report is going to have a bigger impact on lots of products. I don't know, does it make sense for the Council to just send a more urgent memo about this? The IDA is for the draft report, this is now just insufficient data, right?

DR. BERGFELD: Right.

MS. FIUME: Yeah, it would go out as a tentative report with insufficient data conclusion.

DR. COHEN: Okay.

MS. STANTON: We definitely can send out another request for data, and have it as an urgent request, and have all this information. It's used in a lot of products, at least that's what we're seeing. Is there any member that can give us any more information? And if this goes out -- did you say, Monice, was it a tentative?

MS. FIUME: It should go out as a tentative report, yeah.

MS. STANTON: Okay.

MS. FIUME: And it'll have a 60-day comment period.

MS. STANTON: Yep. And then during that comment period, that's when we can start to see if we can collect any more information.

DR. ROSS: I think the IDA was reasonable from the last time. I don't have your IDA right in front of me, but from what I recall it was no dermal tox. We needed ocular tox, we needed genotox, and we needed dermal irritation and sensitization, particularly on the seed oil at its maximum concentration of use. I think all these things are needed and hopefully they exist somewhere in the archive. The question is finding them.

DR. COHEN: David, of my recollection is that when we went out to the team meeting on Tuesday, there was rather unanimity on what we needed.

DR. ROSS: Yeah.

DR. COHEN: There wasn't one group going as safe as used in another one with an IDA that was an arm long. Which happened sometimes, but it wasn't with this one I don't think.

DR. ROSS: Correct. No, I think we were aligned.

DR. COHEN: Okay.

DR. TILTON: Yeah, there was general agreement. In the data that has been provided, there's not very much that's concerning in terms of oral toxicity, systemic irritation, sensitization data that was provided. But there is just quite a bit of missing information.

DR. COHEN: Okay.

DR. BERGFELD: Are you going to stand with the list that has been put together in the previous meeting of what the needs are?

DR. COHEN: Yeah, it will be interesting if there's any different comments. But we went out with the IDA and now we have an insufficient data conclusion, which was worrying to me.

DR. BERGFELD: Could I ask a question if that's concluded what your action will be? I noted in the draft Discussion, first of all, the list of what is needed is not there.

But there is in the third paragraph the expressed concern about heavy metals, pesticide residues and other plant species may be present in botanical ingredients. And they stressed to minimize impurities in cosmetic formulations according to limits set by the US FDA and EPA. I don't remember seeing EPA before. I don't remember seeing FDA and EPA together that we said something different, something like according to the current standards of manufacturing.

MS. FIUME: That change came as a result of Panel discussions a few years ago, because you're right, Wilma, it had been based on current specifications. But I think the Panel wanted to give a little bit of guidance as to where those specifications are found and they said it was determined that USFDA and EPA is who it should be looked to for those specifications in the United States.

DR. BERGFELD: No, I understand you're focusing on that, but is that now occurring as a boilerplate?

MS. FIUME: Yes, that's probably been for about two years now.

DR. BERGFELD: I don't remember seeing that before. Okay? The other question I have is the developmental reproductive toxicity studies on the bark. Is it possible that any of that study, the bark/root could be part of the toxicology studies that are being requested? It's non embryonic toxin.

DR. ROSS: I think they had -- that was an in vitro study, was it not?

DR. BERGFELD: Yeah, in vitro.

DR. COHEN: I thought we needed 28-day dermal tox.

DR. BERGFELD: I saw you needed that, but how about genotox and carcinogenicity?

DR. ROSS: Genotox we asked for on the previous IDA.

DR. BERGFELD: Yeah.

DR. COHEN: I don't know that if it's non-embryotoxic that's going to cover our needs, right?

DR. BERGFELD: I'm just asking the question as a derm, yeah.

DR. ROSS: No, I don't think it would.

DR. BERGFELD: Okay.

DR. ROSS: I mean, we didn't request more DART data on this one, did we?

DR. BERGFELD: I don't think so.

DR. COHEN: And if positive, data on systemic toxicity endpoints, reproductive toxicity.

DR. ROSS: Oh, I see. Okay.

MS. FIUME: It's typical to provide an example of what types of data that would include.

DR. COHEN: You mean make the IDA more specific? Is that what you mean, or? But we didn't receive anything.

DR. ROSS: I think we'd be lucky.

DR. COHEN: It's not like they didn't hit on some of the points, but not the others. We didn't anything.

DR. ROSS: Yeah, this was a total strikeout. Maybe as Kathy said, going back to others in a more urgent way might get us something, but there are a lot of uses.

DR. COHEN: Yes. And this new reporting data sort of highlights some of the -- but the urgency. But, Monice, you already mentioned that PCRP had a lot of uses.

All right. Listen, I don't think we're going to be able to get anything out of this stone. We'll move. And let's see what happens tomorrow, if there's something new that comes from the other group.

Full Panel - December 3, 2024

DR. COHEN: So this is a draft tentative report on Paeonia Suffruticosa. According to 2023 VCRP data, it's reported that it has many reported uses, which is corroborated by the RLD from 2024. At the June meeting, the Panel determined the data were insufficient to support the safety of these ingredients and additional data requests were extensive. And they were listed in the report. But they included components for the root bark, the seed oil, the bark extract, extract, root extract. We also wanted dermal tox. And we wanted irritation and sensitization for all ingredients except the root extract.

Since the IDA was issued, we received RIPT on .0015 percent root extract, which didn't fulfill any of the IDA needs that we had asked. So our motion is insufficient data conclusion.

DR. BERGFELD: Is that a motion? And a second, Don, or not?

DR. BELSITO: Well, we thought we may be able to go with the seed oil as being safe as used. It's used in a low concentration. The composition is essentially fatty acids and we have a negative 90-day oral on it. But otherwise we would agree with the Cohen team.

DR. BERGFELD: Comment on that, David or Susan?

DR. COHEN: Susan. David, do you have any comment?

I'm trying to look back on what we have on the seed oil.

DR. ROSS: That's exactly where I am. I'm digging around in the dossier right now.

DR. COHEN: Don, was there a reason we didn't clear seed oil last time? Or it was just because the IDA was so large?

DR. BELSITO: I think that that was the case, it was a large IDA.

DR. ROSS: I think it's got a very small number of uses, right? The biggest problem we had with this was that there were a large number of uses on an ingredient we weren't going to clear, the root extract.

DR. TILTON: Right. Our discussion is primarily focused on the root extract.

DR. ROSS: Yeah.

DR. COHEN: We don't have any irritation on the seed oil, but you're clearing it because of composition and impurity?

DR. BELSITO: Yeah. I mean, if you look, it's basically fatty acids and we've already found that the fatty acids are safe as use at very high concentration.

DR. SNYDER: We also have a 90-day oral.

DR. ROSS: The tox wasn't the problem, Paul, I don't think.

DR. BELSITO: On the seed oil.

DR. ROSS: The tox looked pretty good, I think.

DR. TILTON: I would support --

DR. COHEN: Let me just -- so it counted for 98.46 percent of the total weight.

DR. HELDRETH: Yeah, and max use is 0.0025 percent.

DR. COHEN: We're almost there.

DR. BERGFELD: Why, you're thinking if that is so then that would be in a Discussion of why you did that?

DR. COHEN: Yeah. We have to include that. David, any comment?

DR. ROSS: Were there any impurities at all in the seed oil? Maybe Allan can answer that question. I didn't see any in that composition.

DR. COHEN: The IDA has a seed oil request for clarification of ingredient constituents. We have that in the IDA.

DR. DIYABALANAGE: Actually, I can explain it. Because I think what happened was that this was written by a previous writer before. So I took over the project because when I looked at the literature, because there was an initial error that was made.

So when she was listing the composition of the seed, seed composition, she has listed the composition of the seed instead of listing the composition of the seed oil. So when she listed the composition of the seed oil, she included some ingredients, some flavonoids and some secondary metabolites that are commonly present in plants that could be suspicious, hat might be allergens so that could create issues. But the composition of the seed oil is very clear. It does not have any of these material because it was purified and extracted.

DR. COHEN: Okay and the seed oil is --

DR. DIYABALANAGE: It's like a refined material with a high amount of unsaturated fatty acids.

DR. ROSS: It looks like it's all fatty acids, right?

DR. SNYDER: And it's only .0025 percent, so I think we're pretty comfortable.

DR. COHEN: Yeah.

DR. RETTIE: Yeah.

DR. COHEN: So, Wilma, I'd like to amend my motion.

DR. BERGFELD: Thank you.

DR. COHEN: My motion has been amended that we are safe as used for seed oil and insufficient data conclusion for the rest of the ingredients.

DR. BERGFELD: Thank you. Any second, Don?

DR. BELSITO: Second.

DR. BERGFELD: Any other discussion? Obviously, there are editorial changes that will be made. Okay, I'm going to call -- I'm sorry, go ahead.

DR. COHEN: So this is draft tentative, this is going to go final next.

DR. BERGFELD: I know, right?

DR. COHEN: And it has so many uses. It has over 700 uses. The seed oil is the least of the issue.

DR. BELSITO: But that's not our problem.

DR. COHEN: No, I know that. It's just that there's a lot of product out there, right, so. There'll be another opportunity before the final for additional data to come in, correct?

DR. HELDRETH: Yeah. So if you issued this as a tentative report it'll get posted for at least a 60-day comment period. And that'll be the first time that a true insufficient data conclusion was posted out there as a stick or carrot, depending on how you look at it, for those interested to come forward and say, hey, hey, I've got all the safety data that we did in house and help clear those things.

So yeah, they're absolutely more chances. And if stuff comes in when we present the draft final to the Panel, we can always do a revised draft final, you know, back and forth and until we get to a conclusion that everybody's comfortable with.

DR. COHEN: Okay.

DR. BERGFELD: Okay. Any other comments before I call the question? And the motion is okay for seed oil, or safe, and the rest all insufficient with the list that has been generated. Going to call the question. All those that opposed? Abstain? I don’t see anything. This is approved. Okay, thank you.

Safety Assessment of *Paeonia suffruticosa*-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.; Cohen, M. Samuel, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Thomas J. Slaga, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Preethi Raj, M.Sc., former Senior Scientific Analyst/Writer, CIR, and Thushara Diyabalanage, Ph.D., Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

ABTS	2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)
ALP	alkaline phosphatase
CAS	Chemical Abstracts Service
CHL	Chinese hamster lung
CIR	Cosmetic Ingredient Review
CO_2	carbon dioxide
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMEM	Dulbecco's modified Eagle medium
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOPA	dihydroxyphenylalanine
DPPH	2,2'-diphenyl-1-picrylhydrazyl
ECVAM	European Centre for the Validation of Alternative Methods
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GLP	good laboratory practices
GPDAP	glyceraldehyde-3-phosphate dehydrogenase
HFF	human foreskin fibroblasts
HRIPT	human repeated-insult patch test
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonization
IL	interleukin
KFDA	Korea Food and Drug Administration
LAP	leucine amino peptidase
MDM2	mouse double minute 2 homolog
mLIF	murine leukemia inhibitory factor
MoCRA	Modernization of Cosmetics Regulation Act
α-MSH	α-melanocyte stimulating hormone
MTS	3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
OECD	Organisation for Economic Co-operation and Development
p53	tumor protein p53
Panel	Expert Panel for Cosmetic Ingredient Safety
PARP	poly (adenosine diphosphate-ribose) polymerase
PBS	phosphate-buffered saline
Rac1	Ras-related C3 botulinum toxin substrate 1
RCF	relative centrifugal force
RhE	reconstructed human epidermis
RLD	Registration and Listing Data
ROS	reactive oxygen species
RPMI	Roswell Park Memorial Institute
SA-β-gal	senescence-associated β-galactosidase
SLS	sodium lauryl sulfate
STE	short-time exposure
TG	test guideline
TNF-α	tumor necrosis factor alpha
UN GHS	United Nations Global Harmonization System
VCRP	Voluntary Cosmetic Registration Program
VEGFR-3	vascular endothelial growth factor receptor-3

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 5 *Paeonia suffruticosa*-derived ingredients, most of which are reported to function as skin conditioning agents in cosmetic products. The Panel reviewed the available data to determine the safety of these ingredients. Industry should minimize impurities that could be present in cosmetic formulations, such as heavy metals and pesticide residues, according to limits set by the US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA). The Panel concluded that Paeonia Suffruticosa Seed Oil is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the available data are insufficient to make a determination of safety for the other 4 ingredients (i.e., Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, Paeonia Suffruticosa Root Extract and Paeonia Suffruticosa (Tree Peony) Root Bark Extract) under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This assessment reviews the safety of 5 *Paeonia suffruticosa*-derived ingredients as used in cosmetic formulations:

Paeonia Suffruticosa Bark Extract
Paeonia Suffruticosa Extract
Paeonia Suffruticosa Root Extract
Paeonia Suffruticosa Seed Oil
Paeonia Suffruticosa (Tree Peony) Root Bark Extract

Paeonia Suffruticosa (Tree Peony) Root Bark Extract is not included in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*); however, it had reported uses in 2023 in the US FDA Voluntary Cosmetic Registration Program (VCRP) database and thus is included in this review. According to the *Dictionary*, the other 4 ingredients are all reported to function in cosmetics as skin-conditioning agents; Paeonia Suffruticosa Seed Oil is also reported to function as a hair conditioning agent and a skin protectant (Table 1).[1]

Natural complex substances, such as *Paeonia suffruticosa*, may contain hundreds of constituents. Thus, in this assessment, the Expert Panel for Cosmetic Ingredient Safety (Panel) is evaluating the safety of each of the *Paeonia suffruticosa*-derived ingredients as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical ingredients.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted in April 2025. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, without italics. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics will be followed (i.e., *Paeonia suffruticosa*). Often in the published literature, a general name (e.g., *Paeonia suffruticosa* extract) is used. If it is not known whether the substance being discussed is equivalent to the cosmetic ingredient, the test substance will be identified by the name used in the publication that is being cited. However, if it is known that the substance is a cosmetic ingredient, the *Dictionary* nomenclature (e.g., Paeonia Suffruticosa Extract) will be used. For some studies, the genus and species of the test article is not specified and it is referred to by the common name, peony; in these instances the common name is used (e.g., peony seed oil). Additionally, the root bark of *Paeonia suffruticosa* can be referred to as moutan cortex, or cortex moutan, in traditional Chinese medicine. However, this term may not be exclusive to the genus and species being reviewed in this report. Thus, test articles have been presented as described in the literature and data potentially referring to *Paeonia suffruticosa* root bark extract has been placed under the Paeonia Suffruticosa (Tree Peony) Root Bark Extract heading herein.

CHEMISTRY

Definition and Plant Identification

The definitions of 4 of the 5 *Paeonia suffruticosa*-derived ingredients reviewed in this assessment are presented in Table 1.[1] (One ingredient included in this report, Paeonia Suffruticosa (Tree Peony) Root Bark Extract, is not in the *Dictionary*.) Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, Paeonia Suffruticosa Root Extract, and Paeonia Suffruticosa Seed Oil all share the generic CAS No. 223747-88-4.

Generally, the bark is the tough protective covering of the woody stems and roots of trees and other woody perennial plants, consisting of cells produced by a cork cambium.[2] Many secondary metabolites with important biological activities biosynthesized by the plants are also stored in the bark. In woody plants, the cortex is a layer of undifferentiated parenchyma cells located between the outer bark and vascular tissues. The root is the organ of a plant that absorbs and transports water

and nutrients, lacks leaves and nodes, and is usually underground. In the roots of the vascular plants, the cortex occupies a larger volume than in herbaceous stems.

The seed is a propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm, or seed coat; seeds can also result from non-sexual reproduction through apomixis and similar processes. Peony seeds are aggregate, oblong follicles with dense, yellowish-brown bristles that can be obtained after the peony follicles are cracked.[3] Peony seed is comprised of a hard shell and seed kernel.

Paeonia suffruticosa is commonly known as tree peony, moutan, or moutan peony, and has historically been cultivated in China.[4,5] It grows as a shrub, up to 4 m in height, has oval leaves, and its flowers are white, pink, red, or reddish-purple in color.[4] The root extends over 1 m into the ground and is 5 - 12 mm in diameter. The outer surface of the root is grayish or yellowish-brown, and pink when the bark falls off.[5]

Chemical Properties

Paeonia suffruticosa bark extract, *Paeonia suffruticosa* extract, *Paeonia suffruticosa* root bark extract, and *Paeonia suffruticosa* root extract are crude solid extracts, and *Paeonia suffruticosa* seed oil is a liquid.[6-10] Peony seed oil is semi-transparent and orange-yellow in color.[11] According to the *Japanese Standard of Quasi-Drug Ingredients*, Paeonia extract, which is an ethanolic extract of *Paeonia suffruticosa* root bark, is a yellowish-brown liquid.[12] Further data on the chemical properties of the ingredients being reviewed were not found.

Method of Manufacture

Most of the methods below are general to *Paeonia suffruticosa*-derived ingredients, and it is unknown if they apply to cosmetic ingredient manufacturing. In some cases, the definition of the ingredients, as given in the *Dictionary*, provides insight as to the method of manufacture.

Paeonia Suffruticosa Bark Extract

A methanolic *Paeonia suffruticosa* bark extract was prepared using 370 g of dried *Paeonia suffruticosa* bark.[6] The dried bark was pulverized and extracted with methanol under reflux.

Paeonia Suffruticosa Extract

According to a submission from a manufacturer (personal communication), the whole plant parts were dried, sliced and extracted with water and butylene glycol at room temperature. Subsequently, the mixture was filtered with membrane filters and the filtrate was separated.

Paeonia Suffruticosa Root Extract

According to a supplier, Paeonia Suffruticosa Root Extract was produced via extraction of dried raw material with 90 vol% ethanolic solution.[13] This extract was processed further by filtration, concentration, adjustment, sedimentation, secondary filtration and adjustment, prior to packaging.

Paeonia Suffruticosa Seed Oil

A *Paeonia suffruticosa* seed oil was obtained via cold press extraction.[10] *Paeonia suffruticosa* seeds (1000 g) were pressed at room temperature, using a screw press. The expressed liquid was centrifuged at 8000 relative centrifugal force (RCF) for 10 min at 4°C, and the resulting *Paeonia suffruticosa* seed oil was collected and stored.

Paeonia suffruticosa seed oil was also extracted from dried ground seed powder via supercritical carbon dioxide (CO_2) extraction, Soxhlet extraction, and screw press expression methods.[14] For the CO_2 extraction, ground *Paeonia suffruticosa* seeds (100 g) were added to an extraction vessel. Liquid CO_2 was then transferred to the vessel via a high-pressure pump under optimized conditions (24 MPa, at a rate of 21 l/h, at 46 °C for 124 min) screw press expression method is also a method where solvents are not used. *Paeonia suffruticosa* seed powder (1000 g) was fed from the hopper to the screw press on demand by an expeller and the oil was collected at the oil outlet. The oils obtained from each method were separated by centrifuging at 9000 rpm for 10 min and kept at 4°C.

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

According to the *Japanese Standard of Quasi-Drug Ingredients*, Paeonia extract is defined as product obtained from the root bark of *Paeonia suffruticosa* Andrews.[12] The method of manufacture of this *Paeonia suffruticosa* root bark extract, was described as the extraction of root bark with a solution of ethanol.

Composition and Impurities

Phytochemical studies on *Paeonia suffruticosa* showed that flavonoids, tannins, terpenoids, phytosterols, paeonols (a group of phenols), and other phenols as the main constituents.[15] The most important groups of secondary metabolites present in this plant are these phenolic compounds and monoterpenoids glycosides.[5] Among the compounds that are most significant are paeonol (2-hydroxy-4-methoxyacetophenone), paeoniflorin (monoterpenoid glycoside) and 1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucopyranose. The presence of various constituents by *Paeonia suffruticosa* plant part is outlined in Table 2.

Paeonia Suffruticosa Extract

Essential oil obtained from hydro-distilled *Paeonia suffruticosa* flowers was analyzed via gas chromatography-mass spectroscopy.[16] The main constituents in the *Paeonia suffruticosa* flower oil were identified as alkanes, alkenes, terpenes, aliphatic alcohols, aliphatic aldehydes, "benzoids," terpene alcohols, and other oxygenated terpenes.

Paeonia Suffruticosa Root Extract

According to a supplier, Paeonia Suffruticosa Root Extract is composed of tannins, paeonol, and saccharides (amounts not specified).[13] It also contained not more than 20 ppm heavy metals and not more than 2 ppm arsenic.

Paeonia Suffruticosa Seed Oil

A nutritional study on peony seeds indicated the presence of crude oil (34.35%).[18] In another compositional analysis of *Paeonia suffruticosa* seed oil, fatty acids accounted for 98.46% of the total weight. Interestingly, 89.34% of this was comprised of unsaturated fatty acids.[10,18,19] Polyunsaturated fatty acids were found in the following amounts: n-3 α-linolenic acid (38.86%), n-6 linoleic acid (26.74%), and oleic acid (23.74%). The fairly low ratio of n-3 to n-6 fatty acids (0.69), uncommonly higher levels of α-linolenic acid, and much higher levels of γ-tocopherol compared to other conventional seed oils were the unique features observed in peony oil.

These fatty acids form corresponding glycerol esters and are present in the form of 12 triacylglycerol components in peony seed oil.[10] The major triacyclglycerols identified were dilinolyl-linolenoyl-glycerol + dilinolenoly-oleoyl-glycerol (21.69 - 25.89%), dilinolenoly-linoleoyl-glycerol (14.27 - 18.01%), oleoyl-linoleoyl-linolenoly-glycerol (13.33 - 16.03%), dioleoyl-linolenoyl-glycerol + oleoyl-dilinoleoyl-glycerol (14.08 - 16.3%), and trilinolenoyl-glycerol (11.24 - 15%). As is often observed with botanical extracts, the percent yield and resulting phytochemical composition of *Paeonia suffruticosa* seed oil is affected by the utilized solvent and method of extraction.[10,14]

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

Root bark of *Paeonia suffruticosa,* also known as the moutan cortex, is extremely rich in biologically active secondary metabolites.[5,20,21] It has been reported that about 163 compounds have been isolated and characterized from this material.[5] Phenolic compounds and monoterpenoid glycosides have been identified as the major chemical groups present in this extract. Amongst them, the main characteristic compounds were paeonol and its glycosides, such as paeoniside, paeonolide, apiopaeonoside and suffruticosides A-D. The total phenolic content found in 8 extracts of *Paeonia suffruticosa* root bark ranged from 63.81 ± 3.96 to 112.95 ± 3.97 mg gallic acid equivalents/g extract.[22]

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 *Paeonia suffruticosa* -derived ingredients in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was discontinued in 2023 and, as of 2024, manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[23] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

According to 2023 VCRP survey data, Paeonia Suffruticosa Root Extract was reported to be used in 213 formulations, 173 of which are leave-on formulations[24] (Table 3). RLD submitted in 2024 indicate that this ingredient is used in 736 total formulations.[25] Although all 5 ingredients are listed as in use in the RLD and/or the VCRP, according to a concentration of use survey conducted by the Council in 2022, with results updated in 2024 and 2025, only Paeonia Suffruticosa Root Extract and Paeonia Suffruticosa Seed Oil had concentrations of use reported.[26] Paeonia Suffruticosa Root Extract is reported to be used at a maximum concentration of 0.5% in paste masks and mud packs, and the greatest leave-on maximum use concentration is 0.05% in face powders. For Paeonia Suffruticosa Seed Oil, the only reported concentration of use is 0.0025% in bath soaps and detergents.

Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, and Paeonia Suffruticosa Root Extract are reported to be used in products applied near the eye (concentrations of use not reported). Additionally, most of the ingredients are used in formulations that could come in contact with mucous membranes (e.g., Paeonia Suffruticosa Seed Oil at up to 0.0025% in

bath soaps and detergents). Some of these ingredients are used in cosmetic powders and possibly cosmetic sprays, and can possibly be inhaled; for example, Paeonia Suffruticosa Root Extract is reported to be used at 0.05% in face powders. 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 cosmetics 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.

Some products containing *Paeonia suffruticosa*-derived ingredients may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. Some of the reported product categories for these ingredients as listed in the RLD do require designation if airbrush application is used (e.g., foundations make-up bases, and other makeup preparations), but no airbrush use was indicated. Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available, when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, 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. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

All of the *Paeonia suffruticosa*-derived ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[27]

Non-Cosmetic

The root bark of *Paeonia suffruticosa* is often referred to as moutan cortex, cortex moutan, mockdanpi, or mu dan pi, and is extensively used in traditional Chinese medicine for its anti-inflammatory, antioxidant, anti-tumor, anti-diabetic, cardiovascular-protective, neuroprotective, and hepatoprotective effects.[20,28-31] *Paeonia suffruticosa* root bark extract is listed in Japanese Standards for quasi-drug ingredients in 2021.[12] Traditionally, the raw material from the root bark is administered to treat fever and its alcoholic solutions are used to improve circulation and remove stasis.[5] Fresh *Paeonia suffruticosa* flowers are also considered edible in China.[32] In 2011, the Chinese Ministry of Health acknowledged the high level of α-linolenic acid (≥ 38%) present in peony seed oil and approved the oil as a new resource food.[33]

TOXICOKINETIC STUDIES

No relevant toxicokinetic studies on *Paeonia suffruticosa*-derived ingredients were found in the published literature, and unpublished data were not submitted. In general, toxicokinetic data are not expected to be found on natural complex substances because they are a complex mixture of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Paeonia Suffruticosa Seed Oil

Kunming mice (10/sex) were administered a single oral dose of 15,000 mg/kg bw peony seed oil, via gavage.[18,34] All of the animals survived and the acute LD_{50} was determined to be > 15,000 mg/kg bw. Further details could not be gleaned (original article is in Chinese).

In another acute oral toxicity study, ICR mice (10/sex/group) were given 0, 30, or 60 ml/kg peony seed oil in 2 doses, 6 h apart, via gavage.[11] Controls received water. On the first day of dosing, mice showed reduced food intake and decreased activity; oily feces and anal oil staining were more pronounced in the 60 ml/kg group. By the second and third day of dosing, activity levels in all groups normalized. No deaths occurred during the 7-d observation period and no statistically significant pathological changes occurred in the heart, liver, spleen, lungs, kidneys, and gastrointestinal organs of treated mice, compared to controls. Further details were not provided (article is in Chinese).

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

The acute oral toxicity of a *Paeonia suffruticosa* tree peony bark extract was evaluated as part of a developmental toxicity study in mice. The LD_{50} was determined to be 3400 mg/kg. No further details were provided for either study.

In an acute oral toxicity study conducted with rats, the LD_{50} for an herbal mixture containing 14.29% moutan cortex was determined to be > 5000 mg/kg.[30] The mixture comprised a total of 2100 g, including 28.57% (600 g) *Rehmannia radix*

preparata, 14.29% (300 g) moutan cortex, 14.29% (300 g) *Schisandrae fructus*, 14.29% (300 g) *Asparagi tuber*, 10.71% (225 mg) *Armeniacae semen*, 10.71% (225 mg) *Scutellariae radix*, and 7.14% (150 mg) *Stemonae radix*.

A single oral administration of 6 g/kg of a powdered methanolic extract of moutan bark dissolved in distilled water was given to 5 male ddY mice and 5 male Wistar rats.[35] No toxic effects were observed and no mortalities were reported.

Parenteral

Powdered moutan bark dissolved in distilled water was administered via intraperitoneal injections (a dose of 6 g/kg).[35] Potent toxic effects were evident in both rats and mice. All mice and rats treated with the test material died within 6 and 12 h, respectively.

Short-Term Toxicity Studies

Oral

Paonia Suffruticosa Seed Oil

Healthy rats (12/sex) were administered 1250, 2500, or 5000 mg/kg bw/d peony seed oil, via gavage, for 30 d.[18,34] Vegetable oil (5000 mg/kg bw/d) was given to controls. No abnormal changes in health status, biochemical indexes, hematological and blood biochemical indexes or immune organ indexes were observed at the end of dosing. Based on these results, the maximum non-effective dosage, which is equivalent to the no-observed-effect-level (NOEL), was estimated to be > 5000 mg/kg bw. Further details could not be gleaned (article is in Chinese).

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

Male Wistar rats, 7/group, were dosed with a methanolic extract of moutan bark (powdered, dissolved in distilled water) orally at a daily dose of 1.5 or 3 g/kg for 21 d.[35] A control group was given water only. Hematological examinations and urinalysis were performed, and the animals were killed at study termination. The analysis of the composition of the blood showed that erythrocyte and hematocrit count have decreased in in the low- and high-dose groups. It was also noted that the hemoglobin levels have decreased in high-dose group while the total bilirubin level in the serum increased. Urinalysis showed that protein and creatinine levels in the urine have increased. The liver enzymes also exhibited changes in the form of increases of liver alkaline phosphatase (ALP), glyceraldehyde-3-phosphate dehydrogenase (GPDAP) and leucine aminopeptidase (LAP). The pathological examination demonstrated a moderate deposition of hemosiderin in the spleen.

The short-term oral toxicity of an herbal mixture containing 14.29% (300 of 2100 g) moutan cortex was evaluated in accordance with Korea Food and Drug Administration (KFDA) Notification no. 2005-60 "The Standards of Toxicity Study for Medicinal Products" and KFDA Notification no. 2005-79 "Good Laboratory Practice (GLP)."[30] Other components of the herbal mixture included: 28.57% (600 g) *Rehmannia radix preparata*, 14.29% (300g) *Schisandrae fructus*, 14.29% (300 g) *Asparagi tuber*, 10.71% (225 g) *Armeniacae semen*, 10.71% (225 g) *Scutellariae radix*, and 7.14% (150 g) *Stemonae radix*. In a 4-wk study, groups of rats were dosed with 800, 2000, or 5000 mg/kg/d of the herbal mixture, via gavage. A decrease in serum sodium was observed in 5000 mg/kg/d females was considered test article-related. Increased liver weights were observed in the 2000 and 5000 mg/kg/d groups, although the statistical significance was not confirmed (no further details provided).

Subchronic Toxicity Studies

Oral

Paeonia Suffruticosa Seed Oil

Groups of Sprague-Dawley rats (10/sex/group) were administered 0, 5, or 10 ml/kg/d peony seed oil, via gavage, for 90 d.[11] Controls received water. Body weights were measured every 10 d. After 90 d, the heart, liver, spleen, lungs, kidneys, brain, adrenal glands, testes, uterus, and ovaries were removed, weighed, and organ: body weight ratios were calculated. Blood was collected and analyzed for hematological analyses (hemoglobin, red blood cell and white blood cell counts, neutrophils, lymphocytes, and platelets) and biochemical markers (serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, urea nitrogen, total protein, albumin, total cholesterol, total bilirubin, creatinine, blood sugar, triglycerides, and uric acid). Besides lower blood sugar levels in treated rats, no other statistically significant differences were observed in treated rats and controls. No significant histopathological findings, such as tissue degeneration, inflammation, bleeding, or necrosis, were observed upon necropsy. (No further details provided; article is in Chinese).

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

In a 13-wk oral toxicity study, groups of male and female Sprague-Dawley rats (10/sex/group) were administered 0, 750, 1500, or 3000 mg/kg of the previously described herbal mixture (containing 14.29% moutan cortex), dissolved in saline, via gavage.[30] No mortality, clinical changes related to test article administration, or statistically significant differences in body weight or food consumption between treated and control animals were observed. A statistically significant increase in white blood cell values was observed in both male and female rats in the 750 and 3000 mg/kg/d groups; a statistically significant decrease was observed in hematocrit and mean corpuscular hemoglobin values for 750 mg/kg/d female rats, compared to controls. Hemoglobin distribution width and hemoglobin concentrations were notably lower for 3000 mg/kg/d females, compared to controls. However, these values were within the normal range and were not considered to be test-article related. Similarly, notably increased alkaline phosphatase and total bilirubin levels in female rats from the 3000

mg/kg/d group and increased relative liver weight in males from the 3000 mg/kg/d treatment group were within the normal range and occurred in the absence of histopathological effects in the liver, indicating that these changes were not test article-related. No systemic or toxicologically significant changes related to the test article were observed. The no-observed-adverse-effect-level (NOAEL) of the herbal mixture was determined to be 3000 mg/kg/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In Vitro

Paeonia Suffruticosa Bark Extract

The embryotoxic potential of an aqueous *Paeonia suffruticosa* tree peony bark extract was evaluated in an embryonic stem cell test, consisting of differentiation and cytotoxicity experiments, validated by the European Centre for Validation of Alternative Methods (ECVAM).[31,36] For the cardiomyocyte differentiation experiment, undifferentiated mouse embryonic stem cell line was maintained in complete medium containing Dulbecco's modified Eagle medium (DMEM) with 20% fetal bovine serum, 2 mM L-glutamine, 0.5% penicillin/streptomycin, 1% non-essential amino acids, 0.1 mM β-mercaptoethanol, and 103 U/ml murine leukemia inhibitory factor (mLIF). For generation of mouse embryonic stem cell line embryoid bodies, cells were cultured in DMEM without mLIF, and were seeded in the complete medium as hanging drops (20 µl each) in the presence of the aqueous extract at concentrations of 0.01, 0.1, 1, 10, 100, 1000, or 10,000 µg/ml for 3 d. Subsequently, embryoid bodies formed at each concentration were plated onto a non-adhesive petri dish for 2 d and then transferred to 24-well plates (1 embryoid body/well) for 5 d. The beat rate of cardiomyocytes from treated-cells was compared with that from untreated cells. These ratio values and corresponding concentrations were used to calculate ID_{50} values, expressed as the concentration of test materials that inhibited differentiation of cardiomyocytes in comparison to the DMEM solvent control. The cytotoxicity of test materials (ranging from $1 \times 10^{-1} - 1 \times 10^{6}$ µg/ml) were determined using mouse embryonic stem cells and mouse fibroblast cell lines in a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay after 10 d of treatment. The *Paeonia suffruticosa* bark extract exerted a growth inhibition IC_{50} of 316.7 µg/ml and a cardiomyocyte differentiation inhibition ID_{50} of 342.8 µg/ml in the embryonic mouse stem cell line, both of which were considered non-embryotoxic. In mouse fibroblast cells treated with the *Paeonia suffruticosa* bark extract, cytotoxicity was observed before stem cell cytotoxicity or inhibition of differentiation (IC_{50} = 113.8 µg/ml), suggesting a lack of embryotoxicity. These results were confirmed by an in vitro prediction model and *Paeonia suffruticosa* bark extract was classified as non-embryotoxic.

Animal

Oral

Paeonia Suffruticosa Seed Oil

The effect of peony seed oil on sperm abnormality was evaluated in male rats.[34] Sexually mature male rats were administered 1250, 2500, or 5000 mg/kg bw/d peony seed oil, via gavage, for 30 d. Vegetable oil (5000 mg/kg bw) was given to negative controls and cyclophosphamide (40 mg/kg bw) was given to positive controls. On day 35, animals were killed and both epididymides were collected, sperm specimens were prepared, and eosin staining was performed. Sperm deformity rates were in the normal range (0.8 – 3.4%) and no significant difference in the abnormality rate was observed between each dose group and the negative controls.

In an embryonic development study, pregnant rats were orally administered 0.55, 0.75, or 1.1 ml/kg bw/d peony seed oil for 20 d.[18] No significant differences in maternal weight gain, early embryonic development, live fetal development, live fetal bone development, or organ development were observed, compared to controls, suggested that peony seed oil did not have embryotoxic or teratogenic effects. No further details were provided or could be gleaned (articles are in Chinese).

GENOTOXICITY STUDIES

In Vitro

Paeonia Suffruticosa Root Extract

An Ames test was performed on a test material containing 1.5% Paeonia Suffruticosa Root Extract (in 49.25% alcohol/49.25% water) at 0, 313, 635, 1250, 2500, 5000 µg/ plate with *Salmonella typhimurium* TA100, TA1535, TA98 and TA1537 and *Escherichia coli* WP2*uvrA* strains, with and without metabolic activation, under International Council for Harmonization (ICH) guidelines S2(R1).[37] Appropriate positive controls were used. The test article was not mutagenic.

An in vitro micronucleus assay was conducted on 1.5% Paeonia Suffruticosa Root Extract (in 49.25% alcohol/49.25% water solution) according to ICH guidelines S2(R1).[37] Chinese hamster lung fibroblasts (CHL/IU cells) were treated for 24 h with 500, 250 and 125 µg/l of test substance in the absence of an activation system. In short-time treatment, the cells were treated with test substance for 6 h with and without metabolic activation, and the culture continued for 18 h. Mitomycin C was used as the positive control. The 1.5% Paeonia Suffruticosa Root Extract was judged as non-genotoxic.

CARCINOGENICITY STUDIES

In Vitro Cell Transformation

Paeonia Suffruticosa Extract

The antimigration and antiproliferative effects of an aqueous *Paeonia suffruticosa* extract upon 786-O renal carcinoma cells were evaluated in several tests.[7] In MTT and cell migration assays, the aqueous *Paeonia suffruticosa* extract exhibited an inhibitory effect on cancer cell growth (IC_{50} growth = 1.5 mg/ml) and a cancer cell proliferation and migration ratio that indicated the same effect on (IC_{50} growth/$IC_{50\ migration}$ = 5.0). Polymerization of the actin filament was suppressed and the ratio of F-actin to G-actin was significantly reduced in *Paeonia suffruticosa* extract-treated cells, compared to controls. Cells treated with *Paeonia suffruticosa* extract had inhibited expression of vascular endothelial growth factor receptor-3 (VEGFR-3) and remarkably reduced phosphorylation of focal adhesion kinase, both of which are involved in the activation of Ras-related C3 botulinum toxin substrate 1 (Rac -1), a modulator of cytoskeletal dynamics.

Paeonia Suffruticosa Root Extract

The oncolytic activity of an aqueous *Paeonia suffruticosa* root extract was investigated in a triple negative breast cancer cell line, MDA-MB-231.[9] Human keratinocyte cells and MDA-MB-231 cells were treated with 0.6, 2.5, or 4 mg/ml aqueous *Paeonia suffruticosa* root extract for 48 h. Cell viability was measured using a 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. A biphasic dose-response with cell proliferation at low concentrations (0.6 mg/ml) and reduced cell viability at concentrations greater than 2 mg/ml was observed. Notably, for human keratinocyte cells, 2.5 and 4 mg/ml aqueous *Paeonia suffruticosa* root extracts did not reduce cell viability, which was indicative of a selective oncolytic effect. Cytokine production in MDA-MB-321 cells after 48-h treatment with aqueous *Paeonia suffruticosa* root extracts was examined in an enzyme-linked immunosorbent assay (ELISA). A statistically significant decrease in interleukin-6 (IL-6), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-α) levels were observed in cells treated with 0.6 mg/ml aqueous extract, but subsequently increased at concentrations greater than 2.5 mg/ml. Levels of interleukin-24 (IL-24) were notably increased at the 2.5 and 4 mg/ml concentrations, when measured by an indirect ELISA, compared to controls; this increase of IL-24 was considered an up-regulation caused by increased IL-2 production. Caspase-Glo assays were performed to measure caspase 3/7, 8, and 9 and to analyze anti-apoptotic effects of the *Paeonia suffruticosa* root extracts. Caspase 3/7 and 9 activities decreased at the 0.6 mg/ml concentration but increased in a dose-dependent fashion in cells treated with 2.5 and 4 mg/ml aqueous extracts; caspase-8 activity was observed to decrease or remain at vehicle-control levels at every concentration. The increase in caspase-9 activity coupled with a decrease in caspase-8 activity indicated a mechanism of action of apoptosis that is intrinsic and possibly mediated through IL-24.

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

The ability of a *Paeonia suffruticosa* root bark extract (root bark powder extracted with RPMI 1640 medium to affect cell viability, cell cycle stage, apoptosis, and cell invasion in human bladder papillary transitional cell carcinoma 5637 cells and mouse bladder carcinoma MB49 cells was examined.[28] MB49, 5637, and SV-HUC1 (human normal epithelium) cells were incubated with 0, 0.5, 1, 2, 3, or 3.5 mg/ml *Paeonia suffruticosa* root bark extract for 24 and 48 h. The IC_{50} values of *Paeonia suffruticosa* root bark extract were 1.6 mg/ml at 24 h and 1.3 mg/ml at 48 h in mouse bladder cancer cells, and 2.0 mg/ml at 24 h and 1.4 mg/ml at 48 h in human bladder cancer cells; the IC_{50} value in human normal epithelium at 24 h was 3.5 mg/ml. In the cell cycle analysis, exposure to *Paeonia suffruticosa* root bark extract increased the number of cells in the G1 and S phase in mouse bladder cells and human bladder carcinoma cells, showing that the *Paeonia suffruticosa* root bark extract induced the activation of caspase-3, and -8 (via extrinsic apoptosis) in a dose-dependent manner. The invasive activity of the *Paeonia suffruticosa* root bark extract was examined in 5637 cells in the cell assay. The *Paeonia suffruticosa* root bark extract inhibited cell invasion in a dose dependent manner; the inhibition percentage was higher than that of cell growth at the same dose, suggesting anti-invasive activity.

Several tests were performed to investigate whether an ethanolic *Paeonia suffruticosa* root bark extract displays growth suppressive activity and induces apoptosis in human gastric cancer cells.[29] The viability of human gastric cancer cells treated with 0, 0.01, 0.05, 0.1, 0.25, or 0.5 mg/ml *Paeonia suffruticosa* root bark extract for 48 or 72 h, was tested in an MTT assay. Untreated human gastric cancer cells served as negative controls. The *Paeonia suffruticosa* root bark extract inhibited cell growth in both a dose- and time-dependent manner; compared to controls, the IC_{50} values of *Paeonia suffruticosa* root bark extract were approximately 220 and 200 µg/ml at 48 and 72 h, respectively. The lethal concentration (LC_{50}) values of human gastric cancer cells treated with 0, 0.01, 0.05, 0.1, 0.25, or 0.5 mg/ml ethanolic *Paeonia suffruticosa* root bark extract for 48 or 72 h, in a cell cytotoxicity test, were approximately 140 and 190 µg/ml at each time point. To further study the cytotoxic effects of the extract, human gastric cancer cells were treated with 200 µg/ml ethanolic *Paeonia suffruticosa* root bark extract for 12 - 36 h and then analyzed for cell cycle stage and deoxyribonucleic acid (DNA) content using flow cytometry. At this concentration, the *Paeonia suffruticosa* root bark extract increased the sub-G1 apoptotic fraction from 3.81% at 12 h to 18.75% at 36 h in a time-dependent manner; neither untreated controls or positive controls (DMSO-treated cells) showed statistically significant changes in apoptotic fractions. Furthermore, results from a DNA fragmentation ladder analysis showed that ethanolic *Paeonia suffruticosa* root bark extract decreased monolayer cell growth and changed cell morphology in a similar manner to cells treated with cisplatin, an anti-cancer agent. Additionally, the ethanolic *Paeonia suffruticosa* root bark extract was found to cause apoptotic cell death via the extrinsic caspase-dependent apoptosis pathway, due to its

activation of the Fas death receptor protein and cleaving of caspase-8, caspase-3, and poly (adenosine diphosphate-ribose) polymerase (PARP). The extract was also shown to increase the expression of the active, phosphorylated form of tumor protein p53 (p53), and to decrease the expression of the active form of phosphorylated mouse double minute 2 homolog (MDM2), a negative regulator of p53. To confirm that p53 is implicated in the apoptosis induced by the *Paeonia suffruticosa* root bark extract, cells were treated with p53 inhibitor, pifithrin-α, and Western blot analysis was performed. Cleavage of caspase-8, caspase-3, and PARP were inhibited by the p53 inhibitor, suggesting that the ethanolic *Paeonia suffruticosa* root bark extract induced apoptosis via the MDM2-p53-dependent pathway in human gastric cancer cells.

Inhibition of Tumor Growth

Paeonia Suffruticosa Extract

The effects of an aqueous *Paeonia suffruticosa* extract upon tumor growth was evaluated using renal carcinoma cells in a mouse model.[7] Mice were subcutaneously inoculated with 786O renal carcinoma cells in the flank; 2 days after injection, mice (4/group) were orally administered either water or aqueous *Paeonia suffruticosa* extract (290 mg/kg) 5 d/wk and tumors were measured every 5 d till necropsy at 45 d. Statistically significant lower tumor weights were observed in treated mice compared to controls (234.8 vs. 437.5 mg; $p < 0.05$). For pulmonary tumor metastasis experiments, 8 female NOD-SCID mice were intravenously inoculated with 786O renal carcinoma cells (2×10^6) in the lateral tail vein. Two days after injection, mice were randomly divided into 2 groups (4/group) and orally administered water or aqueous *Paeonia suffruticosa* extract (290 mg/kg) 5 d/wk and body weight was measured every 5 d, for 48 d. Lungs of the mice were excised and metastatic nodules were counted to evaluate the approximate pulmonary tumor content. There were a statistically significant lower number of pulmonary nodules in treated mice compared to controls (10 ± 1.2 vs 18 ± 3.3 nodules/lung; $p < 0.01$). No statistically significant effect on the body weight of the mice was observed, suggesting low oral toxicity of the *Paeonia suffruticosa* extract.

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

In another study, MB49 mouse bladder cancer cells were implanted in female C57BL/6 mice (age 6 wk).[28] After MB49 inoculation, mice were randomly assigned to 2 groups (8 mice/group). One group was intravesically treated with RPMI 1640 medium, and the other group received 2.5 mg/mouse *Paeonia suffruticosa* root bark extract intravesically every other day from day 16 to 24. On day 26, the mice were killed and bladder volumes were measured before formalin fixation. After cutting the paraffin-embedded bladder tissues into 4 μm sections, slides of each mouse bladder were examined under a microscope in histological analysis by hematoxylin and eosin staining. No statistically significant differences between the body weights of control and treated mice were observed. Treatment with *Paeonia suffruticosa* root bark extract caused a statistically significant decrease in bladder volume and retarded the invasion of tumor tissue into the muscle layer. No notable differences in the blood urea nitrogen, serum creatinine, serum glutamic-oxaloacetic transaminase, or serum glutamic pyruvic aminotransferase levels were observed between both groups. The researchers considered that these results may suggest that intravesical treatment with the *Paeonia suffruticosa* root bark extract decreased bladder tumor size without adversely affecting the liver or kidney.

OTHER RELEVANT STUDIES

Tyrosinase Inhibition

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

The anti-melanogenesis properties of several *Paeonia suffruticosa* root cortex extracts were tested in murine melanoma B16 cells.[38] Plant material was extracted with 95% ethanol (extract 1) and the resulting extract was partitioned between ethyl acetate (extract 2) and water (extract 3). The ethyl acetate layer was partitioned with n-hexane (extract 4) and 90% methanol (extract 5). Subsequently, the 90% methanol layer was subjected to a Sephadex LH-20 column and eluted with methanol to obtain three fractions (extract 6, extract 7, and extract 8). Based on results from an MTT assay, extract 1, extract 3, extract 4, and extract 6 did not induce observable morphological changes in human skin fibroblast Hs68 and B16 cells and were chosen for further anti-melanogenesis analyses. To measure cellular tyrosinase activity, B16 cells were treated with 1 μM α-melanocyte-stimulating hormone (α-MSH) alone and with 50 or 100 μg/ml of the extracts, arbutin, or ascorbic acid for 72 h. Extract 1 and extract 6 inhibited cellular tyrosinase activity by 79.6 and 65%, respectively, compared to controls. Extract 1 and extract 6 also decreased dihydroxyphenylalanine (DOPA)quinone and melanin content in melanoma B16 cells as compared to controls. Notably, extract 6 had an inhibitory effect on melanin formation similar to that of arbutin and ascorbic acid, but with lower cytotoxicity. Extract 3 and extract 4 did not reduce tyrosinase activity, DOPA quinone content, or melanin formation, and were, thus, not included in further tests.

In a fluorescence staining quantitative analysis, melanoma B16 cells were treated with α-MSH alone or with 100 μg/ml of extract 1 or extract 6 for 72 h to determine melanogenesis-related protein expression and nuclei content. Both extracts did not reduce the percentage DNA content or change cell nuclear morphology. Cells treated with 100 μg/ml of either extract showed markedly lower expressions of melanocortin-1 receptor, microphthalmia-associated transcription factor, tyrosinase, and tyrosinase-related protein-1 (tyrosinase-related protein-2 levels were not affected). The researchers surmised that extract 1 and extract 6 may inhibit melanin synthesis through the downregulation of these associated enzymes.

The inhibitory effect of 2 *Paeonia suffruticosa* root bark extracts (aqueous and ethanolic) upon tyrosinase activity was evaluated in A2058 human melanoma cells. First, cells were incubated with 0.5, 1, 2, 2.5, or 5 mg/ml of the extracts, paeonol (a bioactive component of the extract), or arbutin (positive control) for 24 h and followed by ultraviolet (UV) irradiation, in a cellular tyrosinase assay. The ethanolic *Paeonia* suffruticosa root bark extract and paeonol were both found to be noncompetitive inhibitors in a kinetic analysis of tyrosinase inhibition. Furthermore, the ethanolic *Paeonia suffruticosa* root bark extract exhibited a greater tyrosinase inhibition rate compared to the aqueous extract ($p < 0.01$) and was used for additional studies. The ethanolic extract (6.25, 12.5, 25, or 50 µg/ml) showed a moderate and consistent reduction in the melanin content of A2058 melanoma cells when incubated for 24 h in a melanin synthesis assay; no statistically significant difference in melanin content was observed when compared to paeonol and arbutin-treated cells. In an L-DOPA oxidation assay, cells were treated with 6.25, 12.5, or 25 µg/ml of the ethanolic *Paeonia suffruticosa* root bark extract, paeonol, or arbutin for 24 h; paeonol exhibited the greatest tyrosinase inhibition compared to the ethanol extract and arbutin, but these differences were not statistically significant. Tyrosinase activity was downregulated in a dose-dependent manner by the ethanolic *Paeonia suffruticosa* root bark extract.

Anti-Photoagaing Effects

In Vitro

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

The photoprotective potential of a *Paeonia suffruticosa* root bark extract was investigated using multiple experiments employing several in vitro antioxidant assays, in vitro inhibition assays with HaCaT cells and human foreskin fibroblasts (HFF) cells, and a 3D reconstructed human full T-Skin model.[39] A 2,2'-diphenyl-1-picrylhydrazyl (DPPH) assay and a 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay, performed to determine the free radical scavenging activity, showed the test material possesses antioxidant properties. A collagenase inhibition assay and a hyaluronidase assay performed with the test article indicated that it enhanced the rates of inhibition of both enzymes.

In vitro anti-photoaging assays were conducted by irradiation of UVB on HaCaT cells pre-treated with the *Paeonia suffruticosa* root bark extract and by irradiation of UVA on similarly pre-treated HFF cells.[39] These studies showed that the *Paeonia suffruticosa* root bark extract significantly reduced UV-induced reactive oxygen species (ROS) levels and senescence-associated β-galactosidase (SA-β-gal) activity. Mechanistic investigations performed with RT-qPCR of the RNA extracted from both cell types indicated that the test material inhibited UV-triggered activation of IRS1/P13K/AKT/mTOR signaling pathway which is known to play a key role in skin aging and photodamage.

Human

During a human efficacy evaluation study, the effect of a *Paeonia suffruticosa* root bark extract on skin parameters associated with skin roughness, skin elasticity and transepidermal moisture content were evaluated.[39] Improved skin elasticity and moisture content were reported.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

In Vitro

Paeonia Suffruticosa Bark Extract

The skin irritation potential of an aqueous *Paeonia suffruticosa* bark extract was predicted in an EpiDerm™ skin irritation test, as outlined by ECVAM and Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 439.[31] A previously incubated reconstructed human epidermis (RhE) tissue sample was moistened with 25 µl of sterile Dulbecco's phosphate-buffered saline (PBS), followed by application of 100 ml aqueous *Paeonia suffruticosa* bark extract. Two separate solutions containing 1% (v/v) sodium dodecyl sulfate in either sesame seed oil or saline solution were used as positive controls and Dulbecco's PBS-treated epidermis was used as the negative control, respectively. The tissue sample was incubated for 3 h in an MTT reduction assay. Compared to the negative control, cell viability of the skin tissue sample exposed to *Paeonia suffruticosa* bark extract was within the range of 87.5 – 101.1% (> 50%) indicating that the tested extract did not produce irritation.

Human

Paeonia Suffruticosa Root Extract

Undiluted Paeonia Suffruticosa Root Extract (extracted with a 90% ethanolic solution) was tested neat in a 24-h closed patch dermal irritation test using 20 subjects.[13] The test article was deemed non-irritating. No further details were provided.

Sensitization

Human

Paeonia Suffruticosa Root Extract

A human repeated-insult patch test (HRIPT) was completed in 52 subjects with a lotion containing 0.0015% Paeonia Suffruticosa Root Extract.[40] Occlusive patches containing approximately 25 - 38 mg/cm^2 of the test material (0.375 - 0.57 µg/cm^2 Paeonia Suffruticosa Root Extract) were applied to the back of each subject for 24 h, and the test sites were evaluated

24 or 48 h after patch removal. This procedure was repeated 3 times/wk for 3 wk, for a total of 9 induction applications. After a 2-wk non-treatment period, challenge applications were made to a previously untreated test site, and the site was evaluated 24 and 72 h after application. No reactions were observed during induction or challenge; accordingly, the lotion containing 0.0015% Paeonia Suffruticosa Root Extract was not an irritant or sensitizer.

A face mask formulation containing 0.5% Paeonia Suffruticosa Root Extract was tested in a HRIPT using 106 subjects.[41] During induction, nine, 24-h occlusive applications containing approximately 0.2 g of the undiluted test article (0.64 µg root extract/cm^2) were applied over a 3-wk period. The test article was applied to a 0.6 in^2 absorbent pad, which was then placed on the upper back to form an occlusive patch. At least 10 d following the final induction patch application, a challenge application was applied to a virgin test site, adjacent to the original induction patch site, following the same induction procedure. No adverse reactions were observed during the induction or challenge phases; the test article did not cause dermal irritation or sensitization.

OCULAR IRRITATION STUDIES

In Vitro

Paeonia Suffruticosa Root Extract

A short-time exposure (STE) test was conducted to determine the potential ocular irritation of a material containing 1.5% Paeonia Suffruticosa Root Extract (solvent; 49.25% alcohol/49.25%water) at 0.05 and 5% concentrations using SIRC rabbit corneal cells, following OECD TG 491.[37] The positive control used was sodium lauryl sulfate (SLS). The test samples, at 0.05 and 5% concentrations, showed cell viability of > 70% and therefore the test material was classified as United Nations Globally Harmonized System (UN GHS) No Category (not classified for eye irritation or serious eye damage).

SUMMARY

The safety of the following 5 *Paeonia suffruticosa*-derived ingredients as used in cosmetics is reviewed in this safety assessment: Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, Paeonia Suffruticosa Root Extract, Paeonia Suffruticosa Seed Oil, and Paeonia Suffruticosa (Tree Peony) Root Bark Extract. Paeonia Suffruticosa (Tree Peony) Root Bark Extract is not included in the *Dictionary*; however, it has reported uses in the 2023 VCRP database and in 2024 RLD and thus included in this review. According to the *Dictionary*, the other 4 ingredients are reported to function as skin-conditioning agents in cosmetics. Paeonia Suffruticosa Seed Oil is also reported to function as a hair conditioning agent and a skin protectant.

Paeonia Suffruticosa Root Extract is reported to have the greatest frequency of use according to 2023 VCRP data (213 uses) and RLD submitted in 2024 (736 uses). Results reported in a concentration of use survey conducted by the Council in 2022, and updated in2024 and 2025, indicate that Paeonia Suffruticosa Root Extract also has the highest reported concentration of use (up to 0.5% in paste masks and mud packs), and the greatest leave-on maximum use concentration (0.05% in face powders).

Peony seed oil had oral LD_{50}s of > 15,000 mg/kg bw and 60 ml/kg in mice. A *Paeonia suffruticosa* tree peony bark extract had an oral LD_{50} of 3400 mg/kg in mice, and an herbal mixture (2100 mg) containing 14.29% moutan cortex (300 g) an oral LD_{50} of > 5000 mg/kg in rats. In mice and rats, a single 6 g/10 ml/kg of a methanolic extract of moutan bark (as powdered test material dissolved in distilled water) did not result in any toxicity or deaths when administered orally, but produced 100% mortality when administered intraperitoneally.

Peony seed oil, when administered to rats via gavage for 30 d, had an NOEL > 5000 mg/kg bw/d, and administration of up to 10 ml/kg/d, no significant findings were noted. Oral administration of a methanolic extract of moutan bark (powdered, dissolved in distilled water) to rats at a daily dose of 1.5 or 3 g/kg for 21 d resulted in some changes in hematological and urinalysis parameters, and a moderate deposition of hemosiderin in the spleen. Short-term (4-wk) oral administration of up to 5000 mg/kg/d of an herbal mixture containing 14.29% moutan cortex (300 g of total 2100 g) resulted in a test article-related decrease in serum sodium, and in a 13-wk oral study in rats, the NOAEL was 3000 mg/kg/d (which was the highest dose).

An embryonic stem cell test, validated by ECVAM, was used to evaluate the developmental toxicity of an aq. *Paeonia suffruticosa* bark extract. The *Paeonia suffruticosa* bark extract exerted a growth inhibition IC_{50} of 316.7 µg/ml and a cardiomyocyte differentiation inhibition ID_{50} of 342.8 µg/ml in the embryonic mouse stem cell line, both of which were considered non-embryotoxic. In mouse fibroblast cells treated with the *Paeonia suffruticosa* bark extract, cytotoxicity was observed before stem cell cytotoxicity or inhibition of differentiation (IC_{50} = 113.8 µg/ml), suggesting a lack of embryotoxicity. These results were confirmed by an in vitro prediction model. Peony seed oil, ≤ 5000 mg/kg bw/d given by gavage for 30 d, had no adverse effects on the sperm of male rats, and up to 1.1 ml/kg bw/d administered orally to gravid female rats for 20 d did result in embryotoxic or teratogenic effects.

The genotoxic potential of a test material containing 1.5% Paeonia Suffruticosa Root Extract (in 49.25% alcohol/49.25% water) was evaluated in an Ames test (at up to 5000 µg/ plate, with and without metabolic activation) and an in vitro micronucleus assay (at up to 125 µg/l in CHL/IU cells) The test material was not genotoxic in either study.

An aqueous extract of *Paeonia suffruticosa* exhibited an inhibitory effect on 786O renal carcinoma cell growth ($IC_{50\ growth}$ = 1.5 mg/ml), which was reflected in the ratio between inhibitory effects on cancer cell proliferation and migration ($IC_{50\ growth}/IC_{50\ migration}$ = 5.0). Cells treated with aqueous *Paeonia suffruticosa* extract had inhibited expression of VEGFR-3 and remarkably reduced phosphorylation of focal adhesion kinase involved in the activation of Rac -1. The oncolytic activity of an aqueous *Paeonia suffruticosa* root extract was investigated using multiple tests in a triple negative breast cancer line, MDA-MB-231. In an MTS assay, a biphasic dose-response with cell proliferation at low concentrations and reduced cell viability at concentrations > 2 mg/ml was observed in triple negative breast cancer cells treated with up to 4 mg/ml aqueous *Paeonia suffruticosa* root extract. In an ELISA, significant decrease in IL-6, IL-2, and TNF-a levels occurred at the 0.6 mg/ml concentration, but subsequently increased at concentrations > 2.5 mg/ml. IL-24 levels were notably increased with a dose of 2.5 and 4 mg/ml, compared to controls. In Caspase-Glo assays, caspase 3/7 and 9 activity increased in a dose-dependent manner at concentrations 2.5 and 4 mg/ml ; caspase-8 activity was decreased or remained at vehicle-control levels at every concentration.

The IC_{50} values of a *Paeonia suffruticosa* root bark extract were 1.6 mg/ml and 2.0 mg/ml in mouse bladder and human bladder cancer cells, respectively, compared to a 3.5 mg/ml IC_{50} value in human normal epithelium at 24 h. An ethanolic *Paeonia suffruticosa* root bark extract inhibited cell growth in human gastric cancer cells with IC_{50} values approximately 220 and 200 µg/ml at 48 and 72 h, respectively. The LC_{50} values of human gastric cancer cells treated with up to 0.5 mg/ml ethanolic *Paeonia suffruticosa* root bark extract were approximately 140 and 190 µg/ml at 48 or 72 h, respectively. In a cell cycle stage and DNA fragmentation analysis, 200 µg/ml *Paeonia suffruticosa* root bark extract increased the sub-G1 apoptotic fraction in a time-dependent manner; the extract also decreased monolayer cell growth and changed cell morphology. Tumor weights of the *Paeonia suffruticosa* extract-treated (0.29 g/kg) 5 d/wk, NOD-SCID mice subcutaneously injected with 786O renal carcinoma cells were remarkably lower than that of the control group (234.8 mg vs. 437.5 mg). In a pulmonary metastasis test, the mice intravenously inoculated with aqueous *Paeonia suffruticosa* extract had lower number of pulmonary nodules compared to controls. Treatment with *Paeonia suffruticosa* root bark extract caused a statistically significant decrease in bladder volume in C57BL/6 female mice implanted with MB 49 bladder cancer cells and retarded the invasion of tumor tissue into the muscle layer.

The anti-melanogenesis properties of 8 *Paeonia suffruticosa* root cortex extracts (including sequential subfractions) were tested in murine melanoma B16 cells. The 95% ethanol extract and a subfraction inhibited cellular tyrosinase activity by 79.6 and 65%, respectively, and decreased DOPAquinone and melanin content in B16 cells compared to controls. Notably, this subfraction had an inhibitory effect on melanin formation similar to that of arbutin and ascorbic acid, but with lower cytotoxicity in the presence of α-MSH; treated cells showed markedly lower expressions of melanocortin-1 receptor, microphthalmia-associated transcription factor, tyrosinase, and tyrosinase-related protein-1. In a tyrosinase inhibition assay conducted with A2058 human melanoma cells, a *Paeonia suffruticosa* root bark ethanol extract exhibited a greater tyrosinase inhibition rate compared to the aqueous extract. In subsequent studies, the ethanolic extract (tested at ≤ 50 µg/ml) showed a moderate and consistent reduction in the melanin content of human melanoma cells which was not statistically significant. In an L-DOPA oxidation assay, paeonol exhibited the greatest tyrosinase inhibition compared to the ethanol extract and arbutin, but these differences were not statistically significant. Tyrosinase activity was downregulated in a dose-dependent manner by the ethanolic *Paeonia suffruticosa* root bark extract.

The photoprotective potential of a *Paeonia suffruticosa* root bark extract was evaluated in several studies. The test material was shown to possess antioxidant properties, and a collagenase inhibition assay and a hyaluronidase assay indicated that it enhanced the rates of inhibition of both enzymes. In a clinical study, it appeared to improve skin elasticity and moisture content.

In an EpiDerm™ skin irritation test, an aqueous *Paeonia suffruticosa* bark extract did not produce irritation, In a 24-h occlusive path test with 20 subjects, undiluted Paeonia Suffruticosa Root Extract (extracted with a 90% ethanolic solution) was non-irritating. A lotion containing 0.0015% Paeonia Suffruticosa Root Extract and a face mask formulation containing 0.5% Paeonia Suffruticosa Root Extract were not an irritants or sensitizers in HRIPTs completed in 52 and 106 subjects respectively.

The ocular irritation potential of a material containing 1.5% Paeonia Suffruticosa Root Extract (solvent; 49.25% alcohol/49.25%water), at 0.05 and 5%, was evaluated in an STE test. The test material was classified as UN GHS No Category (not classified for eye irritation or serious eye damage).

DISCUSSION

This assessment reviews the safety of 5 *Paeonia suffruticosa*-derived ingredients as used in cosmetic formulations, in accordance with the product categories and concentrations of use identified in the Use section and Use table; one ingredient included in this report, Paeonia Suffruticosa (Tree Peony) Root Bark Extract, is not named in the *Dictionary*, but was reported in 2023 in the VCRP database. The Panel concluded that the available data are sufficient to determine that Paeonia Suffruticosa Seel Oil is safe in cosmetics in the present practices of use and concentration, but are insufficient to determine the safety of the remaining 4 ingredients. For those 4 ingredients, the Panel requires the following information to determine safety:

- For Paeonia Suffruticosa (Tree Peony) Root Bark Extract
  - Clarification on the definition, methods of manufacture, and composition as applicable to cosmetic use
  - Clarification as to whether Paeonia Suffruticosa Root Extract includes the root bark of the plant
- For Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, and Paeonia Suffruticosa Root Extract
  - Maximum concentration of use
  - Ocular irritation data (in vitro) at the maximum reported concentration of use for near the eye.
- For all 4 ingredients
  - 28-d dermal toxicity assay
    - If positive, data on systemic toxicity endpoints (e.g. developmental and reproductive toxicity) may be needed
  - Genotoxicity data
- For Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, and Paeonia Suffruticosa (Tree Peony) Root Bark Extract
  - Dermal irritation and sensitization data

The Panel considered the composition of the Paeonia Suffruticosa Seed Oil with 98.46% fatty acids and the absence of other undesirable components as a significant factor contributing to its decision to consider it as safe as used in cosmetic products. The fact that the maximum use concentration reported in cosmetic product formulations is 0.0025% further supported this conclusion. Also, the absence of any harmful events in the toxicological data included in this report, and the fact that this ingredient has been used as an edible oil favored this conclusion.

Data included in this report indicate that the root bark of *Paeonia suffruticosa* may have a skin lightening effect. The Panel noted that skin lightening is considered a drug effect, and should not occur during the use of cosmetic products. Because of that caveat, the Panel's knowledge of the mechanism of action (i.e., inhibition of tyrosinase activity resulting in reduced melanin synthesis), and clinical experience, concern for this effect in cosmetics was mitigated. Nevertheless, cosmetic formulators should only use this ingredient in products in a manner that does not cause depigmentation.

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

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

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and/or concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded the data are 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 Paeonia Suffruticosa Seed Oil is safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the available data are insufficient to make a determination of safety for Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract, Paeonia Suffruticosa Root Extract and Paeonia Suffruticosa (Tree Peony) Root Bark Extract under the intended conditions of use in cosmetic formulations.

TABLES

Table 1. Definitions and functions of *Paeonia suffruticosa*–derived ingredients[1*]

Ingredient/CAS No.	Definition	Function
Paeonia Suffruticosa Bark Extract 223747-88-4 (generic)	Paeonia Suffruticosa Bark Extract is the extract of the bark of *Paeonia suffruticosa*.	Skin-conditioning agents - miscellaneous
Paeonia Suffruticosa Extract 223747-88-4 (generic)	Paeonia Suffruticosa Extract is the extract of the whole plant, *Paeonia suffruticosa*.	Skin-conditioning agents - miscellaneous
Paeonia Suffruticosa Root Extract 223747-88-4 (generic)	Paeonia Suffruticosa Root Extract is the extract of the roots of *Paeonia suffruticosa*.	Skin-conditioning agents - miscellaneous
Paeonia Suffruticosa Seed Oil 223747-88-4 (generic)	Paeonia Suffruticosa Seed Oil is the fixed oil expressed from the seeds of *Paeonia suffruticosa*.	Hair conditioning agent Skin protectants Skin-conditioning agents – emollient Skin conditioning agents – humectant Skin conditioning agents - miscellaneous

*Paeonia Suffruticosa (Tree Peony) Root Bark Extract is not included in this table because it is not an INCI ingredient

Table 2. Constituents in *Paeonia suffruticosa*, by plant part[5,16,20,21]

Constituent*; **	Flower	Fresh leaves	Root	Root Cortex	Seed
Monoterpenoid Glycosides					
α-(benzolyloxy)paeoniflorin				•	
β-(benzoyloxy)paeoniflorin			•	•	
(-)-paeonisuffrone				•	
(galloyloxy)paeoniflorin				•	
6-*O*-vanillyloxypaeoniflorin				♦	
albiflorin			•	•	
benzoylpaeoniflorin			•	•	
deoxypaeonisuffrone				•	
galloylpaeoniflorin			•	•	
isopaeonisuffral				•	
mudanpioside A				•	
mudanpioside B				•	
mudanpioside C				•	
mudanpioside D				•	
mudanpioside E				•	
mudanpioside F				•	
mudanpioside G				•	
mudanpioside H				•	
mudanpioside I				•	
mudanpioside I				•	
mudanpioside J				•	
oxypaeoniflorin			•	•	
paeoniflorigenone				•	
paeoniflorin			•	•	•
paeonisothujone				•	
paeonisuffral			•		
paeonisuffrone			•		
Flavonoids					
5,6,4'-trihydroxy-7,3'-dimethoxyflavone					•
apigenin 7-neohesperidoside	•				
apigenin 7-rhamnoside	•				
astragalin	•				
catechin				•	•
chalcone (flower)	•				
cosmosin	•				
cyanidine 3,5-glucoside	•				
cyanidine-3-glucoside	•				
kaempferol				•	
kaempferol 3,7-*β*-D-diglucoside	•				
kaempferol 7-rhamnoglucoside	•				
luteolin					•
luteolin 7-glucoside					
pelargonin	•				
peonidin 3,5-di-*O*-*β*-D-glucopyranoside	•				
peonin chloride	•				
populnin	•				

Table 2. Constituents in *Paeonia suffruticosa*, by plant part[5,16,20,21]

Constituent*; **	Flower	Fresh leaves	Root	Root Cortex	Seed
quercetin				•	
Phenols and their glycosides					
apiopaeonoside				•	
paenol				•	
paeonolide				•	
paeonoside				•	
suffruticoside A				•	
suffruticoside B				•	
suffruticoside C				•	
suffruticoside D				•	
suffruticoside E				•	
2,3-dihydroxy-4-methoxyacetophenone				•	
2,5-dihydroxy-4-methoxyacetophenone				•	
3-hydroxy-4-methoxyacetophenone				•	
3-hydroxy-4-methoxybenzoic acid				•	
4-hydroxyacetophenone				•	
4-hydroxybenzoic acid				•	
acetovanillone				•	
gallacetophenone				•	
gallic acid				•	
methyl 3-hydroxy-4-methoxybenzoate				•	
methyl gallate				•	
mudanoside A				•	
resacetophenone				•	
trans-caffeic acid stearyl ester				•	
Tannins					
mudanoside B				•	
1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucose				•	
1,2,3,6-tetra-*O*-galloyl-*β*-D-glucose		•			
6-*O*-(*m*-galloyl)galloyl-1,2,3,4-tetra-*O*-galloyl-*β*-D-glucose		•			
(-)-epigallochatechin gallate				•	
Stilbenes					
(*Z)*-resveratrol					•
suffruticosol A					•
suffruticosol B					•
suffruticosol C					•
Terpenoids and Steroids					
β-sitosterol				•	
betulinic acid				•	
campesterol				•	
daucosterol				•	
oleanolic acid				•	
Others					
adenosine				•	

• indicates specific compound detected
*quantities of chemicals were not provided
**Blank cells indicate specific compounds were not detected

Table 3. Frequency (RLD/VCRP) and concentration 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
	RLD (2024)[25]	VCRP (2023)[24]	% (2024)[26]	RLD (2024)[25]	VCRP (2023)[24]	% (2024)[26]	RLD (2024)[25]	VCRP (2023)[24]	% (2025)[26]
	Paeonia Suffruticosa Bark Extract			Paeonia Suffruticosa Extract			Paeonia Suffruticosa Root Extract		
Totals*	**1**	**8**	**NR**	**49**	**18**	**NR**	**736**	**213**	**0.000029 – 0.5**
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*6*	*NR*	***	*14*	*NR*	***	*173*	*0.00009 - 0.05*
Rinse-Off	***	*2*	*NR*	***	*4*	*NR*	***	*40*	*0.000029 - 0.5*
Diluted for (Bath) Use	***	*NR*	*NR*	***	*NR*	*NR*	***	*NR*	*NR*
Exposure Type									
Eye Area	***	1	NR	***	3	NR	***	9	NR
Incidental Ingestion	***	NR	NR	***	NR	NR	***	2	NR
Incidental Inhalation-Spray	***	4[a]	NR	***	4[a]; 5[b]	NR	***	84[a]; 46[b]	0.0011[b]
Incidental Inhalation-Powder	***	4[a]	NR	***	4[a]	NR	***	84[a]; 2[c]	0.05; 0.0014 - 0.005[c]
Dermal Contact	***	8	NR	***	16	NR	***	193	0.000029 - 0.5
Deodorant (underarm)	***	NR	NR	***	NR	NR	***	1[b]	NR
Hair - Non-Coloring	***	NR	NR	***	2	NR	***	12	0.00009 - 0.0011
Hair-Coloring	***	NR	NR	***	NR	NR	***	2	NR
Nail	***	NR	NR	***	NR	NR	***	NR	NR
Mucous Membrane	***	2	NR	***	1	NR	***	14	0.0025
Baby Products	***	NR	NR	***	NR	NR	***	3	NR
as reported by product category									
Baby Products									
Baby Shampoos							NR	1	NR
Baby Lotions/Oils/Powders/Creams							NR	2	NR
Bath Preparations							***3***		
Bath Oils, Tablets, and Salts							1	NR	NR
Other Bath Preparations							2	NR	NR
Eye Makeup Preparations (not children's)				***1***			***16***		
Eyebrow Pencil							NR	1	NR
Eye Shadow				NR	1	NR	NR	1	NR
Eye Lotion				1	NR	NR	2	2	NR
Eye Makeup Remover							3	NR	NR
Mascara							NR	2	NR
Eyelash and Eyebrow Adhesives, Glues, and Sealants							2	NA	NA
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)							5	NA	NA
Eyelash Cleansers							1	NA	NA
Other Eye Makeup Preparations	NR	1	NR	NR	2	NR	3	3	NR
Fragrance Preparations				***2***			***7***		
Cologne and Toilet Water							1	NR	NR
Perfumes				1	NR	NR	5	NR	NR
Other Fragrance Preparation				1	NR	NR	1	NR	NR
Hair Preparations (non-coloring)				***1***			***75***		
Hair Conditioners							3 (l.o.); 17 (r.o.)	3	0.00009
Rinses (non-coloring)							1	3	NR
Shampoos (non-coloring)							42 (r.o.)	5	0.0009
Tonics, Dressings, and Other Hair Grooming Aids				1	NR	NR	11	NR	0.0011

Table 3. Frequency (RLD/VCRP) and concentration 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
	RLD (2024)[25]	VCRP (2023)[24]	% (2024)[26]	RLD (2024)[25]	VCRP (2023)[24]	% (2024)[26]	RLD (2024)[25]	VCRP (2023)[24]	% (2025)[26]
Other Hair Preparations				1 (l.o.)	2	NR	3 (l.o.); 2 (r.o.)	NR	0.00009
Hair Coloring Preparations							**1**		
Hair Dyes and Colors (all types requiring caution statements and patch tests)							NR	2	NR
Hair Shampoos (coloring)							1 (r.o.)	NR	NR
Makeup Preparations (not eye; not children's)				***14***			***22***		
Blushers and Rouges (all types)									
Face Powders							2	NR	0.05
Foundations				11 (traditional application)	NR	NR	2 (traditional application)	NR	NR
Lipsticks and Lip Glosses				1	NR	NR	11	NR	NR
Makeup Bases				1 (traditional application)	NR	NR	4 (traditional application)	3	NR
Makeup Fixatives				1	NR	NR		1	NR
Other Makeup Preparations							4 (l.o.)	1	NR
Manicuring Preparations							***1***		
Cuticle Softeners									
Nail Polish and Enamel Removers									
Other Manicuring Preparations							1	NR	NR
Oral Products							***4***		
Dentifrices							4	NR	NR
Other Oral Products							NR	2	NR
Personal Cleanliness				***3***			***16***		
Bath Soaps and Body Washes				2	NR	NR	10	7	0.0025
Deodorants (underarm)							NR	1	NR
Douches							1	2	NR
Feminine Deodorants							2	NR	NR
Other Personal Cleanliness Products				1 (r.o.)	1	NR	5 (r.o.)	3	NR
Skin Care Preparations	***1***			***26***			***570***		
Cleansing				NR	2	NR	49	9	NR
Depilatories							5	NR	NR
Face and Neck (excluding shaving preps)	NR	4	NR	10 (l.o.); 1 (r.o.)	4	NR	349 (l.o.); 27 (r.o.)	55	0.0014 (not spray)
Body and Hand (excluding shaving preps)							25 (l.o.); 8 (r.o.)	29	0.005 (not spray)
Foot Powders and Sprays							2	NR	NR
Moisturizing	1	NR	NR	3	4	NR	200	55	0.002 (not spray)
Night				2	1	NR	12	29	NR
Paste Masks (mud packs)				11	1	NR	24	55	0.000029-0.5
Skin Fresheners							21	29	NR
Other Skin Care Preparations	NR	1	NR	1 (l.o.); 1 (r.o.)	NR	NR	52 (l.o.); 26 (r.o.)	55	NR
Suntan Preparations							***1***		
Suntan Gels, Creams, and Liquids							1	NR	NR
Tattoo Preparations							***2***		
Other Tattoo Preparations							2	NA	NA
Other Preparations (i.e., those that do not fit another category)				***2***			***29***		

Table 3. Frequency (RLD/VCRP) and concentration 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
	RLD (2024)[25]	VCRP (2023)[24]	% (2024)[26]	RLD (2024)[25]	VCRP (2023)[24]	% (2024)[26]	RLD (2024)[25]	VCRP (2023)[24]	% (2025)[26]
	Paeonia Suffruticosa Seed Oil			Paeonia Suffruticosa (Tree Peony) Root Bark Extract					
Totals*	**21**	**4**	**0.0025**	**NR**	**2**	**NR**			
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*NR*	*NR*	***	*1*	*NR*			
Rinse-Off	***	*1*	*0.0025*	***	*1*	*NR*			
Diluted for (Bath) Use	***	*3*	*NR*	***	*NR*	*NR*			
Exposure Type									
Eye Area	***	NR	NR	***	NR	NR			
Incidental Ingestion	***	NR	NR	***	NR	NR			
Incidental Inhalation-Spray	***	NR	NR	***	NR	NR			
Incidental Inhalation-Powder	***	NR	NR	***	NR	NR			
Dermal Contact	***	4	0.0025	***	1[b]	1[b]			
Deodorant (underarm)	***	NR	NR	***	NR	NR			
Hair - Non-Coloring	***	NR	NR	***	NR	NR			
Hair-Coloring	***	NR	NR	***	NR	NR			
Nail	***	NR	NR	***	2	2			
Mucous Membrane	***	4	0.0025	***	NR	NR			
Baby Products	***	NR	NR	***	NR	NR			
as reported by product category									
Baby Products									
Baby Shampoos									
Baby Lotions/Oils/Powders/Creams									
Bath Preparations (diluted for use)									
Bath Oils, Tablets, and Salts									
Other Bath Preparations	NR	3	NR						
Eye Makeup Preparations									
Eyebrow Pencil									
Eye Shadow									
Eye Lotion									
Eye Makeup Remover									
Mascara									
Eyelash and Eyebrow Adhesives, Glues, Sealants									
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)									
Eyelash Cleansers									
Other Eye Makeup Preparations									
Fragrance Preparations									
Cologne and Toilet Water									
Perfumes									
Other Fragrance Preparation									
Hair Preparations (non-coloring)	***1***								
Hair Conditioner									
Rinses (non-coloring)									
Shampoos (non-coloring)									
Tonics, Dressings, and Other Hair Grooming Aids	1	NR	NR						
Other Hair Preparations									

Table 3. Frequency (RLD/VCRP) and concentration 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
	RLD (2024)[25]	VCRP (2023)[24]	% (2024)[26]	RLD (2024)[25]	VCRP (2023)[24]	% (2024)[26]	RLD (2024)[25]	VCRP (2023)[24]	% (2025)[26]
Hair Coloring Preparations									
Hair Dyes and Colors (all types requiring caution statements and patch tests)									
Hair Shampoos (coloring)									
Makeup Preparations (not eye; not children's)	***1***								
Blushers and Rouges (all types)	1	NR	NR						
Face Powders									
Foundations									
Lipsticks and Lip Glosses									
Makeup Bases									
Makeup Fixatives									
Other Makeup Preparations									
Manicuring Preparations (Nail)	***1***								
Cuticle Softeners	1	NR	NR						
Nail Polish and Enamel Removers	1	NR	NR						
Other Manicuring Preparations									
Oral Products									
Dentifrices									
Other Oral Products									
Personal Cleanliness Products	***4***								
Bath Soaps and Body Washes	4	1	0.0025						
Deodorants (underarm)									
Douches									
Feminine Deodorants									
Other Personal Cleanliness Products									
Skin Care Preparations	***14***								
Cleansing	2	NR	NR						
Depilatories									
Face and Neck (excluding shaving preps)	7 (l.o.)	NR	NR						
Body and Hand (excluding shaving preps)	1 (l.o.)	NR	NR						
Moisturizing	5	NR	NR	NR	1	NR			
Night									
Paste Masks (mud packs)				NR	1	NR			
Skin Fresheners									
Other Skin Care Preparations									
Suntan Preparations									
Suntan Gels, Creams, and Liquids									
Tattoo Preparations									
Other Tattoo Preparations									
Other Preparations (i.e., those that do not fit another category)									

NR – not reported; NA – not applicable (this category was not part of the VCRP)
l.o. – leave-on; r.o. – rinse-off
*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple product categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple exposure types.
**Likely duration and exposure are derived from VCRP and survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
***Because RLD are product-centric and not ingredient-centric, each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.)

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

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 7, 2025

SUBJECT: Paeonia Suffruticosa Root Extract

Anonymous. 2025. Safety data of Paeonia Suffruticosa Root Extract with Appendix 1. Assay procedure and result of Short Time Exposure (STE) test.

Safety data of Paeonia Suffruticosa Root Extract

Here we summarized the Ocular irritation data (*in vitro*) and Genotoxicity data of raw material containing Paeonia Suffruticosa Root Extract.

- ✓ Test sample information:
  - ➢ Composition:

Paeonia Suffruticosa Root Extract	1.5%
Alcohol	49.25%
Water	49.25%

- ✓ Eye irritation:
  - ➢ Short Time Exposure (STE) test (OECD TG491); Appendix 1

    As a result, test sample was judged as GHS No Category.

- ✓ Genotoxicity:
  - ➢ Bacterial reverse mutation test (Ames test) (OECD 471, Japanese pharmaceutical guidance for genotoxicity testing); Appendix 2

    As a result, test sample was judged as negative.
  - ➢ *In vitro* micronucleus test (ICH guideline S2 (R1), Japanese pharmaceutical guidance for genotoxicity testing); Appendix 3

    As a result, test sample was judged as negative.

Appendix 1. Assay procedure and result of Short Time Exposure (STE) test

Procedure of STE test

The assays were performed as described in OECD TG491. Briefly, the SIRC (rabbit corneal cell line, 6 x 10^3 cells/well) cells were cultured in a 96-well plate and exposed to samples at the concentration of 5% and 0.05% for 5 min. Three wells were used for each concentration and three independent tests were conducted. After exposure, the cells were washed and treated with vital dye MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). After a 2 h incubation time, the MTT formazan was extracted, and absorbance was measured at 570 nm. The optical density (OD) values of 570nm obtained for each test chemical were then used to calculate cell viability relative to the solvent control, which is set at 100%. Eye irritation or serious eye damage were classified by the STE test as follow: a test substance was classified as UN GHS Category 1 (serious eye damage) when the 5% and 0.05% concentrations both produce a cell viability of $\leq$ 70%; it was classified as UN GHS No Category (not classified for eye irritation or serious eye damage) when the 5% and 0.05% concentrations both produced a cell viability of > 70%; it was unable to be classified when the 5% concentration produced a cell viability of $\leq$ 70% and the 0.05% produces a cell viability of >70%.

Results

Samples	Concentration (%)	Cell viability (%)					
		1st Run	2nd Run	3rd Run	Average	SD	UN GHS classification
Medium	-	100.0	100.0	100.0	100.0	-	-
Saline	-	99.9	96.5	98.2	98.2	1.7	-
SLS (positive control)	0.01	53.3	52.0	48.0	51.1	2.7	-
Test Sample	0.05	101.3	96.5	99.1	99.0	2.4	No Category
	5	98.3	95.3	94.9	96.2	1.9	No Category

Conclusion

The test sample containing Paeonia Suffruticosa Root Extract at 1.5% was judged as GHS No Category in the STE test.

Appendix 2. Assay procedure and result of bacterial reverse mutation test (Ames test)

Procedure of Ames test

The test was conducted in accordance with “ICH guideline S2 (R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use” (June, 2012). In this test, distilled water (D.W.) was used as a negative control, and 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2), sodium azide (SA), 9-Aminoacridine (9AA) and 2-aminoanthracene (2-AA) were used as a positive control substance.

Salmonella typhimurium (*S. typhimurium*) TA100, TA1535, TA98 and TA1537, and *Escherichia coli* (*E. coli*) WP2*uvrA* were used in the test. Pre-incubation was performed for each strain in the absence of metabolic activation (-S9) and in the presence of metabolic activation (+S9). After incubating the treated plate at 37°C for 48 hours, the number of revertant colonies was counted using a colony analyzer for the plates of the negative control group, test substance-treated group, and positive control group in each test system. Four plates were used for the negative controls, and two plates were used test sample-treated plates and positive controls.

When the average number of revertant colonies in the test sample-treated plate is at least twice that of the negative control group and the number of revertant colonies increases dose-dependently, the test sample was determined to be positive.

Results

With(+) or Without(-) S9 mix	Test sample dose (μg/plate)	Number of revertants (number of colonies/plate, Mean)											
		Base-pair substitution type						Frameshift type					
		TA100			TA1535			WP2*uvrA*			TA98			TA1537		
S9 mix (-)	0	126	130	(120)	9	11	(9)	24	22	(24)	39	37	(41)	5	2	(4)
	D.W.	125	98		11	5		24	26		42	44		5	5	
	313	115		(109)	5		(6)	27		(31)	26		(30)	5		(4)
		102			7			34			34			2		
	625	126		(133)	14		(10)	21		(25)	31		(37)	4		(3)
		140			6			29			42			2		
	1250	132		(117)	9		(6)	30		(25)	30		(30)	5		(4)
		101			2			19			29			2		
	2500	131		(140)	10		(11)	24		(23)	27		(34)	6		(5)
		148			11			21			41			4		
	5000	135		(135)	9		(10)	35		(33)	34		(32)	2		(2)
		135			11			31			29			1		
S9 mix (+)	0	107	102	(107)	12	10	(9)	20	19	(20)	35	36	(35)	10	6	(8)
	D.W.	102	115		9	6		20	22		34	35		9	7	
	313	131		(125)	10		(13)	27		(28)	31		(38)	7		(7)
		118			16			29			44			7		
	625	136		(131)	7		(6)	26		(28)	39		(43)	7		(5)
		125			5			29			47			2		
	1250	130		(127)	9		(8)	20		(23)	36		(41)	12		(9)
		123			6			25			45			6		

	2500	122 (129) 136	9 (8) 6	21 (23) 24	35 (43) 50	4 (5) 5
	5000	137 (125) 113	10 (10) 9	24 (21) 17	32 (33) 34	10 (8) 6
Positive control	Chemical	AF-2	SA	AF-2	AF-2	9AA
	Dose (μg/plate)	0.01	0.5	0.01	0.1	80
S9 mix (-)	Number of colonies/plate	295 (287) 278	504 (523) 541	64 (65) 65	566 (549) 531	555 (572) 588
Positive control	Chemical	2-AA	2-AA	2-AA	2-AA	2-AA
	Dose(μg/plate)	1.0	2.0	10	0.5	2.0
S9 mix (+)	Number of colonies/plate	1525 (1493) 1460	441 (453) 464	206 (260) 313	635 (659) 683	308 (271) 233

Conclusion

The test sample containing Paeonia Suffruticosa Root Extract at 1.5% was judged as Negative in Ames test.

Appendix 3. Assay procedure and result of *in vitro* micronucleus test

Procedure of *in vitro* micronucleus test

The test was conducted in accordance with "ICH guideline S2 (R1) : Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use" (June, 2012). In this test, distilled water (D.W.) was used as a negative control, and the short-time treatment method (-S9)) and in the 24h treatment method, mitomycin C (MMC), in the presence of a short-time treatment method with metabolic activation system (+S9) used cyclophosphamide (CP).

Chinese hamster lung fibroblasts (CHL/IU cells) were used. 1.0×10^4 cells/well were cultured for 3 days after seeding in 6 well plate. It was treated for 24 hours in the absence of the activation system. In short-time treatment (-S9) and short-time treatment (+S9), culture was continued for 18 hours after treatment for 6 hours.

After that, micronucleus specimens were prepared for both the short-time treatment method and the 24h treatment method, Acridine orange was used for the micronucleus stain and the appearance of micronuclei was determined for 2000 cells for each dose using the fluorescence microscope. Cells with micronuclei were counted. Based on the results, the appearance rate of cells with micronucleus was calculated.

Results of micronucleus analysis of CHL cells continuously treated for 24h without S9 mix

24h treatment method Group	Concentration (μg/mL)	No. of cells analyzed	No. of cells with micronuclei	(%)
Negative control	0	2000	25	1.23
Test sample	500	2000	17	1.36
	250	2000	38	1.92
	125	2000	21	1.05
MMC	0.03	2000	169	8.43

Results of micronucleus analysis of CHL cells treated for 6h without S9 mix (Recovery time:18h)

Short-time treatment (-S9) Group	Concentration (μg/mL)	No. of cells analyzed	No. of cells with micronuclei	(%)
Negative control	0	2000	30	1.49
Test sample	500	2000	40	2.00
	250	2000	26	1.28
	125	2000	45	2.23
MMC	0.05	2000	82	4.10

Results of micronucleus analysis of CHL cells treated for 6h with S9 mix (Recovery time:18h)

Short-time treatment (+S9) Group	Concentration (μg/mL)	No. of cells analyzed	No. of cells with micronuclei	(%)
Negative control	0	2000	36	1.82
Test sample	500	2000	45	2.25
	250	2000	41	2.04
	125	2000	44	2.18
CP	5	2000	384	18.69

Conclusion

The test sample containing Paeonia Suffruticosa Root Extract at 1.5% was judged as Negative in the *in vitro* micronucleus test.

Concentration of Use by FDA Product Category – *Paeonia suffruticosa*-Derived ingredients*

Paeonia Suffruticosa Root Extract
Paeonia Suffruticosa Extract
Paeonia Suffruticosa Bark Extract
Paeonia Suffruticosa Seed Oil
Paeonia Suffruticosa (Tree Peony) Root Bark Extract

Ingredient	Product Category	Maximum Concentration of Use
Paeonia Suffruticosa Root Extract	Hair conditioners	0.00009%
Paeonia Suffruticosa Root Extract	Shampoos (noncoloring)	0.0009%
Paeonia Suffruticosa Root Extract	Tonics, dressings, and other hair grooming aids	0.0011%
Paeonia Suffruticosa Root Extract	Other hair preparations (noncoloring)	0.00009%
Paeonia Suffruticosa Root Extract	Face powders	0.05%
Paeonia Suffruticosa Root Extract	Bath soaps and detergents	0.0025%
Paeonia Suffruticosa Root Extract	Face and neck products Not spray	0.0014%
Paeonia Suffruticosa Root Extract	Body and hand products Not spray	0.005%
Paeonia Suffruticosa Root Extract	Moisturizing products Not spray	0.002%
Paeonia Suffruticosa Root Extract	Paste masks and mud packs	0.000029-0.5%
Paeonia Suffruticosa Seed Oil	Bath soaps and detergents	0.0025%

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

Information collected in 2022
Table prepared: July 6, 2022
Updated March 29, 2024 added 0.5% face mask product to paste masks and mud packs
Updated April 11, 2025 added moisturizing products