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

Status:	Draft Tentative Report for Panel Review
Release Date:	November 8, 2024
Panel Meeting Date:	December 2 - 3, 2024

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; 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. This safety assessment was prepared by Preethi Raj, M.Sc., ormer Senior Scientific Analyst/Writer, CIR and Thushara Diyabalanage, Ph. D. Senior Scientific Analysts/Writer, CIR.

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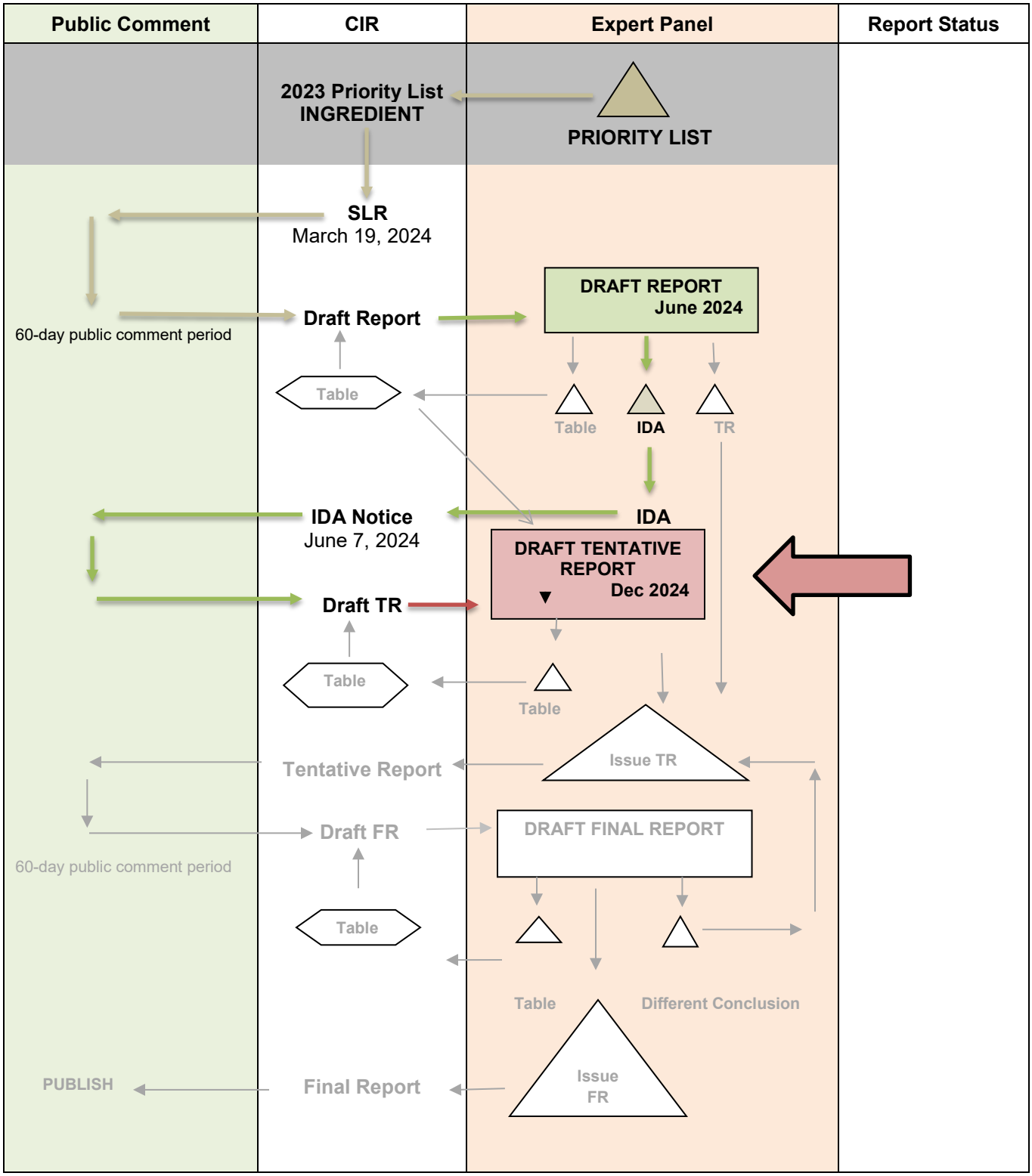
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Paeonia suffruticosa*-Derived Ingredients

MEETING December 2024



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage, Ph.D., Senior Scientific Analyst/Writer, CIR
Date: November 8, 2024
Subject: Amended Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Tentative Report on the Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics. (It is identified as *report_PaeoniaSuffruticosa_122024* in the pdf document.) At the June 2024 meeting, the Panel determined that the data were insufficient to support safety of these ingredients. The additional data requested are:

- For Paeonia Suffruticosa Root Bark Extract
  - Clarification on the definition, methos of manufacture, and composition as applicable to cosmetic use
  - Clarification as to whether Paeonia Suffruticosa Root Extract included the root bark of the plant
- For Paeonia Suffruticosa Seed Oil
  - Clarification of ingredient constituents
- For Paeonia Suffruticosa Bark Extract, Paeonia Suffruticosa Extract and Paeonia Suffruticosa Root Extract
  - Maximum concentration of use
  - Ocular irritation data (invitro) at the maximum reported concentration of use for near the eye.
- For all ingredients
  - 28-d dermal toxicity assay
    - If positive, data on systemic toxicity endpoints (e.g. developmental and reproductive toxicity)
  - Genotoxicity data
- For all ingredients, except Paeonia Suffruticosa root extract
  - Dermal irritation and sensitization data

Since the Insufficient Data Announcement (IDA) was issued, CIR has received a human repeated-insult patch test on a lotion containing 0.0015% Paeonia Suffruticosa Root Extract (*data_PaeoniaSuffruticosa_122024*). This information has been included in this report and is indicated by highlighted text.

Additional supporting documents for this report package include the following documents:

- flow chart (*flow_PaeoniaSuffruticosa_122024)*
- report history (*history_PaeoniaSuffruticosa_122024*)
- a search strategy (*search_PaeoniaSuffruticosa_122024*)
- a data profile (*dataprofile_PaeoniaSuffruticosa_122024*)
- transcripts from the previous meeting (*transcripts_PaeoniaSuffruticosa_122024*)
- PCPC comments on the Draft Report prepared for the June meeting *(PCPCcomments_PaeoniaSuffruticosa_122024)*
- responses to PCPC comments *(response-PCPCcomments_Paeoniasuffruticosa_122024)*

A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider and discuss the data (or lack thereof), and issue a Tentative Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: May 21, 2024

SUBJECT: Draft Report: Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics (draft prepared for the June 2024 meeting)

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

Method of Manufacture, Paeonia Suffruticosa Seed Oil – So it is clear that it is not an essential oil, it would be helpful to identify Paeonia Suffruticosa Seed Oil as a fixed oil in the Method of Manufacture section.

Toxicological Studies, Paeonia Suffruticosa (Tree Peony) Root Bark Extract – In all sections in which studies on the herbal mixture containing 14.29% moutan cortex are described, it would be helpful to state the doses of Paeonia Suffruticosa (Tree Peony) Root Bark Extract in addition to the doses of the mixture.

Tumor Promotion – Since the *Paeonia suffruticosa* preparations did not result in tumor promotion, the title of this section should be changed to Inhibition of Tumor Growth.

Dermal Irritation, Human; Summary – The solvent for the ingredient tested in the 24-hour closed patch study in 20 subjects was 90% ethanol as described on the same summary page that summarizes the irritation study.

Dermal Sensitization, Human; Summary – Since there is enough information to calculate the µg/cm^2 dose used in the HRIPT it should be calculated and stated in the CIR report (0.64 µg root extract/cm^2).

Summary – Since responses vary by cell type, it would be helpful to also state the cell type for which changes in IL-24 levels were described.

***Paeonia suffruticosa*-Derived Ingredients – December 2024 – Thushara Diyabalanage**	
Comment Submitter: Alexandra Kowcz, Industry Liaison to the CIR Expert Panel **Date of Submission: May 21, 2024**	
Comment	**Response/Action**
Method of Manufacture, Paeonia Suffruticosa Seed Oil – So it is clear that it is not an essential oil, it would be helpful to identify Paeonia Suffruticosa Seed Oil as a fixed oil in the Method of Manufacture section.	It is not an essential oil. It is a fixed oil. Addressed
Toxicological Studies, Paeonia Suffruticosa (Tree Peony) Root Bark Extract – In all sections in which studies on the herbal mixture containing 14.29% moutan cortex are described, it would be helpful to state the doses of Paeonia Suffruticosa (Tree Peony) Root Bark Extract in addition to the doses of the mixture.	Addressed
Tumor Promotion – Since the *Paeonia suffruticosa* preparations did not result in tumor promotion, the title of this section should be changed to Inhibition of Tumor Growth.	Addressed.
Dermal Irritation, Human; Summary – The solvent for the ingredient tested in the 24-hour closed patch study in 20 subjects was 90% ethanol as described on the same summary page that summarizes the irritation study.	Addressed.
Dermal Sensitization, Human; Summary – Since there is enough information to calculate the µg/cm2 dose used in the HRIPT it should be calculated and stated in the CIR report (0.64 µg root extract/cm2).	Addressed.
Summary – Since responses vary by cell type, it would be helpful to also state the cell type for which changes in IL-24 levels were described.	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 is being submitted

***Paeonia suffruticosa*-derived Ingredients Data Profile* – December 2-3, 2024 – Thushara Diyabalanage**																															
				Toxicokinetics				**Acute Tox**			**Repeated Dose Tox**			**DART**			**Genotox**		**Carci**			**Dermal Irritation**			**Dermal Sensitization**				**Ocular Irritation**		**Clinical Studies**	
	Reported Use	**Method of Mfg**	**Impurities**	**log P/log K_{ow}**	**Dermal Penetration**	**ADME**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**Inhalation**	**In Vitro**	**Dermal**	**Oral**	**In Vitro**	**In Vivo**	**In Vitro**	**Dermal**	**Oral**	**In Vitro**	**Animal**	**Human**	**In Vitro**	**Animal**	**Human**	**Phototoxicity**	**In Vitro**	**Animal**	**Retrospective/ Multicenter**	**Case Reports**
Paeonia Suffruticosa Bark Extract	X	X											X								X										
Paeonia Suffruticosa Extract	X	X																X													
Paeonia Suffruticosa Root Extract	X	X	X															X					X			X					
Paeonia Suffruticosa Seed Oil	X	X						X			X				X																
Paeonia Suffruticosa (Tree Peony) Root Bark Extract	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

((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 – 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 – 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. We're moving on to the other rereview ingredients. And Dr. Cohen is discussing Cholesterol.

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

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ABBREVIATIONS

CO_2	carbon dioxide
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook*
DMEM	Dulbecco's modified Eagle medium
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOPA	dihydroxyphenylalanine
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
HRIPT	human repeated-insult patch test
IC_{50}	half maximal inhibitory concentration
IL	interleukin
KFDA	Korea Food and Drug Administration
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
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
RPMI	Roswell Park Memorial Institute
TG	test guideline
TNF-α	tumor necrosis factor alpha
US	United States
VCRP	Voluntary Cosmetic Registration Program
VEGFR-3	vascular endothelial growth factor receptor-3

DRAFT 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. Industry should minimize impurities that could be present in cosmetic formulations, such as heavy metals and pesticide residues, according to limits set by the US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA). The Panel reviewed the available data to determine the safety of these ingredients. The Panel concluded that the 5 *Paeonia suffruticosa*-derived ingredients …[to be determined].

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 October 2024. 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] (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] 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 the development of *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, followed by filtration, concentration, adjustment, sedimentation, secondary filtration and adjustment prior to packaging.[12]

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.[13] 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

A *Paeonia suffruticosa* root bark extract was prepared by mixing cortex moutan powder with Roswell Park Memorial Institute (RPMI) 1640 medium and placing in an ultrasonic bath for 60 min.[14] The solution was filtered and concentrated resulting in a stock concentration of 50 mg/ml. An 80% ethanolic *Paeonia suffruticosa* root bark extract was prepared in an ultrasonic bath, filtered, concentrated under reduced pressure, and freeze-dried.[15] The lyophilized extract yielded 20.5 g of root bark extract in powder form.

Composition and Impurities

In a phytochemical analysis, flavonoids, tannins, terpenoids and steroids, paeonols (a group of phenols), and the other phenols were identified as the main constituents present in *Paeonia suffruticosa*.[16] 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-pewnta-*O*-*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.[17] 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).[12] 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 are present in the form of 12 triacylglycerol components in peony seed oil.[10] The major triacylgycerols 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.[10,13]

Paeonia Suffruticosa (Tree Peony) Root Bark Extract; Paeonia Suffruticosa Root Extract

It has been reported that about 119 secondary metabolites have been isolated and characterized from the root bark or the moutan cortex (root bark) of *Paeonia suffruticosa*.[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.[20]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. 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). 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 terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA, and these data are provided as RLD. Because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, it is not appropriate to contrast data from the VCRP and the RLD to determine a trend in frequency of use.

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[21] (Table 3). RLD submitted in 2024 indicate that this ingredient is used in 736 total formulations.[22] The results of the concentration of use survey reported by the Council in 2024 indicate Paeonia Suffruticosa Root Extract also has the highest maximum reported concentration of use at up to 0.5% in paste masks and mud packs.[23]

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 these ingredients may be marketed for use with airbrush delivery systems; however, this information is not available from the VCRP, RLD, or the Council survey. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the

Panel is not able to determine safety of 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.[24]

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.[14,15,25-27] 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.[28] 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.[29]

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.[18,30] 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

In an acute oral toxicity study, the LD_{50} for an herbal mixture containing 14.29% moutan cortex was determined to be > 5000 mg/kg.[26] 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*.

The acute oral toxicity of *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.

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.[18,30] 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 (articles in Chinese).

Paeonia Suffruticosa (Tree Peony) Root Bark Extract

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)."[26] 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.[26] 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).[27,31] 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 1×10^{-1} – 1×10^{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

Paeonia Suffruticosa Seed Oil

The effect of peony seed oil on sperm abnormality was evaluated in male rats.[18,30] Sexually mature male mice 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. No significant differences in maternal weight gain, early

embryonic development, live fetal mouse 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 on maternal and fetal rats. No further details were provided or could be gleaned (articles are in Chinese).

GENOTOXICITY STUDIES

Genotoxicity studies were not found in published literature, and unpublished data were not submitted.

CARCINOGENICITY STUDIES

In Vitro Cell Transformation

Paeonia Suffruticosa Extract

The antimigration and antiproliferative effects of an aqueous *Paeonia suffruticosa* extract upon 786O 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.[14] 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.[15] 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 a tumor promotion study, MB49 mouse bladder cancer cells were implanted in female C57BL/6 mice (age 6 wk).[14] 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.[32] 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, DOPAquinone 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.

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 the European Centre for Validation of Alternative Methods (ECVAM) and Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 439.[27] 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.[12] 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.[33] 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 an HRIPT using 106 subjects.[34] 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

Ocular irritation studies were not found in the published literature, and unpublished data were not submitted.

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. Thus, it is 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, in 213 formulations, 173 of which are leave-on formulations; RLD submitted in 2024 indicate that this ingredient is used in 736 total formulations. Results reported in 2024 for a concentration of use survey conducted by the Council indicate that Paeonia Suffruticosa Root Extract also has the highest reported concentration of use at up to 0.5% in paste masks and mud packs.

Kunming mice (10/sex) were administered a single oral dose of 15,000 mg/kg bw peony seed oil, via gavage. The acute oral LD_{50} was determined to be > 15,000 mg/kg bw. No mortality or statistically significant pathological changes occurred in ICR mice (10/sex/group) administered an oral dose of up to 60 ml/kg peony seed oil. In another acute oral toxicity study, the LD_{50} for a herbal mixture (2100 mg) containing 14.29% moutan cortex (300 g) was determined to be > 5000 mg/kg. The acute oral LD_{50} of a *Paeonia suffruticosa* tree peony bark extract was determined to be 3400 mg/kg in mice.

Healthy rats (12/sex) were administered up to 5000 mg/kg bw/d peony seed oil, via gavage, for 30 d. No abnormal changes in health status, biochemical indexes, hematological and blood biochemical indexes or immune organ indexes were observed; the maximum non-effective dosage, which is equivalent to the NOEL was estimated to be > 5,000 mg/kg bw.

The oral toxicity of an herbal mixture containing 14.29% moutan cortex (300 g of total 2100 g) was evaluated in 4-wk and 13-wk studies in rats, in accordance with KFDA standards for a toxicity study and GLP practices. In the 4-wk study, rats were dosed with 800, 2000, or 5000 mg/kg/d of the herbal mixture; a decrease in the serum sodium levels of 5000 mg/kg/d females was considered test article-related. The statistical significance of increased liver weights in the 2000 and 5000 mg/kg/d groups was not confirmed. In the 13-wk study, male and female Sprague-Dawley rats (10/sex/group) were administered 0, 750, 1500, or 3000 mg/kg/d of the herbal mixture, dissolved in saline, via gavage. No clinical abnormalities related to the test article administration 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 in hematocrit and mean corpuscular hemoglobin values for female rats in the 750 mg/kg/d group was observed. Hemoglobin distribution width and hemoglobin concentrations were notably lower in female rats from the 3000 mg/kg/d group. However, these values, in addition to notable increases in alkaline phosphatase and total bilirubin levels in the female rats from the 3000 mg/kg/d group and in relative liver weight in males from the 3000 mg/kg/d group, were within the normal range and were not considered to be test article-related. The NOAEL of the herbal mixture was determined to be 3000 mg/kg/d. 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. Besides lower blood sugar levels in treated rats, no other statistically significant differences were observed between treated rats and controls.

An embryonic stem cell test, validated by ECVAM, was used to evaluate the developmental toxicity of an aqueous *Paeonia suffruticosa* bark extract. Cultured, undifferentiated mouse embryonic stem cells were treated with the aqueous extract at concentrations of 0.01 0.1, 10, 100, 1000, or 10,000 µg/ml for 3 d. The beat rate of cardiomyocytes from the resultant embryoid bodies in treated embryonic stem cells was compared to those in untreated cells and these ratio values and corresponding concentrations were used to calculate differentiation ID_{50} values. In the cytotoxicity portion of the test, mouse embryonic stem cell and mouse fibroblast cell lines were treated with the test materials (in concentrations ranging from $1 \times 10^{-1} - 1 \times 10^{6}$ µg/ml) and evaluated in an MTT assay after 10 d of treatment. For cells treated with the aqueous *Paeonia suffruticosa* bark extract, cytotoxicity was observed in mouse fibroblast cell lines prior to stem cell cytotoxicity or inhibition of differentiation, 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. Sperm deformity rates were within a normal range for male rats administered up to 5000 mg/kg bw/d peony seed oil, via gavage, for 30 d; no significant differences in sperm abnormality rates were observed between each dose group and the negative controls. No embryotoxic or teratogenic effects were seen in an embryonic development study in which pregnant dams were orally dosed with up to 1.1 ml/kg bw/d peony seed oil for 20 d.

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, both of which are 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 greater than 2 mg/ml was observed in triple negative breast cancer cells treated with up to 4 mg/ml aqueous *Paeonia suffruticosa* root extract. 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. A statistically significant decrease in IL-6, IL-2, and TNF-α levels occurred at the 0.6 mg/ml concentration, but subsequently increased at concentrations greater than 2.5 mg/ml in an ELISA assay. IL-24 levels were notably increased in MDA-MB-231 cells treated with 2.5 and 4 mg/ml aqueous *Paeonia suffruticosa* root extracts, compared to controls; this increase of IL-24 was considered an up-regulation caused by increased IL-2 production. In Caspase-Glo assays, caspase 3/7 and 9 activity 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.

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. Exposure to *Paeonia suffruticosa* root bark extract increased the number of cells in the G1 and S phase in MB49 mouse bladder carcinoma and 5637 human bladder papillary transitional cell carcinoma cells, showing that *Paeonia suffruticosa* root bark extract induced the activation of caspase-3, and -8 (via extrinsic apoptosis) in a dose-dependent manner. *Paeonia suffruticosa* root bark extract inhibited cell invasion in a dose-dependent manner and a higher percentage than that of cell growth at the same dose, suggesting anti-invasive activity.

An ethanolic *Paeonia suffruticosa* root bark extract inhibited cell growth in human gastric cancer cells in both a dose- and time-dependent manner; compared to controls, the IC_{50} values of the *Paeonia suffruticosa* root bark extract were approximately 220 and 200 µg/ml at 48 and 72 h, respectively. In a cell cytotoxicity test, 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 from 3.81% at 12 h to 18.75% at 36 h in a time-dependent manner. The extract also decreased monolayer cell growth and changed cell morphology, similar to cells treated with cisplatin, an anti-cancer agent. Additionally, the ethanolic *Paeonia suffruticosa* root bark extract was suggested to induce apoptosis via the MDM2-p53-dependent pathway, an extrinsic caspase-dependent apoptosis pathway, in human gastric cancer cells.

To investigate the effects of aqueous *Paeonia suffruticosa* extract on tumor growth, female NOD-SCID mice were subcutaneously injected with 786O renal carcinoma cells; the animals (4/group) were orally administered either water or *Paeonia suffruticosa* extract (0.29 g/kg) 5 d/wk, and tumors were measured every 5 d till necropsy at 45 d. Tumor weights of the *Paeonia suffruticosa* extract-treated mice were remarkably lower than that of the control group (234.8 mg vs. 437.5 mg). In a pulmonary metastasis test, there were a statistically lower number of pulmonary nodules found in the mice intravenously inoculated with aqueous *Paeonia suffruticosa* extract compared to controls.

MB49 mouse bladder cancer cells were implanted in female C57BL/6 mice and mice (8/group) that were intravesically treated with either RPMI 1640 medium or 2.5 mg/mouse *Paeonia suffruticosa* root bark extract every other day from day 16 to day 24. Mice were killed and bladder volumes were measured on day 26. 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 statistically significant 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 intravesical treatment with the *Paeonia suffruticosa* root bark extract may decrease bladder tumor size without adversely affecting the liver or kidney.

The anti-melanogenesis properties of 8 *Paeonia suffruticosa* root cortex extracts (including sequential subfractions) were tested in murine melanoma B16 cells. Cells were treated with 1 µM α-MSH, alone, and with 50 or 100 µg/ml of the extracts, arbutin, or ascorbic acid for 72. The extract obtained with 95% ethanol (extract 1) and a methanolic subfraction obtained from the ethyl acetate layer of the ethanolic extract (extract 6) inhibited cellular tyrosinase activity by 79.6 and 65%, respectively, and decreased DOPAquinone and melanin content in B16 cells 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. In a fluorescence staining quantitative analysis, DNA content or nuclear morphology were not altered in B16 cells treated with 100 µg/ml of extract 1 or extract 6, 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 (tyrosinase-related protein-2 levels were not affected). Thus, the researchers surmised that extract 1 and 6 may inhibit melanin synthesis through downregulation of these associated enzymes.

The inhibitory effects of aqueous and ethanolic extracts of *Paeonia suffruticosa* root bark were evaluated in A2058 human melanoma cells in a tyrosinase assay. The ethanolic *Paeonia suffruticosa* root bark extract exhibited a greater tyrosinase inhibition rate compared to the aqueous extract. In subsequent studies, the ethanolic extract (tested at 6.25, 12.5, 25, or 50 µg/ml) showed a moderate and consistent reduction in the melanin content of human melanoma cells; no statistically significant difference in melanin content was observed when compared to cells treated with paeonol or arbutin. 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.

A reconstructed human epidermis tissue sample was treated with 100 ml of an aqueous *Paeonia suffruticosa* bark extract in an EpiDerm™ skin irritation test (measured as percent viability in the MTT reduction assay), in accordance with OECD TG 439. Compared to negative controls, cell viability of skin tissue samples exposed to aqueous *Paeonia suffruticosa* bark extract was within the range of 87.5 – 101.1% (> 50%); the tested extract was not considered irritating. Undiluted Paeonia Suffruticosa Root Extract (extracted with a 90% ethanolic solution) was not irritating in a 24-h closed patch dermal irritation using 20 subjects. A lotion containing 0.0015% Paeonia Suffruticosa Root Extract and a face mask formulation containing 0.5% Paeonia Suffruticosa Root Extract were not irritating or sensitizing when tested neat in an HRIPTs completed with 52 and 106 subjects, respectively.

DRAFT DISCUSSION

[Note: This Discussion is in the draft form, and changes will be made following the Panel meeting.]

The Panel reviewed the available, relevant data on *Paeonia suffruticosa*-dived ingredients and concluded [TBD]. This review included 5 cosmetic ingredients, one of which, Paeonia Suffruticosa (Tree Peony) Root Bark Extract, is not included in the *Dictionary*. However, it had reported uses in 2023 in the VCRP database and thus is included in this review.

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

CONCLUSION

To be determined.

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[16]

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	•				

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

Constituent*	Flower	Fresh leaves	Root	Root Cortex	Seed
peonidin 3,5-di-*O*-*β*-D-glucopyranoside	•				
peonin chloride	•				
populnin	•				
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				•	

*quantities of chemicals not provided; ♦referred to as root bark

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)[22]	VCRP (2023)[21]	% (2024)[23]	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]
	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

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	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]
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	0.0014 (not spray)
Night				2	1	NR	12	29	0.005 (not spray)
Paste Masks (mud packs)				11	1	NR	24	55	0.0014 (not spray)
Skin Fresheners							21	29	0.005 (not spray)
Other Skin Care Preparations	NR	1	NR	1 (l.o.); 1 (r.o.)	NR	NR	52 (l.o.); 26 (r.o.)	55	0.0014 (not spray)
Suntan Preparations							***1***		
Suntan Gels, Creams, and Liquids							1	NR	NR
Tattoo Preparations							***2***		
Other Tattoo Preparations							2	NA	NA

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	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]
Other Preparations (i.e., those that do not fit another category)				***2***	NA	NA	***29***	NA	NA
	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						

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)[22]	VCRP (2023)[21]	% (2024)[23]	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]	RLD (2024)[22]	VCRP (2023)[21]	% (2024)[23]
Other Hair Preparations									
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.

REFERENCES

1. Nikitakis J, Kowcz A, (eds). 2024. Web-Based *International Cosmetic Ingredient Dictionary and Handbook*. https://incipedia.personalcarecouncil.org/winci/. Last Updated: 2024. Date Accessed: May 1, 2024.
2. Shtein I, Gričar J, Lev-Yadun S, et al. Priorities for Bark Anatomical Research: Study Venues and Open Questions. *Plants (Basel, Switzerland)*. 2023;12(10):1985. doi: 10.3390/plants12101985.
3. Deng R, Gao J, Yi J, Liu P. Peony seeds oil by-products: Chemistry and bioactivity. *Ind Crops Prod*. 2022;187:115333–115359.
4. Zhao M, Wu SP. A review of the ethnobotany, phytochemistry and pharmacology of tree peony (Sect. moutan). *S Afr J Bot*. 2019;124:556–563.
5. Ekiert H, Klimek-Szczykutowicz M, Szopa A. *Paeonia* × *suffruticosa* (moutan peony)-A review of the chemical composition, traditional and professional use in medicine, position in cosmetics industries, and biotechnological studies. *Plants (Basel)*. 2022;11(23):3379–3413.
6. Sato T, Shirako S, Okuyama T, Ikeya Y, Nishizawa M. Anti-inflammatory effects of hydrophobic constituents in the extract of the root cortex of *Paeonia suffruticosa*. *Bioact Compd Health Dis*. 2022;5(8):160–173.
7. Wang S, Tang S, Lam S, et al. Aqueous extract of *Paeonia suffruticosa* inhibits migration and metastasis of renal cell carcinoma cells via suppressing VEGFR-3 pathway. *Evid Based Complementary Altern Med*. 2012:409823–409832.
8. Lin D, Wang S, Song T, Hsieh C, Tsai M. Safety and efficacy of tyrosinase inhibition of *Paeonia suffruticosa* Andrews extracts on human melanoma cells. *J Cosmet Dermatol*. 2019;18(6):1921–1929.
9. Kim D, Radin D, Leonardi D. Probing the molecular mechanisms governing the oncolytic activity of *Paeonia suffruticosa* on triple-negative breast cancer cells in vitro. *Anticancer Res*. 2017;37(9):4813–4819.
10. Cao W, Wang Y, Shehzad Q, Liu Z, Zeng R. Effect of different solvents on the extraction of oil from peony seeds (*Paeonia suffruticosa* Andr.): oil yield, fatty acids composition, minor components, and antioxidant capacity. *J Oleo Sci*. 2022;71(3):333–342.
11. Zhou H. M., Ma J. Q., Yang Z. Y., et alLi P. 2009. Toxicity test of peony seed oil on rats and mice. [Abstract in English, article is in Chinese].
12. Anonymous. 2024. Summary Information - Paeonia Suffruticosa Root Extract. [Unpublished data submitted by Personal Care Products Council on April 11, 2024].
13. Qu J, Zhang F, Thakur K, et al. The effects of process technology on the physicochemical properties of peony seed oil. *Grasas y Aceites*. 2017;68(2):e192–e202.
14. Lin MY, Lee YR, Chiang SY, et al. Cortex moutan induces bladder cancer cell death via apoptosis and retards tumor growth in mouse bladders. *Evid Based Complement Alternat Med*. 2013:207279–207287.
15. Choi HS, Seo HS, Kim JH, Um JY, Shin YC, Ko SG. Ethanol extract of *Paeonia suffruticosa* Andrews (PSE) induced AGS human gastric cancer cell apoptosis via fas-dependent apoptosis and MDM2-p53 pathways. *J Biomed Sci*. 2012;19(1):82–94.
16. He C, Peng Y, Zhang Y, Xu L, Gu J, Xiao P. ChemInform Abstract: Phytochemical and biological studies of *Paeoniaceae*. *ChemInform*. 2010;41(27):805–838.
17. Lei G, Song C, Wen X, Gao G, Qi Y. Chemical diversity and potential target network of woody peony flower essential oil from eleven representative cultivars (*Paeonia* × *suffruticosa* Andr.). *Molecules*. 2022;27(9):2829–2849.
18. Deng R, Gao J, Yi J, Liu P. Could peony seeds oil become a high-quality edible vegetable oil? The nutritional and phytochemistry profiles, extraction, health benefits, safety and value-added-products. *Food Res Int*. 2022;156:111200–111234.
19. Yang X, Zhang D, Song LM, Xu Q, Li H, Xu H. Chemical profile and antioxidant activity of the oil from peony seeds (*Paeonia suffruticosa* Andr.). *Oxid Med Cell Longev*. 2017:9164905–9164916.
20. Yang S, Liu X, He J, Liu M. Insight into seasonal change of phytochemicals, antioxidant, and anti-aging activities of root bark of P*aeonia suffruticosa* (cortex moutan) combined with multivariate statistical analysis. *Molecules*. 2021;26(20):6102–6121.
21. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients.College Park, MD. 2023 [Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2023; received February 2, 2023].

22. U.S. Food and Drug Administration Office of the Chief Scientist. 2024. Registration and Listing Data - Frequency of Use of Cosmetic Products.College Park, MD [Obtained under the Freedom of Information Act from the Division of Freedom of Information; requested as "Frequency of Use Data" July 17, 2024; received July 30, 2024].

23. Personal Care Products Council. 2024. Updated Concentration of Use by FDA Product Category: *Paeonia suffruticosa*-Derived Ingredients. [Unpublished data submitted by the Personal Care Products Council on March 29, 2024].

24. European Union. 2024. EUR-Lex: Access to European Union law. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32022D0677&qid=1710175501718. Last Updated: 2024. Date Accessed: May 1, 2024.

25. Wang Z, He C, Peng Y, Chen F, Xiao P. Origins, phytochemistry, pharmacology, analytical methods and safety of cortex moutan (*Paeonia suffruticosa* Andrew): a systematic review. *Molecules*. 2017;22(6):946–973.

26. Chung HS, Lee H, Bae H. Thirteen-week study of PM014 subchronic oral toxicity in rats. *Evid Based Complement Alternat Med*. 2014:189673–189681.

27. Li L, Mou X, Xie H, et al. In vitro tests to evaluate embryotoxicity and irritation of Chinese herbal medicine (Pentaherbs formulation) for atopic dermatitis. *J Ethnopharmacol*. 2023;305:116149–116157.

28. Yin C, Zhang X, Li K, et al. Evaluation on the fresh eating quality of tree peony flowers. *Food Biosci*. 2022;47:101611–101622.

29. Su J, Ma C, Liu C, Gao C, Nie R, Wang H. Hypolipidemic activity of peony seed oil rich in α-linolenic, is mediated through inhibition of lipogenesis and upregulation of fatty acid β-oxidation. *J Food Sci*. 2016;81(4):H1001–H1009.

30. Zhu WX, Li X, Liu SY, Bai XT, Liu K. Toxicological assessment of peony seed oil. *Food Science*. 2010;31(11):248–251. (Abstract in English, article is in Chinese).

31. Genschow E, Spielmann H, Scholz G, et al. The ECVAM international validation study on in vitro embryotoxicity tests: results of the definitive phase and evaluation of prediction models. *ATLA*. 2002;30(2):151–176.

32. Ding HY, Chou TH, Lin RJ, Chan LP, Wang GH, Liang CH. Antioxidant and antimelanogenic behaviors of *Paeonia suffruticosa*. *Plant Foods Hum Nutr*. 2011;66(3):275–284.

33. Anonymous. 2022. Clinical safety evaluation: repeated insult patch test of a lotion containing 0.0015% Paeonia Suffruticosa Root Extract. [Unpublished data submitted by the Personal Care Products Council on July 25, 2024].

34. Anonymous. 2020. Repeated insult patch test (face mask containing 0.5% Paeonia Suffruticosa Root Extract). [Unpublished data submitted by the Personal Care Products Council on March 29, 2024].

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: July 25, 2024

SUBJECT: Paeonia Suffruticosa Root Extract

Anonymous. 2022. Clinical safety evaluation repeated insult patch test (lotion containing 0.0015% Paeonia Suffruticosa Root Extract).

Dose: approximately 25-38 mg/cm^2 of the test material (0.375-0.57 µg/cm^2 Paeonia Suffruticosa Root Extract)

[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

lotion containing 0.0015% Paeonia Suffruticosa Root Extract

Sponsor

[redacted]

Sponsor Representatives

[redacted]

Clinical Testing Facility

[redacted]

Sponsor Code: [redacted]

Date of Final Report

01.26.22

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted]

24 Jan 2022
Date

Laboratory Director
Study Director

[redacted]

1/24/22
Date

Scientific Director
Principal Investigator

[redacted]

1-19-2022
Date

Board-Certified Dermatologist
Medical Investigator

[redacted]

QUALITY ASSURANCE STATEMENT

This study ([redacted]) was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in 21 CFR Part 50 (Protection of Human Subjects – Informed Consent) and the Standard Operating Procedures of [redacted]

For purposes of this clinical study:

_X_	Informed Consent was obtained.
____	Informed Consent was not obtained.
_X_	An IRB review was not required.
____	An IRB review was conducted and approval to conduct the proposed clinical research was granted.

To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the applicable study records and report. This report is considered a true and accurate reflection of the testing methods and source data.

[redacted]
Manager, Quality Assurance

24 Jan 2022
Date

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the irritation and/or sensitization potential of the test article after repeated application under occlusive patch test conditions to the skin of human subjects (exclusive panel).

2.0 SPONSOR

[redacted]

2.1 Sponsor Representatives

[redacted]

3.0 CLINICAL TESTING FACILITY

The study was conducted by:

[redacted]

4.0 CLINICAL INVESTIGATORS

Study Director:
Principal Investigator:
Medical Investigator:

[redacted]

5.0 STUDY DATES

Study initiation: November 24, 2021

Final evaluation: January 7, 2022

[redacted]

[redacted]

6.0 ETHICS

6.1 Ethical Conduct of the Study

This study was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in Title 21 of the U.S. Code of Federal Regulations (CFR), the Declaration of Helsinki and/or [redacted] Standard Operating Procedures.

6.2 Subject Information and Consent

This study was conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed Consent was obtained from each subject in the study and documented in writing before participation in the study. A copy of the Informed Consent was provided to each subject.

7.0 TEST MATERIAL

The test article used in this study was provided by:

[redacted]

It was received on September 24, 2021 and identified as follows:

[redacted] Entry No.	Test Article ID	Description
[redacted]	[redacted]	Beige Lotion*

*The test article was volatilized at least 30 minutes, but less than 90 minutes, on the patch prior to application to the skin.

8.0 TEST SUBJECTS

At least 50 male and female subjects ranging in age from 18 to 79 years were to be empanelled for this test. Subject demographics are listed in Table 1.

The subjects chosen were to be dependable and able to read and understand instructions. The subjects were not to exhibit any physical or dermatologic condition that would have precluded application of the test article or determination of potential effects of the test article.

[redacted]

[redacted]

9.0 TEST PROCEDURE

The 9 Repeated Insult (occlusive) Patch Test (9-RIPT)[1] was conducted as follows:

9.1 Induction Phase

A sufficient amount of the test article (approximately 0.1 g – 0.15 g) was placed onto a Parke-Davis Readi-Bandage® occlusive patch (approximately 25 - 38 mg/cm^2 of test material) and applied to the back of each subject between the scapulae and waist, adjacent to the spinal mid-line. This procedure was performed by a trained technician/examiner and repeated every Monday, Wednesday and Friday until 9 applications of the test article had been made.

The subjects were instructed to remove the patch 24 hours after application. Twenty-four hour rest periods followed the Tuesday and Thursday removals and 48-hour rest periods followed each Saturday removal. Subjects returned to the Testing Facility and the site was scored by a trained examiner just prior to the next patch application.

If a subject developed a positive reaction of a level 2 erythema or greater during the Induction phase or if, at the discretion of the Study Director, the skin response warranted a change in site, the patch was applied to a previously unpatched, adjacent site for the next application. If a level 2 reaction or greater occurred at the new site, no further applications were made. However, any reactive subjects were subsequently Challenge patch tested.

9.2 Challenge Phase

After a rest period of approximately 2 weeks (no applications of the test article), the Challenge patch was applied to a previously unpatched (virgin) test site. The site was scored 24 and 72 hours after application. All subjects were instructed to report any delayed skin reactivity that occurred after the final Challenge patch reading. When warranted, selected test subjects were called back to the Clinic for additional examinations and scoring to determine possible increases or decreases in Challenge patch reactivity.

Dermal responses for both the Induction and Challenge phases of the study were scored according to the following 6-point scale:

0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

All other observed dermal sequelae (eg, edema, dryness, hypo- or hyperpigmentation) were appropriately recorded on the data sheet and described as mild, moderate or severe.

---

[1] Marzulli FN, Maibach HI. (1976) Contact allergy: predictive testing in man. *Contact Dermatitis.* 2, 1-17.

[redacted]

[redacted]

9.0 TEST PROCEDURE (CONT'D)

9.3 Data Interpretation

Edema, vesicles, papules and/or erythema that persist or increase in intensity either during the Induction and/or Challenge phase may be indicative of allergic contact dermatitis. Allergic responses normally do not resolve or improve markedly at 72-96 hours.

Exceptions to typical skin reactions may occur. These may include, but not be limited to, symptoms of allergic contact sensitivity early in the Induction period to one or more test products. When this occurs in one subject, such a reaction usually suggests either an idiosyncratic response or that the subject had a pre-exposure/sensitization to the test material or component(s) of the test material or a cross-reactivity with a similar product/component. Data for such reactions will be included in the study report but will not be included in the final study analysis/conclusion of sensitization.

10.0 RESULTS AND DISCUSSION

(See Table 2 for Individual Scores)

A total of 55 subjects (12 males and 43 females ranging in age from 18 to 77 years) were empanelled for the test procedure. Fifty-two (52/55) subjects satisfactorily completed the test procedure on Test Article: [redacted]. Three (3/55) subjects discontinued for personal reasons unrelated to the conduct of the study. Discontinued subject data are shown up to the point of discontinuation, but are not used in the Conclusions section of this final report.

Induction Phase Summary

Test Article	Induction Scores (Number of Responses)						Evidence of Irritation
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

Challenge Phase Summary

Test Article	Challenge Scores (Number of Responses)						Evidence of Sensitization
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

There was no skin reactivity observed at any time during the course of the study.

11.0 CONCLUSIONS

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in 52 subjects, Test Article: [redacted] was "Dermatologist-Tested" and was not associated with skin irritation or allergic contact dermatitis in human subjects.

[redacted]

[redacted]

TABLE 1

SUBJECT DEMOGRAPHICS

Test Article: [redacted]

Subject No.	Initials	Age	Sex	Race	Subject No.	Initials	Age	Sex	Race
1	[redacted]	60	F	WH	29	[redacted]	43	F	HS
2		61	M	WH	30		65	F	WH
3		54	M	BH	31		68	F	WH
4		24	F	HS	32		34	M	WH
5		46	F	HS	33		51	F	HS
6		18	F	WH	34		70	F	HS
7		64	F	WH	35		28	F	WH
8		40	M	BH	36		52	M	WH
9		38	F	WH	37		53	M	WH
10		47	M	WH	38		74	F	HS
11		50	F	WH	39		50	F	HS
12		66	M	WH	40		69	F	WH
13		42	F	HS	41		77	F	WH
14		61	F	BA	42		58	F	WH
15		34	F	WH	43		44	F	HS
16		55	F	WH	44		68	F	HS
17		55	F	BA	45		38	F	WH
18		44	F	WH	46		43	F	BA
19		54	F	HS	47		56	F	HS
20		43	F	WH	48		61	M	WH
21		65	F	WH	49		50	F	BA
22		46	F	WH	50		63	F	WH
23		41	F	HS	51		59	M	BA
24		36	F	HS	52		67	M	BA
25		67	F	WH	53		59	F	WH
26		28	F	HS	54		44	F	WH
27		51	F	HS	55		55	F	WH
28		43	M	WH					

BA = Black
BH = Black (Hispanic)
HS = Hispanic
WH = White

Shaded area = Discontinued subject

[redacted]

TABLE 2

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj.	Induction Evaluation Number									Challenge Virgin Site	
No.	1	2	3	4	5	6	7	8	9	24hr	72hr
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0
23	0	Discontinued									
24	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0
29	0	Discontinued									
30	0	0	0	0	0	0	0	0	0	Discontinued	

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

TABLE 2 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj.	Induction Evaluation Number									Challenge Virgin Site	
No.	1	2	3	4	5	6	7	8	9	24hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
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[redacted]