Safety Assessment of *Nelumbo nucifera*-Derived Ingredients as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	February 14, 2025
Panel Meeting:	March 13 - 14, 2025

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; 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. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Preethi Raj, M.Sc., former Senior Scientific Analyst/Writer, CIR, and Thushara Diyabalanage, Ph.D. Senior Scientific Analyst/Writer, CIR.

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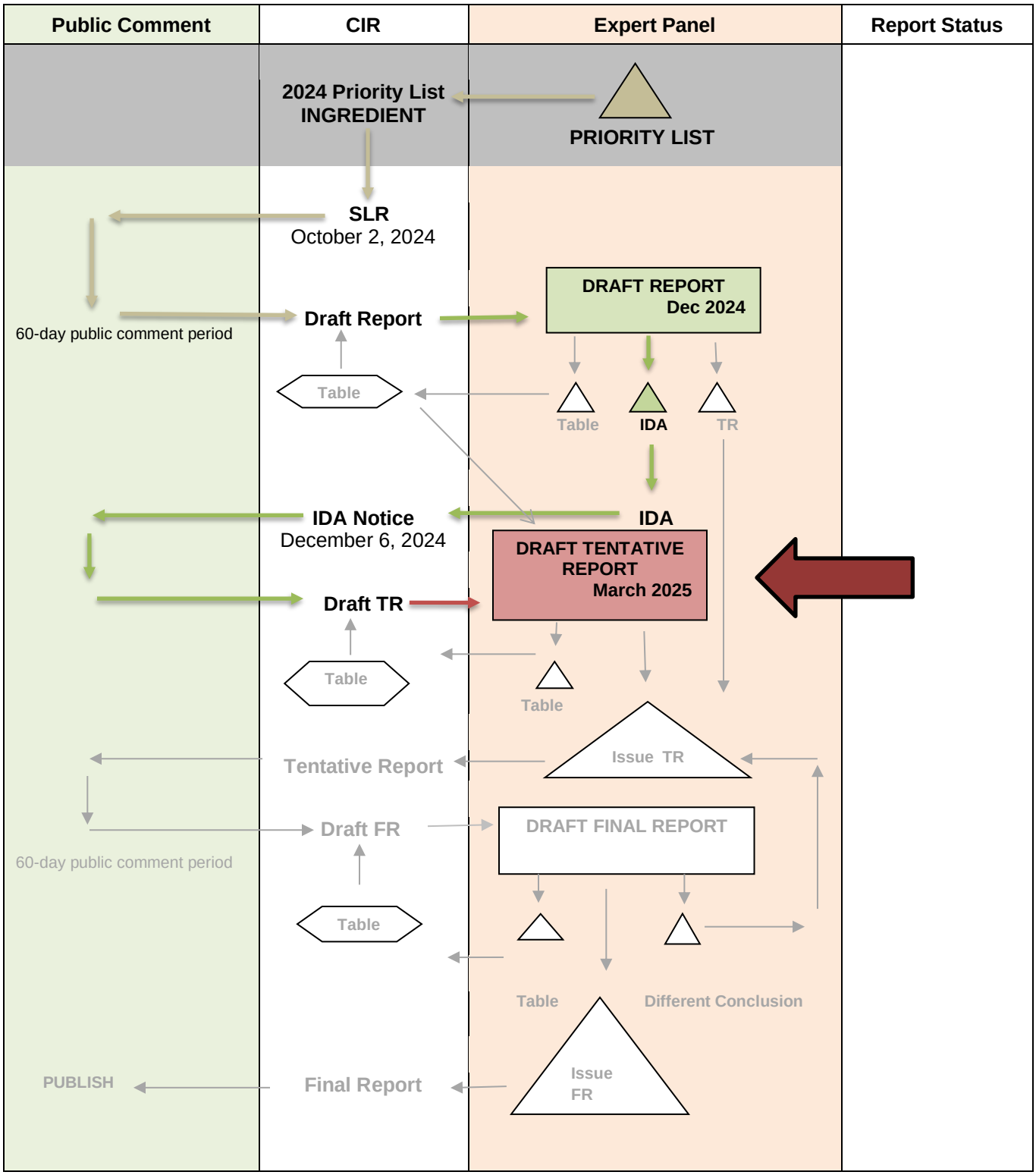
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Nelumbo nucifera* - Derived Ingredients

MEETING March 2025



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: February14, 2025
Subject: Safety Assessment of *Nelumbo nucifera*-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Tentative Report on the Safety Assessment of *Nelumbo nucifera*-Derived Ingredients as Used in Cosmetics. (It is identified as *report_NelumboNucifera_032025* in the pdf document) A draft report was submitted to the Panel in December 2024 for which Panel issued an insufficient data conclusion.

This report reviews the safety of 14 *Nelumbo nucifera*-derived ingredients. Among them, one, Nelumbo Nucifera Flower Oil, is not included in the *Dictionary*. It had reported uses in 2023 in the VCRP database and in 2024 in the RLD, and is thus included in this review.

In its insufficient data announcement, the Panel listed following requirements

- For all ingredients
  - Composition and impurities
  - Methods of manufacturing
  - 28-day dermal toxicity assays
    - if positive, additional data (e.g., developmental and reproductive toxicity data) may be needed
  - In vivo genotoxicity data
  - UV absorption spectra
- For the callus, phytoplacenta and stamen-derived ingredients
  - Dermal irritation and sensitization data at maximum concentration of use
- For all except the flower and germ-derived ingredients
  - In vitro genotoxicity data
- Flower and whole plant-derived ingredients
  - Developmental and reproductive toxicity data
- For all except flower-derived ingredients
  - In vitro ocular irritation data

The following information received from the Council in response to the IDA is included with this submission and has been incorporated into the report and highlighted in yellow.

- Personal Care Product Council. 2025. Concentration of use by FDA product category: Nelumbo Nucifera Phytoplacenta Extract (*data1_NelumboNucifera_032025*)
- Anonymous. 2024. Summary Information - UV absorption of Nelumbo Nucifera Germ Extract in water and butylene glycol. (*data2_NelumboNucifera_032025*)
- Anonymous. 2024. Summary Information – Trade name mixture containing a maximum of 1.2% Nelumbo Nucifera Leaf Extract (*data3_NelumboNucifera_032025*)
- Anonymous. 2024. Summary Information - Studies completed on a foundation containing 0.2% Nelumbo Nucifera Flower Water (*data4_NelumboNucifera_032025*)
- Anonymous. 2024. Summary Information - Studies completed on a foundation containing 0.2% Nelumbo Nucifera Root Water (*data4_NelumboNucifera_032025*)
- Anonymous. 2017. Clinical safety evaluation repeated insult patch test of a foundation containing 0.00001% Nelumbo Nucifera Flower Extract tested as received. (*data5_NelumboNucifera_032025*)
- Anonymous. 2009. Clinical safety evaluation repeated insult patch test (emulsion containing 0.0001% Nelumbo Nucifera Germ Extract tested as received) (*data5_NelumboNucifera_032025*)

Comments received from the Council on the Draft Report prior to the last review have been addressed (*PCPCcomments_NelumboNucifera_032025* and *response-PCPCcomments_NelumboNucifera_032025*, respectively).

The following supporting documents are also included in this package.

- search strategy (*search_NelumboNucifera_032025)*
- data profile (*dataprofile_NelumboNucifera_032025)*
- history *(history_NelumboNucifera_032025)*
- flow chart (*flow_NelumboNucifera_032025*)
- transcripts *(transcripts_NelumboNucifera_032025)*

The Panel should carefully consider and discuss the data (or lack thereof) and be prepared to 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: November 26, 2024

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

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

Composition and Impurities, Nelumbo Nucifera Seed Powder – For the minerals, please clarify what the percentages represent (likely a percentage of the mineral component rather than a percentage of the of the seeds).

Cosmetic Use – It is misleading to call the VCRP data "ingredient-centric". The raw VCRP data are also "product-centric", it is just that FDA provided the VCRP data to CIR in a format that was "ingredient-centric". It is a difference in how the data were provided to CIR.

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

Cosmetic Use – Please correct: "leg and body parts" ("parts" should be "paints")

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

Table numbers – Please correct the table numbers in the text. For example, the repeat oral dose studies are now in Table 11 not Table 10 as stated in the text.

Short-Term, Subchronic, Chronic; Summary; Table 11 – The 1.44 and 4.32 g/kg/day doses for the study of the herbal mixture capsule containing 33% *Nelumbo nucifera* appear to be the doses of the mixture. It would be helpful to make this clear by stating the doses of the mixture and the dose of *Nelumbo nucifera* (at least in the table where more details of the study are provided).

Effects on Pigmentation – What concentration of arbutin was used as the positive control?

Summary – Please correct: "According to 2024 RLD that were submitted, Based on RLD of 2024," (one of these phrases needs to be deleted)

Table 4 – Combining composition information from multiple studies is difficult. All of the blank cells in Table 4 are confusing as it is not clear what they mean. The information in Table 4 suggests that only one study looked for flavonoid glycosides in the stamen as the rest of the cells for stamen are blank. At a minimum, the information on stamen should be removed from Table 4 as the information on composition of the stamen in Table 6 is much more useful. Also consider doing research on the constituents in the other compounds section of Table 4 to see if they can be placed with the other categories. For example, isoquecetrin is a flavonoid and should be moved to that section of the table.

Please correct: "3-O-β-d[-]xylopyranosyl-(1-2)-β-d-galactopyranoside" (add [-])

Nelumbo nucifera-derived Ingredients – March 2025 – Thushara Diyabalanage	
Comment Submitter: Alexandra Kowcz, MS, MBA Industry Liaisons to the CIR Expert Panel **Date of Submission: November 26, 2024**	
Comment	**Response/Action**
Nelumbo Nucifera Seed Powder- for minerals please carify what the percentage represents (likely a percentage of the mineral component rather than a percentage of the of the seeds)	The paper describes the percentage of different minerals out of the total mineral content in seeds.
Cosmetic Use – It is misleading to call the VCRP data "ingredient-centric". The raw VCRP data are also "product-centric", it is just that FDA provided the VCRP data to CIR in a format that was "ingredient-centric". It is a difference in how the data were provided to CIR.	Addressed
The Cosmetic Use section should also note that small businesses are exempt from MoCRA reporting for most cosmetic product categories. MoCRA defines a small business as average gross annual sales of cosmetic products in the United States for the previous 3 years of	Addressed
Cosmetic Use – Please correct: "leg and body parts" ("parts" should be "paints")	Addressed
It should be noted that FDA is collecting data for airbrush use of four makeup product categories (foundations, leg and body paints, makeup bases, other makeup preparations) and indoor tanning products. The PCPC surveys also request that airbrush uses be identified	Addressed
Short-Term, Subchronic, Chronic; Summary; Table 11 – The 1.44 and 4.32 g/kg/day doses for the study of the herbal mixture capsule containing 33% Nelumbo nucifera appear to be the doses of the mixture. It would be helpful to make this clear by stating the doses of the mixture and the dose of Nelumbo nucifera (at least in the table where more details of the study are provided).	Addressed
Effects on Pigmentation – What concentration of arbutin was used as the positive control?	The publication does not directly indicate the concentration of arbutin used. However, based on the trosinase inhihibition assay and DOPA oxidase inhibition assay, test substances and positive controil were used in same concentrations in each concentration tested (10, 50, 100, and 200µg/ml)
Summary – Please correct: "According to 2024 RLD that were submitted, Based on RLD of 2024," (one of these phrases needs to be deleted)	Addressed
Table 4 – Combining composition information from multiple studies is difficult. All of the blank cells in Table 4 are confusing as it is not clear what they mean. The information in Table 4 suggests that only one study looked for flavonoid glycosides in the stamen as the rest of the cells for stamen are blank. At a minimum, the information on stamen should be removed from Table 4 as the information on composition of the stamen in Table 6 is much more useful. Also consider doing research on the constituents in the other compounds section of Table 4 to see if they can be placed with the other categories. For example, isoquecetrin is a flavonoid and should be moved to that section of the table	Addressed
Please correct: "3-O-β-d[-]xylopyranosyl-(1-2)-β-d-galactopyranoside" (add [-])	Addressed

CIR History of:

Nelumbo nucifera-Derived Ingredients

October 2, 2024
The scientific literature review (SLR) was issued by CIR

October 29, 2024
Council comments were received.

December 2024 Panel – IDA issued
Data needs:

For all ingredients
- Composition and impurities
- Methods of manufacturing
- 28-day dermal toxicity assays
  - if positive, additional data (e.g., developmental and reproductive toxicity data) may be needed
- In vivo genotoxicity data
- UV absorption spectra

- For the callus, phytoplacenta and stamen-derived ingredients
  - Dermal irritation and sensitization data at maximum concentration of use
- For all except the flower and germ-derived ingredients
  - In vitro genotoxicity data
- Flower and whole plant-derived ingredients
  - Developmental and reproductive toxicity data
- For all except flower-derived ingredients
  - In vitro ocular irritation data

Data received:
Personal Care Product Council. 2025. Concentration of use by FDA product category: Nelumbo Nucifera Phytoplacenta Extract
Anonymous. 2024. Summary Information - UV absorption of Nelumbo Nucifera Germ Extract in water and butylene glycol.
Anonymous. 2024. Summary Information – Extract of Nelumbo nucifera (lotus) Flowers in isostearyl isostearate (extraction solvent)
Anonymous. 2024. Summary Information – Extract of Nelumbo nucifera (lotus) Flowers in propanediol and glycerin (extraction solvents) with Nymphaea Caerulea Flower Extract
Anonymous. 2024. Summary Information - Nelumbo Nucifera Germ Extract
Anonymous. 2024. Summary Information – Trade name mixture containing a maximum of 1.2% Nelumbo Nucifera Leaf Extract
Anonymous. 2024. Summary Information - Studies completed on a foundation containing 0.2% Nelumbo Nucifera Flower Water
Anonymous. 2024. Summary Information - Studies completed on a foundation containing 0.2% Nelumbo Nucifera Root Water
Anonymous. 2017. Clinical safety evaluation repeated insult patch test of a foundation containing 0.00001% Nelumbo Nucifera Flower Extract tested as received.
Anonymous. 2009. Clinical safety evaluation repeated insult patch test (emulsion containing 0.0001% Nelumbo Nucifera Germ Extract tested as received)

Nelumbo nucifera -derived ingredients Data Profile* – March 2025 – 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	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Nelumbo Nucifera Callus Culture Extract	X	X																											
Nelumbo Nucifera Extract	X	X	X					X			X																		
Nelumbo Nucifera Flower Extract	X	X	X					X							X						X			X		X			
Nelumbo Nucifera Flower/ Leaf /Stem/ Juice	X	X						X													X			X					
Nelumbo Nucifera Flower Oil	X																												
Nelumbo Nucifera Flower Water	X	X						X																X	X	X			
Nelumbo Nucifera Germ Extract	X	X	X				X								X				X	X	X	X	X	X	X				
Nelumbo Nucifera Leaf Extract	X	X	X																		X			X		X			
Nelumbo Nucifera Phytoplacenta Culture Extract	X																												
Nelumbo Nucifera Root Extract	X	X	X					X													X								
Nelumbo Nucifera Root Water Extract	X																							X	X				
Nelumbo Nucifera Seed Extract	X	X	X					X			X			X							X								
Nelumbo Nucifera Seed Powder	X	X	X																										
Nelumbo Nucifera Stamen Extract	X	X	X					X																					

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

Nelumbo nucifera-derived Ingredients

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Nelumbo Nucifera Callus Culture Extract	85085-51-4	√	NR														
Nelumbo Nucifera Extract	85085-51-4	√	√														
Nelumbo Nucifera Flower Extract	85085-51-4	√	NR														
Nelumbo Nucifera Flower Oil	NA	√	NR														
Nelumbo Nucifera Flower Water	85085-51-4	√	NR														
Nelumbo Nucifera Flower/Leaf/Stem Juice	85085-51-4	NR	NR														
Nelumbo Nucifera Germ Extract	85085-51-4	√	NR														
Nelumbo Nucifera Leaf Extract	85085-51-4	√	NR														
Nelumbo Nucifera Root Extract	85085-51-4	√	NR														
Nelumbo Nucifera Root Water	85085-51-4	√	NR														
Nelumbo Nucifera Seed Extract	85085-51-4	√	NR														
Nelumbo Nucifera Seed Powder	85085-51-4	√	NR														
Nelumbo Nucifera Stamen Extract	85085-51-4	√	NR														

NR – not reported

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	AGRICOLA	IFRA	RIFM
Nelumbo Nucifera Callus Culture Extract	85085-51-4								
Nelumbo Nucifera Extract	85085-51-4								
Nelumbo Nucifera Flower Extract	85085-51-4								
Nelumbo Nucifera Flower Oil	NA								
Nelumbo Nucifera Flower Water	85085-51-4								
Nelumbo Nucifera Flower/Leaf/Stem Juice	85085-51-4								
Nelumbo Nucifera Germ Extract	85085-51-4								

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	AGRICOLA	IFRA	RIFM
Nelumbo Nucifera Leaf Extract	85085-51-4								
Nelumbo Nucifera Root Extract	85085-51-4								
Nelumbo Nucifera Root Water	85085-51-4								
Nelumbo Nucifera Seed Extract	85085-51-4								
Nelumbo Nucifera Seed Powder	85085-51-4								
Nelumbo Nucifera Stamen Extract	85085-51-4								

Search Strategy

((nelumbo nucifera callus culture extract) OR (85085-51-4)) OR (nelumbo nucifera (lotus) callus culture extract)) OR (lotus stem cell)) OR (nelumbo nucifera extract)) OR (nelumbo speciosa extract)) OR (harmoniance)) OR (nelumbo nucifera flower extract)) OR (nelumbo nucifera (lotus) extract)) OR (nelumbo nucifera (lotus) flower extract)) OR (nelumbo nucifera (lotos) extract)) OR (ritualessenz tm lotus p)) OR (nelumbo nucifera flower water)) OR (nelumbo nucifera (lotus) flower water)) OR (vegebios of bali lotus 1.5p)) OR (vegebios of sacred white lotus 1.5p)) OR (mg-relax)) OR (nelumbo nucifera flower/leaf/stem juice)) OR (lotus enriched serum fraction)) OR (nelumbo nucifera (lotus) flower/leaf/stem juice)) OR (nelumbo nucifera germ extract)) OR (nelumbo nucifera (lotus) germ extract)) OR (korea nelumbo nucifera embryo extract)) OR (lotus germ extract bg)) OR (nelumbo nucifera germ extract bg-05)) OR (nelumbo nucifera leaf extract)) OR (nelumbo nucifera (lotus) leaf extract)) OR (oristract nne)) OR (dactortec kissom)) OR (lotus complex ai)) OR (prosveltyl)) OR (yeonip extract)) OR (nelumbo nucifera root extract)) OR (nelumbo nucifera (lotus) root extract)) OR (extract of nelumbio nucifera)) OR (lotus root extract)) OR (yeonkeun extract)) OR (nelumbo nucifera root water)) OR (nelumbo nucifera (lotus) root water)) OR (nf lotus root water)) OR (nf herb extract (2))) OR (extrait originel lotus)) OR (nelumbo nucifera seed extract)) OR (nelumbo nucifera (lotus) seed extract)) OR (actiphyte of sacred lotus seed pg50)) OR (balasu(germination mixed herb water) extract)) OR (lotus extract hg 810)) OR (sid cheogsimyeonjaeum complex)) OR (yeonjayuk extract sfe)) OR (nelumbo nucifera seed powder)) OR (nelumbo nucifera (lotus) seed powder)) OR (lotus exfoliator)) OR (nelumbo nucifera stamen extract)) OR (nelumbo nucifera (lotus) stamen extract)) OR (lotusia bg)) OR (lotusia oss)) AND (toxicity) – [68,749 hits/ 12 useful]

((((((((((((((((((((((((((((((7 flower water) OR (actiphyte of sacred lotus bg50)) OR (actiphyte of sacred lotus lipo s)) OR (actiphyte of sacred lotus pg50)) OR (extrapone lotus flower 111755)) OR (fermented betula platyphylla japonica juice)) OR (five floral complex)) OR (glycolsat bg of lotus up)) OR (hasu liquid b)) OR (hydralphatine asia)) OR (indian lotus extract)) OR (indian lotus extract sb)) OR (jeju lotus purifying extract)) OR (jung yang-dan)) OR (lipidami lotus nelumblum nelumbo)) OR (lotus complex)) OR (lotus complex ai)) OR (lotus herbasec)) OR (lotus herbasol extract pg)) OR (lotusense)) OR (nelupure)) OR (oleat of lotus flowers up)) OR (oriental flower newplex-ns)) OR (oriental flower no.1)) OR (phyto soothing)) OR (renshu extract a)) OR (sacred lotus flowers milk 1.5ps)) OR (sfe aqua extract lotus flower)) OR (vegetol lotus me 169 hydro)) OR (yeonkkoch extract)) AND (toxicity) – [92,394 hits/ 5 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://chem.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/

PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – December 2, 2024

[

NELUMBO NUCIFERA

DR. BELSITO: Then we're going to nelumbo nucifera. Okay, so this report is on 14 nelumbo nucifera derived ingredients. One of them, the flower oil, is not included in the web-based INCI dictionary and handbook but it has reported uses in 2023 in the U.S. FDA Voluntary Cosmetic Registry Program and in the 2024 RLD and so we brought it into this review. The root water is only reported to function as a fragrance ingredient, but RIFM has not looked at this, so we've included it in this safety assessment.

We've got some concentration of use. We got some data on the flowers in an isostearyl isostearate extraction solvent and also data on the flowers and propanediol and glycerin. And then some information on germ extract. And so, this is sort of where we're at.

DR. RETTIE: This was a difficult one to review since we didn't have the summary table. I tried to use Don's markup but still had some problems. So, I hope we'll get that in the next iteration.

DR. BELSITO: Yeah, with the summary table I think it's important that each ingredient be listed. I think it was sort of assumed that we'd be able to read across these various ingredient groups but that's not necessarily the case and so I had gone and tried to put together a summary table for this which I sent out to my panel members. But I think in the future it's really critical that these summary tables include this specific data for each ingredient.

DR. RETTIE: I wasn't sure what to make of the composition of the extract. We had some unusual solvents there. One was an ester. I just assumed that was probably similar to ethyl acetate, but the other one was also rather esoteric. The glycerin.

DR. BELSITO: Yeah, I mean, one of the things that I had a question is this how it's supplied by the manufacturer to industry and when we're looking at the concentrations of use for that flower extract, are we looking at the actual concentration of the flower extract or is it the flower extract possibly an isostearyl isostearate or in propanediol glycerol. Carol, do we know?

DR. EISENMANN: No, we don't know. But I can tell you, I asked for the concentration of the named ingredient. So, they should be giving me the concentration of the material without the solvent.

DR. BELSITO: Okay.

DR. EISENMANN: And usually when they're really low values that's what I presume they are. If they give me high values, I usually go back and ask them, is this really the concentration of the extract or does it include the solvent, and they often will correct it at that point, but I can't guarantee you. I can only tell you what I ask for.

DR. BELSITO: And then under method of manufacture, there's a method of manufacture for the crude fruit extract. I thought that should be deleted. That's not an ingredient and I'm not sure that the information is transferable to whole plant or other extracts. I don't know what other people thought.

DR. RETTIE: Yeah, I had the same note, Don. Delete fruit extract.

DR. BELSITO: Okay.

DR. RETTIE: While we're there on PDF page 18, I was reading that the preparation of the -- we're getting rid of the crude fruit extract then, are we. It was macerated in 98 percent ethanol for 30 days. I just wondered if that was 30 days or 30 hours but that's moot now if we're getting rid of it.

DR. BELSITO: Yeah.

DR. RETTIE: I think we have a garbled sentence on page 20. Let me see what I'm looking at.

DR. BELSITO: While you're looking at that I just want to go back to these other materials which appear to be present in the flower extract. How do we deal with those? The propylene glycol, the parabens, the propanediol, the glycerin. I mean, we have reviewed them and found them safe as used. So, I don't think that's so much of an issue as to -- I mean, I think don't we have to presume that if the ingredient is put into a cosmetic preparation at a certain percentage than looking -- that there could be a certain percentage of propylene glycol, paraben, propanediol, mineral oil in that final preparation as well?

DR. RETTIE: Yeah, on a more general level I have a note that we have some fairly detailed methods for preparation but it's not clear if these apply to cosmetic ingredients or not. Maybe that's a clarification we can get. How have you dealt with that in the past? I guess you just accepted it in the past.

DR. HELDRETH: Yeah, it's very rare that we actually find methods of manufacture that are specific to cosmetic ingredient manufacture in the published literature and that's why we provide some general ones kind of as placeholders until or it's shown to be needed that we need to know the specifics. But it's also very common for the Panel to say, hey, we need the specifics here and this general one doesn't tell us enough. We're going to be insufficient for the specifics.

DR. RETTIE: Yeah, I didn't have that concern. I felt there was enough information -- at least for me -- with what we had.

DR. BELSITO: Is Thushara with us, Bart?

DR. HELDRETH: Yes, he just joined. He was still working on his reports in the other room. He just got in.

DR. BELSITO: Has someone been taking notes for him?

DR. HELDRETH: I have.

DR. RETTIE: So, on PDF 20 I think I found the garbled sentence. It's in paragraph one, two, three. Starts on, "industry submission stated that the extract extracted in propanediol, and glycerin also comprised," the same -- verbiage -- "comprised 0.5 to 1 percent flower extract." So, it seemed that that wasn't meant there.

DR. BELSITO: Yeah, I think the first 0.5 to 1 percent needs to be removed, right? That the flower extract or the flower extract is extracted in propanediol and glycerin and comprises 0.5 to 1 percent of the flower extract. Or something to that effect, right?

DR. RETTIE: Oh, I see what you're saying. So, if you took the first 0.5 to 1 percent out then we get some clarification then with the second one.

DR. BELSITO: Yeah.

DR. RETTIE: Okay.

DR. BELSITO: So, the extract is extracted in propanediol 70 to 90 percent, in glycerin 10 to 30 percent, and comprises 0.5 to 1 percent of nymphaea caerulea flower extract.

DR. RETTIE: Okay.

DR. BELSITO: But on the other hand, nymphaea caerulea is not what we're looking at, right? Is this even needed here?

DR. RETTIE: Yeah.

DR. BELSITO: Now, there is a flower extract that has both, right? Under --

DR. EISENMANN: Yes, someone is selling a trade name mixture with two plants in it.

DR. BELSITO: Right.

DR. RETTIE: Okay.

DR. EISENMANN: And they have data on the mixture.

DR. BELSITO: So, I'm wondering if that's not the mixture that's being referred to there, right? Is it the same concentrations, Carol?

DR. EISENMANN: They gave a concentration of each of the plant material that -- I haven't looked at the sentence, though.

DR. BELSITO: Which one was the two plants? I'm not finding that now.

DR. EISENMANN: And yes, that extract did contain the same amount -- the range -- the range was the same for those two different plants.

DR. BELSITO: Yeah. That's what I thought.

DR. EISENMANN: I do have some additional data on these ingredients, but the comment period ended yesterday so there wasn't enough time to give you it before the meeting. So, there's --

DR. BELSITO: Additional data.

DR. EISENMANN: You know, it's all summary information. Some of it just came in today. Some on the leaf extract and I think the other data there is root extract information and I'd have to look at it. I can't remember. But I had some questions to go back for them and they've answered them and so then now I can put together the submissions. But there are some additional information that you'll be getting.

DR. BELSITO: Okay. Well, I mean, we're not going to look at those now. We just need to look at --

DR. EISENMANN: Right.

DR. BELSITO: So, there were lots of hormonal effects that we're seeing with the seed. Do we discount those given oral data and low concentration of use? How are you dealing with those hormonal effects? Those were described under the DART toxicity studies.

DR. RETTIE: Given the route of administration, I was discounting them. What do you say, Paul?

DR. SNYDER: I would agree with that.

DR. BELSITO: Okay, so that would go in the discussion. Also, the tables are all mislabeled here -- were off by one. Like the table for DART is Table 12.

DR. RETTIE: On PDF 22 under non-cosmetic, I just wanted to have clarification about the seeds being used to produce milk. How's that work? Seeds are used to produce milk and other food products. I guess I can say used to make other food products. Milk didn't seem right to me.

DR. BELSITO: Well, like soy milk, almond milk, I don't know.

DR. RETTIE: Oh, you think that's what it means?

DR. BELSITO: Yeah.

DR. SNYDER: That's what I interpreted it to mean, yeah.

DR. RETTIE: Okay. Thank you. Thank you.

DR. BELSITO: Okay. There was a PCPC comment about striking the VCRP were ingredient centric and the RLD as product centric. But I noticed Bart used the same terminology this morning in his introduction so do we want to strike that language? I mean, I guess PCPC's argument was that the ingredient centric nature of VCRP was how it was presented to us. Is that correct, Carol?

MS. KOWCZ: That's exactly right, Don.

DR. BELSITO: Okay.

MS. KOWCZ: It's the way the data was presented. They were always getting product information.

DR. HELDRETH: I'm not sure I understand, though, what that means for the data we actually have in our reports, though. The data that we receive is the data we're talking about.

DR. EISENMANN: I just don't think you need to say that information. I think it would be perfectly fine without that sentence to saying it's product centric. The data are different, that's the point right now. You don't necessarily in your report say one was product centric, and one was -- the VCRP data was collected product centric they just were able to reorganize it for you in an ingredient centric manner.

Hopefully someday they'll be able to reorganize the current data in an ingredient centric manner so it's more useful for you, but I just don't think you need that to say that because if the FDA changes how they provide you the data, then this becomes not important anyway.

MS. KOWCZ: And the most important thing, Bart, is that you have the data. I don't know if Prashiela's on this group or not. I saw her before in the big one, but I don't think she's on right now, but I know that they don't have the electronic systems right now. They don't have the IT support that they need to do that right now.

DR. HELDRETH: Right. Yeah. I actually met with Prashiela and Jannavi and a number of the other folks working with the data that came in for the RLD and that they agree. They are working on it but it's massive. You know, 350,000 product submissions up through July and I'm hearing indications that they've received that many more again already since July. So, it's a big problem and it's growing.

But yeah. I mean, we just kind of wanted to alert the reader to the difficulties of the differences in those data but we're not stuck on the language of whether it's centric to products or ingredients.

DR. BELSITO: Okay. So maybe we can just say consequently the RLD and VCRP data are significantly different and it's not appropriate to contrast data from one to the other or something to that effect.

DR. HELDRETH: Right. I can do that.

MS. KOWCZ: Thank you for your consideration, Bart, and team.

DR. HELDRETH: Of course.

MS. KOWCZ: Appreciate it.

DR. HELDRETH: Of course.

DR. BELSITO: So that would be all the reports where we used that terminology about product versus ingredient centric.

DR. RETTIE: On PDF 30 we have in the summary we refer to skin lightening effects in vitro but we don't have any in vivo skin lightening concerns with these ingredients, do we? I wondered if it was unnecessarily drawing attention to something that wasn't really necessary. It's the second --

DR. BELSITO: We typically put in all this type of data and then just discuss it in the discussion and the usual for anything that has hints of skin lightening is that this would not be a cosmetic effect and should not occur.

DR. RETTIE: Okay, so that would be developed in the discussion which is to be developed. That's fine.

DR. BELSITO: Yeah. Just a little terminology here on PDF page 22. The fourth full paragraph down, it says, "Some products containing these ingredients may be marketed for use with airbrush delivery systems; however, this information is not available from VCRP, RLD, or Council survey." That's not true and we actually have indications of airbrush use here.

DR. HELDRETH: Right. We now do have data in the RLD that shows uses of ten airbrush categories. We have yet to receive any concentration of use data back from industry but it's not to say it's not possible.

DR. BELSITO: Yeah, but we have indications that there are airbrush uses for this so it's not appropriate to say that it's not available. It is available.

DR. HELDRETH: Right.

DR. BELSITO: So that sentence needs to be changed.

DR. HELDRETH: Yes.

DR. BELSITO: And then the last sentence under cosmetic use, just for clarification, says all of these derived ingredients named in this report are not restricted from use in any way. I think it would be more straightforward to say none are restricted.

DR. RETTIE: Yep.

DR. BELSITO: And again, I think it was starting with Table 9, all the tables were mislabeled. So, on PDF page 23, the third sentence down it says, "The acute oral LD_{50} of the leaf, flower, and root extract" -- was this each individual component or was this a mixture of the leaf, flower, and root extract were greater than two grams per kilogram? I wasn't clear on that. Because it says leaf, flower, and root extract, leaf and root extract, and then flower extract were two grams per kilogram.

So, I wasn't certain of the first -- was that a combination product of leaf, flower, and root?

DR. SNYDER: I interpreted it to be individual because of the previous sentence. The acute oral toxicity of "several" extracts. Yeah.

DR. BELSITO: You could also argue based upon the next one where it says nelumbo nucifera leaf and root extract, that the first is a combination of all three.

DR. SNYDER: Yeah, so we just need to clarify that.

DR. BELSITO: Yeah. Okay, so just looking at all this I thought it was insufficient and I'm not sure that the data on the composition is adequate. I just, you know, we have data on how the flavonoids break down, data on how a specific chemical category breaks down but I didn't see any data where we looked at exactly what was in these plant products per se. How much of them were flavonoids, et cetera.

I thought the data and the composition was actually inadequate, so I'll throw that out as a first inadequacy for Allan and Paul and Curt's comments.

DR. SNYDER: I'm okay with that, Don.

DR. BELSITO: Okay. So, we need more specific data on the composition of all of these ingredients. We need manufacturing and impurities for the whole plant, the flower, leaf, stem, the phytoplacenta. We have food use for flower, flower leaf, stem, germ, leaf rhizomes, and seeds. So, I think we can probably clear the systemic endpoints with these. Would everyone feel comfortable with that?

DR. SNYDER: Yes.

DR. BELSITO: Okay. So, we would still need root for systemic endpoints. Is that right or does rhizomes clear root? Comments?

DR. RETTIE: I'm not sure it does. Doesn't the root go down and the rhizome go out so it's actually a different part of the plant?

DR. BELSITO: I'm just throwing it out there.

DR. DIYABALANAGE: It has the rhizome.

DR. BELSITO: Pardon?

DR. DIYABALANAGE: It has the rhizome even though it is named as root in various -- when they name the cosmetic ingredients like a scientifically it's the rhizome in nelumbo.

DR. EISENMANN: Yes, I agree with that because sometimes when they were naming things a while back, they did not distinguish. They were trying to use as few English words as possible, so they used root for rhizome and root often.

DR. BELSITO: Okay.

DR. EISENMANN: Now they use rhizome also but earlier on they were using root for anything underground.

DR. BELSITO: Okay. So, for systemic endpoints we still need the whole plant, the callus, the phytoplacenta, and the stamen. We need tox data or 28-day dermal for those. We need in vitro genotox on all except the flower and the germ and in vivo genotox on all. Does everyone feel that that is correct for the genotox needs? Curt, Paul, Allan?

DR. SNYDER: Yes, I think we should ask for it.

DR. BELSITO: Okay.

DR. RETTIE: There's no genotox signals but the data is very sparse.

DR. BELSITO: The dermal sensitization and irritation on the callus, phytoplacenta, and stamen. UV absorption, it's something that I want to bring up. You know, we seem to have lost our focus on the potential for the materials we're reviewing to cause photosensitization, and I think that I have a request for UV absorption on all except the germ, leaf seed -- leaf and seed rather. But I just want to open that for discussion because so many of our reports do not have a UV absorption specter or any photosensitization/photo irritation data.

DR. KLAASSEN: Yes, we used to be much more stringent in requiring that then we have been the last couple of years.

DR. BELSITO: Paul, Allan, your thoughts?

DR. SNYDER: I think it's a good discussion to have tomorrow because I agree.

DR. RETTIE: Yeah, this one predated me so I'll be interested in the discussion.

DR. BELSITO: Okay, so I think at this point UV absorption on all except the germ, leaf, and seed. And then we need in vitro ocular on all except the flower. And, again, it comes back to this -- the flower extract, there's one with the nymphaea caerulea that's extracted in propanediol, and glycerol and it's used in -- how do we deal with that when we're given manufacturing data that suggests there's a considerable component of other than the ingredient?

In fact, propanediol, parabens, glycerin, isopropyl isostearate are at higher concentration in the material that's supplied by industry than the actual ingredients we're looking at.

DR. SNYDER: I think we have to deal with that in the discussion. And like you said, I think the majority of them have been reviewed and found them safe.

DR. BELSITO: They've all been reviewed.

DR. SNYDER: I think we need to address it in the discussion.

DR. BELSITO: Yeah. Propanediol is safe as used to 39.9 percent in non-spray deodorants. Glycerin is safe as used up to 79.2 percent and of course parabens there are restrictions on total amount of parabens in a cosmetic product. Isopropyl isostearate is safe as used. And then the other question that I had was how do we deal with the nymphaea caerulea which is the Egyptian lotus which we're told is part of flower extract provided by one ingredient when it's not listed as what we're reviewing here which is a different type of lotus then a nelumbo nucifera.

And I don't have an answer for that. I mean, it's not what we're reviewing, and we don't have any composition data on the Egyptian lotus. Bart, how do we deal with that?

DR. HELDRETH: So, we're talking about the instances where we have a mixture of nelumbo nucifera flower extract, propanediol, glycerin, and also the nymphaea caerulea flower extract, right?

DR. BELSITO: Yeah.

DR. HELDRETH: So, I think study by study if we saw positive reaction we'd have a problem. What did it/what caused it? But if it comes up negative, then can we not just view all of those other things, the propanediol, the glycerin, and the nymphaea caerulea simply as vehicle and we're really just saying the 0 to 1.5 percent of the nelumbo nucifera flower extract had negative result. Is that not true?

DR. SNYDER: I think if we're going to do that, I think we just in discussion need to say that we consider those to be vehicle. I think we need to address it don't we, Don?

DR. BELSITO: Yeah, but it's -- I mean, we have propanediol supposedly 70 to 90 percent, glycerin is 10 to 30 percent and then we have 0.5 to 1 percent of the nucifera flower extract. I mean, how much of this nymphaea caerulea flower extract are we looking at? But it seems to be a part of that extract and not a vehicle.

DR. HELDRETH: Okay, I think I understand now. So, I think the problem is that it's written poorly here. For example, we're not looking at nelumbo nucifera flower extract and saying that ingredient is 0.5 to 1 percent of itself and some propanediol and some glycerin and nymphaea caerulea flower extract. I think instead what we're talking about here is we're talking about a trade name mixture, sometimes we'll call it pre-formulation, where we have all of these other components in the test article.

I mean, when something goes before the ingredient nomenclature committee, let's say this nelumbo nucifera flower extract goes before them, they're not going to give nelumbo nucifera flower extract as the name if it contains all of these other things. Like, even for example, if a submitter turned nelumbo nucifera flower extract into them and it contained 40 percent propanediol, they would go back to the submitter and say, okay, nelumbo nucifera flower extract needs to go on the label for that 0.5 to 1 percent but you also need to put propanediol on the label for that 40 percent as well.

So, it does give the misconception, I think, here that all of these things are part of the nelumbo nucifera flower extract. I don't think that that is reality, though, when we're talking about what goes into the cosmetic products. I think that's really just the test article here. Maybe in-house at some manufacturer, this a pre-formulation or a trade name mixture, but I don't think even though it seems to represent that here I don't think that these things are part of the ingredient itself.

DR. BELSITO: But the flower extract, at least from what we're being told, is not being supplied as whatever percent pure beyond the 0.5 to 1. Right? I mean, it's very difficult.

DR. HELDRETH: I mean, if we look up into PDF page 27 and we're looking under the dermal irritation/sensitization studies under human, we had nelumbo nucifera flower extract. We have there a nelumbo nucifera flower extract one to five percent extracted in isostearyl isostearate. So, I mean, the ingredient itself is not 95 to 99 percent isostearyl isostearate, that is just what's provided here in this test article. The ingredient is still the nelumbo nucifera flower extract which has the composition that's provided on the later tables.

DR. BELSITO: Right. Okay.

DR. HELDRETH: So, I mean, I think the same situation for this mixture is the case as well. They tested something that had nelumbo nucifera flower extract and propanediol and another solvent and another plant extract in it together, but it doesn't change what the composition of the ingredient we're reviewing is it just muddies up the test mixture/the test article.

DR. SNYDER: I just think we have to be clear of how we interpret that data.

DR. BELSITO: Well, but I mean it also has implications for this group of ingredients because if we eventually get to the point where we say the flower extract is safe as used, we know that it's used in combination with the nymphaea caerulea flower extract and therefore we ruling on nymphaea caerulea flower extract at 0.5 to 1 percent as well?

DR. HELDRETH: I don't think that's true because, I mean, all of these ingredients even though we're reviewing them as individual ingredients, they're being put into formulations with 10, 15, 20 other ingredients in there and by ruling on this ingredient, we're not ruling on everything else in the formulation sold on the market.

DR. BELSITO: Okay. Okie doke. Well, we still have a whole bunch of insufficiencies here. So, let me go through my list again. I felt that the data on composition was inadequate for all of them and so are we comfortable asking for composition on all because what we really got was just a breakdown of specific flavonoids for one. We don't know what percentage of these plants are actual flavonoids and that's true for all of the composition tables we received.

So, I had data on composition, manufacturing and impurities for the whole plant, flower, leaf, stem, phytoplacenta. We had food use and so that mitigated systemic endpoints needs for flower, flower leaf, stem, germ, leaf, rhizomes, and seeds. But we still needed systemic endpoints for dermal tox for the whole plant, the callus, the phytoplacenta and the stamen. And I'm assuming we're all comfortable with the discussion we had before that rhizomes equals roots, so we don't need to ask for root.

I thought we needed in vitro genotox on all except the flower and the germ and in vivo genotox on all. Are we comfortable with that?

DR. SNYDER: Yes, I think you've summarized it quite well and you're presenting tomorrow so that's good.

DR. BELSITO: Right. We need dermal sensitization and irritation on the callus, the phytoplacenta, and the stamen. We need UV absorption on all except the germ, the leaf, the seed. And in vitro ocular irritation on all except the flower.

DR. RETTIE: So, with the current discussion on photosensitization and the need for UV absorbance here, do we need to go back and add that to some of the other ingredients that we've already looked at?

DR. BELSITO: Well, I mean, I think we need to discuss this in the Panel. I don't think we need to go back and add other ingredients, but it just struck me when we're reopening a report based on the fact that there was photosensitization and photo irritation data in the original that we really didn't comment on that we've been ignoring for the past several years the need for photo data in our ingredients. I think that David and I would've picked something up if there were photo issues but, you know, particularly when you're getting down into plants now it can be very tricky.

And under discussion we'd have our usual boilerplate on pesticides and heavy metals in these plant products. I don't think at this point we need a formulation to be non-sensitizing because I'm not sure that it has any sensitizing components, but again I need composition here. And then we do have the airbrush uses reported so we need to get rid of that statement that we don't have that airbrush data. We do. What we don't have is current data that looks at median particle size and distribution from airbrush use.

We also don't have concentration of use in these airbrush devices although it looks like overall the concentration of uses are very low but we don't know the airbrush uses. Anything else with this group?

DR. SNYDER: No, I think you did a nice job, Don. That was a really tough one.

DR. BELSITO: Yeah. Thushara we were discussing before you came on that when you provide the tables on data summary, you need to look at all the individual ingredients, not just the data we have for the entire group. We need to break those out by data that we have for each of the different ingredients.

DR. DIYABALANAGE: Okay. Yeah.

DR. BELSITO: Okay. So, we'll move onto the potassium cocoyl hydrolyzed collagen.

DR. HELDRETH: Dr. Belsito, do we want to break for lunch here since the RAWG will be meeting at 1:00?

DR. BELSITO: Well, it's only 12:24, no?

DR. HELDRETH: Okay, it's up to you guys. I just wanted to remind you of the time.

CohenTeam - December 2, 2024

NELUMBO NUCIFERA

DR. COHEN: Let's move on to Nelumbo Nucifera. It's a draft report on 14 Nelumbo Nucifera-derived ingredients. They include a callus culture extract and extract, the flower extract, the flower/leaf/stem juice, flower oil, flower water, germ extract, leaf extract. Culture extract, which is from the phytoplacenta, root extract, root water, seed extract, seed powder, stamen extract.

The flower oil is not in the dictionary. Included in in the report are VCRP and RLD, just to make this a little bit of a briefer presentation. The root water is only reported to function as a fragrance ingredients which we don't typically review. It doesn't seem like there's a RIFM monograph for this, though, so we'll include it here since there's nothing else.

One comment on PDF 10, it's all rolled up into one and we don't have the individual 14 ingredients listed, and that's really hard to follow this report without that table.

DR. ROSS: That was one of my comments, yeah.

DR. COHEN: Yeah. So, we can't have them rolled up. I mean, you can have a top line roll up, but then we need all 14 ingredients and what sort of boxes have been checked?

DR. ROSS: So, the data summary table needs to be totally changed, yeah.

DR. COHEN: We have descriptions of method of manufacturing on the whole plant -- we do not have method of manufacturing on the whole plant extract, which we find very useful because it allows us to roll other things in. We have method of manufacturing for the fruit extract. Number of other things. Table 2 speaks to a juice, but I don't see that list on our list to adjudicate.

We have method of manufacturing for callus culture extract, flower extract, germ, leaf, root extract, seed extract, seed powder and stamen, and not for flower/leaf/stem juice or flower water.

We have a max use on the root extract at .2 percent in foundation. We have cosmetic products that incidentally come in contact with the eyes, for the flower extract at .0015 percent in eye lotions. The flower extract is a .1 percent in lipsticks and it is used as a baby product, .00055 percent.

We have some ingredients that can possibly be inhaled. I'll stop. I have a lot of other comments but maybe I can open it up to the group. Susan, you want to start?

DR. TILTON: Yeah. Because that table and the way it was created, it did make it difficult to go through. You almost had to create your own table, right, break down everything and look at it.

I mean, we certainly had a good amount of data for the flower extract. There were just a number of insufficiencies, I guess, when it comes down to it, with all of these, the fact that we have so many ingredients here. And this is a draft report.

DR. COHEN: Yes. Yeah, I get it. We have irritation on flower extract, germ extract. On a number of things. We have sensitization on flower extract at .15 percent and germ extract at 1.5 percent. Do we want to just start putting our IDA, our list of needs together, which I was hoping you got one.

DR. ROSS: I got long laundry list here, so.

DR. TILTON: Yeah.

DR. COHEN: You know what, let me start taking some notes, because I have a lot of what we have. But all right, IDA. Who wants to start?

DR. ROSS: So Susan started. Do you want me to go with an IDA, Susan? Or you want to keep going? your choice.

DR. COHEN: Can we start making a bullet list for me and then we'll just go?

DR. ROSS: Okay.

DR. COHEN: You want to do it by item, by derived ingredient? Because I have them listed and I can -- or how do you want to do this?

DR. ROSS: Well, I didn't split mine out that way. But you had a nice summary about how all these things were used with ocular with incident, ingestion, baby inhalation, and we got an airbrush use on the flower extract also. So there's lots going on here.

I really had no oral toxicity or genotoxicity issues with this. There were no dermal irritation or sensitization issues with the leaf, the flower, the root or the stem. They were all Okay. No sensitization issues with the flower at max, so that's pretty good.

DR. COHEN: Wait. So, you had -– no -- okay for irritation and sensitization, you said?

DR. ROSS: Yeah, with leaf, flower, root and stem, those are extracts.

DR. TILTON: Germ, germ flower, leaf --

DR. ROSS: I didn't have germ on my list as okay, but --

DR. TILTON: -- seed and stem.

DR. ROSS: -- I'll take your word for it.

DR. COHEN: Susan, what did you have again?

DR. TILTON: So generally I had that we didn't have any dermal irritation or sensitization needs.

DR. ROSS: No. Well, here we go. I think what we do need, right up front, we need the concentrations of all these ingredients, Okay? We have 5 of 14 that I detailed -- by my account.

So we need, you know, Thushara, if we split out that table right up front, we would figure out quite quickly where we have concentrations of use and where we don't. But I think it's something like 5 of 14 we have. We need the rest. Because it's hard to do a tox evaluation – Monice, do you want to say something there?

MS. FIUME: David, all of these have been surveyed for concentration of use. So, if there's none reported, it means industry hasn't come back as reporting any use concentrations for the ingredients.

DR. ROSS: Precisely.

MS. FIUME: I mean, we can include that and mention it, because this is a draft report, that the Panel does need further information for these ingredients that are reported in use that have no concentrations listed. But they've all been surveyed for concentration of use.

DR. ROSS: No, I understand that. But what we do need, as you pointed out, are the concentrations of use. So we have to ask for that and if we don't get it then we move ahead with that lack of response. So we need concentrations of all ingredients.

There were DART issues with the seed extract, in both males and females. And so we don't have the maximum concentration of use of the seed extract, so that, I think, might throw some light on whether those DART issues are irrelevant or not.

And the troublesome thing for me, I suppose, I don't really know how to handle this and I would like you guys opinions on it. But the flower extract contains many of the same alkaloids and flavonoids as a seed extract, if you look at Table 4. But we have no DART there. And the flower extract, of course, is the one with all the uses. Well, not all of them but the majority of the uses.

I mean it would be very good to discount this as a concern. Do we request DART data on the flower extract or not? I think I'm going to leave that question out there and ask for some input from my expert colleagues here.

DR. COHEN: Whether we need DART on the flower?

DR. ROSS: Correct. Okay, well we can discuss that tomorrow.

DR. COHEN: I'll put it in our IDA.

DR. ROSS: Okay. The other issue that I came up with is if you look at method of manufacturer, the flower extract is detailed as a water extract. That's in the method of manufacture section. Now you go to the data, Thushara, and most of the data with the flower is an organic solvent extract. It's either petroleum ether or it's ethanol.

And so, the question is the alkaloids and flavonoids that are listed in Table 4, is that from a water extract, or is it from an ethanol extract, or is it from an ether extract? I think generally in Table 4, where you have all that content of what stuff is in there, we need to specify which extract it is. And maybe it was in there and I didn't see it. Maybe I missed it.

DR. COHEN: Wasn't there a propylene glycol component to the extract? I'm trying to remember if that was this one.

DR. ROSS: Yeah, there were different extracts. There was three or four different extracts along the way when you looked at the data here. So it's not a consistent extract that was used. So again that's another complication, so I think we need to get that straightened out.

DR. TILTON: David, with regard to the DART, I think what I had noted was that we are lacking any kind of information on dermal absorption and potential for systemic exposure. And that if we had that data, that would inform whether or not we would need additional studies like DART.

DR. COHEN: So you're saying if we need dermal tox on flower?

DR. TILTON: We don't have 28-day dermal tox for any of them. I think you mentioned that already, David.

DR. ROSS: Yeah.

DR. COHEN: Let me make sure I have that.

DR. TILTON: We also don't have any dermal absorption data.

DR. ROSS: I mean, the problem with this is we got very, very little data on the whole extract. So we can't use that to clear all these sub ingredients. That's usually our first approach is that we try and go via that root, but we can't do that here, so.

DR. COHEN: Yeah, my opening comment was like we don't have that whole plant. If we had the whole plant we can clear, but now it's going to be a slog through 14 individual things.

DR. ROSS: Yeah. Yeah.

DR. COHEN: There is a propylene glycol extract listed, I think, for the flower.

DR. ROSS: I'm on one screen here so I don't have the document in front of me. But I recall there was an ether and an ethanol and another extract. And so, I'm just trying to get a handle on, you know, when I look at the --

DR. DIYABALANAGE: Is it the flower extract or flower water extract?

DR. ROSS: Well, can you just check that for me in the method of manufacturer under the flower extract?

DR. DIYABALANAGE: I'm trying to check it, actually.

DR. ROSS: Is it -- I mean, I looked at it and it was a water extra.

DR. BERGFELD: Yes.

DR. DIYABALANAGE: Is says, Nelumbo Nucifera flower extract was prepared by extracting freeze-dried and ground Nelumbo Nucifera flowers. And so you have water extraction there. And then they have a propylene glycol extraction as well.

DR. ROSS: Oh they do?

DR. COHEN: The 3rd extraction has 20 percent propylene glycol, which may capture some of those – right -- some of those ethanol. The other thing is the petals have coumarin reported in them, and coumarin is a known sensitizer.

So the question is, will this go out as formulated to be non-sensitizing? But we don't have enough there yet, right? And so, there is an issue with the DART and test size and the estrous cycle, right?

DR. ROSS: Yeah. Well, depending what you were looking at, there were repro effects in both males and females. With a seed extract, I think. relatively low doses, 7.5 megs per keg, that was an ether extract. With the seed and -- that was males and females. And there was another study with an ethanol extract at a much higher dose, 800 megs per keg. But obviously you're getting different flavonoids and alkaloids out with the ethanol versus the ether.

So that was in females. Yeah. So there were effects in males and females. Testes, epididymis, adrenal glands, sperm count and females vaginal opening in ovary and uterus weights. Again, that's at 7.5 megs per keg.

DR. COHEN: Yeah. It's a lot of action for a little dose.

DR. ROSS: Yeah.

DR. TILTON: And that was across several studies.

DR. ROSS: I think it's reasonable to, at this stage, ask to see if there's any DART data out there for the flower extract. Simply because if you look at that table, which compared the difference alkaloids and flavonoids, there are some -- obviously, they're different, but there are a fair few similarities between the flower and the seed.

DR. BERGFELD: And the embryo.

DR. ROSS: Yeah.

DR. COHEN: So you want the DART --

DR. ROSS: On the flower.

DR. COHEN: That was for the pedal extract, right?

DR. ROSS: Yeah, one study was a pedal extract. It was an in vitro reproductive study using rats sperm. And it increased sperm viability. You could argue that's on the good side. But the classic developmental and repro studies, you know, the 15 day with the seed extract, that's where the problem was.

Now it may be that the other team don't think that it's worth going after the DART and I'll certainly listen to their opinions. But we've got effects both in males and females, and as David said, it's a relatively low doses. But it's seed extract, it's not flower extract. And so, if we can get a concentration of use for seed, that would be enormously helpful. And then if we can clear flower extract. Because flower is closest to clearing with the data we have. It's close, so.

Anyway, they were my comments. Oh, there was one other thing Thushara. There was a trade name germ extract in the data, and that keeps cropping up in the dossier. It has concentrations between .5 to 1.5 percent. But when I looked at the concentration of use for the germ extract, there was no concentrations of use, none reported. So we know there's a trade name extract out there that has concentration of use .5 to 1.5, but we don't have it in our tables. But we have it in our data.

MS. FIUME: So, David, reported concentration of use in test data doesn't always translate into actual use concentration.

DR. ROSS: Yeah.

DR. COHEN: Yeah, we've seen that.

DR. ROSS: Yeah, but we keep referring to this trade name product. So, obviously there's something there, Monice.

MS. FIUME: Thushara, can you confirm, when we say trade name mixture it's normally because something is submitted under a trade name and we don't include trade names, or is that just how it was stated in the data that were submitted?

DR. DIYABALANAGE: I think that's how it was stated in the data submitted.

DR. ROSS: And then Thushara and I had an offline conversation about a Gaertn, and I didn't really know what that was, but.

DR. DIYABALANAGE: Gaertn, it's the guy who did the taxonomy of the plant.

DR. ROSS: Okay.

DR. DIYABALANAGE: For each plant usually in order to have a very clear taxonomic identification, the guy who collected the plant and classified it, he gets the opportunity of, like, his name goes along with the plant, like Linnaeus.

DR. ROSS: Well, I mean, he was obviously immortalized in this one because he had some data in this one, I seem to recall. On short term sub-chronic and chronic tox. It just said the nucifera Gaertn, whatever that is.

DR. TILTON: It's describe as an herbal mixture capsule, containing a certain percent of that.

DR. ROSS: Whatever that is.

DR. COHEN: Yeah. Also, Wilma, there's a discussion about skin lightening in the report.

DR. BERGFELD: I saw that.

DR. COHEN: And so, what are we -- we're commenting on that, but that ultimately in the Discussion that these products shouldn't lighten the skin?

DR. BERGFELD: That's correct.

DR. ROSS: And we have some inhalation possibilities with the flower extract. And then we also have one airbrush use with the flower extract. So, I don't if we need anything around that.

DR. COHEN: Well, so the question is, is this the start of this? Is there an IDA -- let me just -- we have a report in airbrush for -- what'd you say, flower extract?

DR. ROSS: Yeah, that's where I got it. One use of flower extract for airbrush from the RLD.

DR. TILTON: That's correct.

DR. COHEN: Right. So is this the beginning of new IDAs when we have this, right, because we have it listed. So do we need particle size? Do we need method of use?
I mean, do we need an IDA that's very, very long for us -- eventually, we may need to clear or not clear airbrush, right?

DR. BERGFELD: And all airbrushes aren't equal, I believe.

DR. COHEN: Well, that's the issue. But we sort of can't ignore it. And we can't say use not supported in a draft report when we didn't issue an IDA.

DR. BERGFELD: Correct.

DR. COHEN: So what are our needs on that airbrush?

MS. FIUME: David, as far as the use not supported on airbrush, that's going to come down to, I think, how that language is crafted for the Use section. Because the Use section makes it clear that if you don't have those information, which we never have because they're not evaluated in those manners, to provide practices of use, that the Panel does not have the information they need in any instance to make a conclusion on it.

You can ask for it every time you put out an IDA, but I don't think that it would have to hold up every report that could have airbrush, if you state it in the Use section that these information are not available to the Panel across the board and therefore you can't evaluate safety in those conditions.

DR. COHEN: I completely agree, Monice. But for us to say the information is not available, we at least have to say we've asked for the information. Right? It's like why even send out a request for information? We could just say we didn't receive any information. Well, you didn't ask for it. Right?

Isn't the IDA supposed to be an announcement to industry that there are data needs to adjudicate the chemical at hand, or the product at hand? If we're going to go use not supported, we have not -- we don't have a level playing field on that.

MS. FIUME: But I think it goes back to Wilma's point that they can all be different. Is the Panel going to take it to the direction where if there's an airbrush use that they know of, via the RLD, but they don't know based on concentration of use, and they get information on one airbrush apparatus, is the conclusion or something going to be specific to state that only used in this airbrush manner? Because there are so many different airbrush uses across the board that can change?

I don't know enough about it to know if each cosmetic artist does it differently and use their own. I think the product goes into the apparatus, but the apparatus can be different. That's why that paragraph was created. because just because you have the ingredient, the Panel doesn't have jurisdiction over the apparatus?

DR. COHEN: Just so you know, I completely agree with you. But couldn't the same argument be made when we're looking at underarm deodorant or hair sprays. We look at the chemical, I have no idea whether it's a pump, whether it's a propellant, whether it's a cream or a lotion going under the arms, right. We get this range of what pump and aerosol sprays are going to put out as far as particle size. And then we do an MOE based on the worst case scenario on the particle size, right? But that same argument can be made. Like I don't know what can or spray the underarm deodorant or the hair spray is going in either, right?

DR. TILTON: But that's what the resource document is for. I mean it would describe -- and it does break it down based on types of exposure. I agree, we're not going to get information on all of the different devices, so we don't know how it's being applied. And it comes down to if the particle size is the most important aspect of it, and that would be device dependent.

DR. BERGFELD: But if you put it in your IDA as a request and you see the response, and then you can address the response in your Discussion.

DR. COHEN: You're in favor of an IDA, it sounds like.

DR. BERGFELD: Yeah, I'm in favor of asking and then dealing with it, as you stated so nicely about the fairness of that, rather than just assume all are bad.
That we at least made an attempt to describe the device, the concentrations and the particle size.

DR. ROSS: What do we have so far in this IDA? Can we recap? Dr. Cohen, have you been taking notes, or can I recap for you?

MS. FIUME: I'm sorry, doctors, can we backtrack for a second first, because we're talking about the devices.

DR. COHEN: Sure.

MS. FIUME: Is it true that part of the difference is that if it's a hairspray or if it's a deodorant, the cosmetic industry is selling that as a whole product. And it's already in the -- it's more standardized, for a lack of any better term. Whereas for the airbrush -- at least the way I believe what it is, is they'll sell a foundation and a makeup artist uses that in whatever equipment they have.

So with a hairspray or with an antiperspirant, you know what the cosmetic industry is doing. It sold as a product. It's not an ingredient that's then later placed into a can that someone is using and it can be anything. Whereas with the airbrush, it's two different items.

DR. COHEN: It's a good argument, but the point is that it's just a matter of when the two come together, right? Are they coming together in a single unit sold as a skew, as a pump or as an aerosol spray, versus they're disconnected and they're connected at the user end, right, as opposed to at the store.

But I don't have any more information about how aluminum is going to be dispersed in an underarm deodorant, even if it's prepackaged. I have no idea what the particle sizes are going to be other than the resource document discussion.

MS. FIUME: Which I think used industry information. I don't know -- Jinqiu, are you in this meeting? I don't know if he's in this one or the other one right now. Or Kathy or Kim, can you speak to that? I believe that the studies that have been done have used industry information as to -- at least at one point there were numbers that were involved with it.

DR. COHEN: I think the research document does give a range, right?

MS. FIUME: Right.

DR. COHEN: So, the question is, if industry has provided a range in a mechanical device used to deliver the product we're adjudicating, right, and we're going to be issuing use not supported statements for airbrushes, is it not incumbent upon us to say to the industry, right, tell us what the range is of the particle sizes and the appropriate use for these. Because I imagine there are more spray cans and pump devices than there are airbrush devices in the world, but we haven't asked for any information on the airbrush device.

I guess we can have the conversation tomorrow. But if we're going to say use not supported, right, we've given nobody a chance to at least substantiate their use.

MS. FIUME: So use not supported is if the data are insufficient. Use not supported, used first where something is not in use we know. We don't know anything. Use not supported is a weightier conclusion because it almost equates to unsafe. We're saying we don't have enough data -- or the Panel is saying -- we don't have enough data to come to a conclusion. We're not saying the use of that's not supported.

DR. COHEN: Right, insufficient data.

MS. FIUME: Yeah.

DR. COHEN: Insufficient data conclusion. I'm being -- this is more of a provocative conversation, right?
When was the last time, Monice, that the CIR has ever issued an insufficient data conclusion without providing an insufficient data announcement?

MS. FIUME: I do believe that comes down to the difference of why it's in the Use section and the Discussion versus the conclusion itself. David, I totally see what you're saying. But early on with the Panel at that time was the decision of we can't discuss it because we don't have enough information, regardless of what ingredient it is.

But I see the concern and I see the question around it. And it may be something that, yes, needs a bigger Panel discussion again as to what the overall feeling is about that. But the way this came up was because no one could give you that information, because no one has measured it.

DR. COHEN: As far as we know, right?

MS. STANTON: Yeah. And I think one of the things -- this is Kathy from PCPC. The way that things are split up now in the cosmetic use, FDA in the new categories actually split this into four categories. And that means that data is still being collected here and I don't think that at present we have enough yet. But that data is incoming.

MS. FIUME: And that's for ingredients that will be supplied to be used with the device?

MS. STANTON: Correct. As far as we can tell from the surveys.

DR. ROSS: Monice, I think it sounds like you are right then. There's the ingredient that's supplied and then there is the device. So, yeah, getting a handle on what particle size comes out of that is quite a complex equation really.

DR. COHEN: It sure is.

MS. FIUME: Which is why that paragraph was developed a few years ago because it's two different parts versus one unit. That's where the concern of the Panel had been at that time, was you don't know how to get that information. FDA couldn't supply it. Consumer Product Safety Commission didn't have it. There was no way to get the use and practices information to be able to take that a bit further.

DR. ROSS: Yeah, unless you standardize the airbrush devices, this is a nonstarter then. Because the particle sizes will probably -- you know, I don't know this for a fact, but I expect it will be different from different devices. Maybe Susan knows. So, can we pass opinion on that? Probably not.

MS. FIUME: Because the key word there is it is a device. To my understanding it's not a cosmetic. And that was part of the other problem with the discussions back then is, is it a device? Who really regulates this?

That's where we found out was Consumer Product Safety Commission. It's not under FDA. That was part of the problem as to why a paragraph needed to be developed to say the Panel really can't review this because we don't have the information.

DR. COHEN: Okay.

DR. BERGFELD: It seems to me that we're going in circles right now. I think everybody understands that the particle size in the device are important to know. We don't know and we can't know. But I think that paragraph under the Use section is good, but I think there has to be a sentence in the Discussion that relates to that. And whether that be a reflection on the research --

MS. FIUME: And I thought there typically was.

DR. COHEN: So, we will include it in the conclusion. I think, just as a bigger picture, we've been talking about airbrushes now a couple of years. And everyone, I believe, appropriately was saying this is under this regulatory body or that regulatory

body. All the while, there are tens or hundreds or thousands of people who are using these things and we have no idea how safe they are. And we don't, in the near term future, see anybody looking to study this. Right?

So, we can't keep passing the buck on it because people are using it and they're using the products that were adjudicating and we're just saying we're not able to comment on it. So at what point -- who's going to comment on it?

MS. FIUME: And that was the question. Because I think it came down to the Panel would like to be able to declare safety because technically the ingredient is a cosmetic. But based on just the procedures, because it's the device and the Panel doesn't oversee devices, and that plays a role in the safety, is it within your purview to be able to give any type of conclusion on that type of safety? And I think that's where the -- like you said, Wilma -- it is a big circle and it was a big circle back then, which is why that came about? But yes, it is concerning.

DR. COHEN: Okay.

DR. BERGFELD: When you can't conclude on something we just have to mention that. But has to be highlighted in a couple places, as I mentioned, and the Discussion being one place.

MS. FIUME: And it is in the Discussion, Wilma. here's a paragraph that states it in the Discussion of the reports.

DR. BERGFELD: I don't see it here and I'm looking at the report, but.

MS. FIUME: This is a draft; it doesn't have a Discussion yet. But if you look at, say Inositol, the discussion does say it? Yeah.

DR. BERGFELD: Okay.

DR. COHEN: I think we have to get back to our IDA list.

DR. BERGFELD: Right.

DR. COHEN: So, David, what I have is concentration of use of ingredients of the 9 of the 14, particularly the seed extract because of DART issues.

DR. ROSS: Yep.

DR. COHEN: Then 28-day dermal tox for all of them and, if positive, DART for the flower extract at least.

MS. FIUME: Sorry, what was that last request, David?

DR. COHEN: It was 28-day dermal tox for all of them and, if positive, DART for the flower -- well, we need DART for the flower extract.

DR. ROSS: I think Susan mentioned she wanted absorption rather than –

DR. COHEN: Yeah.

DR. ROSS: But I think the problem, Susan, of getting absorption, is these are massive mixtures so what are you looking at?

DR. TILTON: Yeah.

DR. ROSS: We don't normally request absorption on botanicals because you don't know what to measure.

DR. COHEN: Yes, right.

DR. ROSS: I'm not sure that's the way to go. And do we really need 28-day dermal tox on these?

DR. COHEN: Hold on.

DR. ROSS: Primarily for me, I guess it was the issue with the DART. And I just looked actually at the -– I managed to get the report up as well here and I just looked. Indeed, the flower extract in the method of manufacturer is a water extract. The propylene glycol is added at the end as a preservative. It's not extracted with propylene glycol, so the extract is a water extract.

And you know this, David, and I agree, that there's a fair bit of data in here with organic solvent extracts, tox data of the flower. And so, again, in Table 4, I guess, I'd like some detail as to when I'm looking at comparing these alkaloids and flavonoids across product, what are these extracted with? We have embryo, flower, leaf, seed, and stamen. Are they all the same as what's detailed in method of manufacture? And if that's the case, that's fine, we just need a footnote to say that.

DR. COHEN: So then why don't you run your IDA list again?

DR. ROSS: Okay. I've got concentrations of all ingredients that that we don't have. Currently, by my estimation, we have about 5 of 14. I'd like, particularly, the seed extract because we've got some DART issues there. The flower extract because it contains many of the same alkaloids and flavonoids. We do not have DART on the flower extract and I'd like to have some discussion around whether or not we need DART.

DR. COHEN: Because they're similar.

DR. ROSS: They’re not obviously all the same, but there are similarities.

DR. COHEN: So we want DART for the flower extract?

DR. ROSS: Yeah.

DR. COHEN: Got it.

DR. ROSS: And then I'd like details of the composition in Table 4 of these things, what does that refer to, those compositions? What extracts? What were they extracted with?

And so that will allow you, for example, to take whatever data is in there with an ethanol extract, and then you can compare across and see what's in the ethanol extract versus the water extract, et cetera, et cetera. Now you may not have that data, you may just have the composition with one extract, which is fine, but at least you'd know what it was.

And you know, you could argue, David, you want dermal irritation and sensitization of all products where we do not have data. It would be so much simpler if we had the total extra, but we don't have that. And again, we need that data summary table split out so. That was me.

DR. COHEN: Now I think we have sensitization on flower and germ, right?

DR. ROSS: We had quite a bit of data, I think.

DR. COHEN: We have irritation on a lot of them.

DR. ROSS: Yeah.

DR. TILTON: We do have irritation on quite a bit of them and I didn't separate out sensitization.

MS. FIUME: Yes, sensitization is on the flower and the germ extract in humans.

DR. COHEN: Okay. Yeah, that's what we have. So irritation on those we don't have.

DR. ROSS: Yeah.

DR. COHEN: And remember the lotus petals have coumarin.

DR. ROSS: Yeah.

DR. COHEN: So this may go out as formulated to be non-sensitizing for the flower, even though we have -- let's see, what's the concentration of use for the flower?

MS. FIUME: It's 0.13 percent, I believe, on the extract.

DR. COHEN: Yeah. And we have data above that.

DR. TILTON: It's 1.5 percent.

MS. FIUME: But it was tested at 20 percent, right? So --

DR. COHEN: I have a .15 percent. Let me look at that.

DR. ROSS: Yeah. The other thing is how, Thushara, that this was listed in the irritation and sensitization. You know, the concentrations of the product used led the sentence. And then in parentheses, you know, at the back end of the sentence it was the final concentrations tested.

DR. COHEN: Which is the most important sentence.

DR. ROSS: Yeah. So, I would lead with a final concentrations tested so you can easily get to that.

DR. BERGFELD: Yeah.

DR. COHEN: Yeah, 0.15 percent, Monice, for the flower. They used the 1 percent extract, but then they dilute it down.

DR. ROSS: Yeah, it was difficult to get to that, yeah.

MS. FIUME: We'll correct that.

DR. COHEN: These are complicated. They're always very complicated and you're new to this process, so that's understandable. It's just that that initial table is real important for us to help barrel through it, but we'll get those in the future. Any other comments?

DR. TILTON: It sounds like the table will be updated for the individual ingredients, but there were some errors in the data profile table, with regard to some of the data that was reported. So there is some acute dermal and oral. I think it was just marked oral. And the repeat dose studies are oral not dermal.

DR. COHEN: I didn't use the table, ultimately. When I saw it, I stopped there.

DR. TILTON: Yeah.

DR. ROSS: Yeah.

DR. TILTON: I tried not to but I found myself glancing back and getting confused.

DR. COHEN: It's habit.

MS. FIUME: We will definitely correct that. Can I ask for clarification for two things for the list? I know you said for the flower because it's the highest use. Is DART needed for the -- how should I say it right -- for the extract as a whole because it would include seed? Is it needed for that ingredient as well?

DR. COHEN: That would clear the whole thing, right?

DR. ROSS: You mean the complete extract?

MS. FIUME: Yeah. Or do you have enough information knowing because you already know what the seed entails?

DR. ROSS: Look, if you had information on the complete extract, that would be marvelous.

MS. FIUME: The DART on the complete extract?

DR. COHEN: Yes.

DR. ROSS: That would clear everything. That's one way to go, yeah.

MS. FIUME: Then my other question was -- and you may have mentioned it and I might have missed it. So method of manufacture, with the exception of the germ extract, I don't believe anything was from an industry submission. And from what I'm hearing the solvent can really make a difference at times. Is that one of the data requests, is method of manufacture for the ingredients as used in cosmetics, especially the solvents? Is that something that was needed as well?

DR. ROSS: What we were after was clarification in the table of how those things were extracted.

DR. COHEN: Yeah, but I think Monice is getting more to the heart of the IDA question which is, what is the cosmetic method of manufacturing, which would drive Table 4, right? She has led us down the path holding our hands. But this is really what we do need. So we need method of manufacturing for cosmetic materials.

I mean, yes, that's clarifying our IDA more specifically as opposed to saying -- even if they did -- right, that is what we're asking from Table 4. What are the extracts, alcohol or water? But fundamentally, we're saying what's the method of manufacture?

MS. FIUME: Because table 4 is based on the published data, which may or may not be similar to the cosmetic ingredient. Whereas, sometimes different solvents are used based on how the ingredient is manufactured. Because I thought you said composition. I heard you say composition, but I didn't know if it was method of manufacture and composition. Okay.

DR. COHEN: That was composition Table 4 with the extracts water or alcohol? But really the fundamental question is method of manufacturing for the cosmetic material. And as far as the glycol, I just wanted to make sure there was clarity --

DR. ROSS: Oh you mean for the flower extract?

DR. COHEN: Huh?

DR. ROSS: For the flower extract?

DR. COHEN: Yeah.

DR. DIYABALANAGE: I actually found out the answer to the flow extract. I think David is right. It is, like, in the report we have mentioned that it is as a water extract. But elsewhere in the report there's a mention that the other solvents have been used, so we need to correct it.

DR. COHEN: It's in there, right?

DR. DIYABALANAGE: Yeah. I think we got a submission much later; I think the very last moment. So it needs to get added into the other section.

DR. COHEN: Ah. Okay.

DR. ROSS: But the glycol was added as a preservative in the current method of manufacture.

DR. DIYABALANAGE: The glycol is a preservative. But there are other things like stearyl something.

DR. ROSS: Yeah, yeah.

DR. COHEN: So again, that's a method of manufacturing question.

DR. DIYABALANAGE: Yeah, yeah. I have a question regarding Table 4. Because for the composition, most of this information -- because, actually, when you get different plant parts, there are no specific chemical investigations other than what is reported in literature.
So they have used various different solvents and various different isolation methods. So, to put this Table 4, I think a lot of publications provide the base. So how should we include everything, like all the solvents and different methods?

DR. ROSS: So that's a tricky question. Unless you're sitting there with all of them in front of you, I don't know how to answer that.

DR. DIYABALANAGE: This is like about 20 to 30 papers.

DR. COHEN: Wait, what are there 20 or 30 papers for?

DR. DIYABALANAGE: David asked, we want to have information about how do you confirm the composition of various plant parts. So, there are no simple or single study about them, because there are several different studies. Like in different papers some have studied the leaf, some have studied the root, likewise. So to get that data you need to have several different studies which have used different extraction methods.

DR. COHEN: Right. It can make the tables voluminous.

DR. DIYABALANAGE: It makes it very complicated, yeah.

DR. ROSS: Could we just get a sense of where all of that compilation of data in Table 4 comes from? For example, you know the flower extract, is it a water, is it an ethanol, is it a petroleum, ether? Which ones have been used to generate that data?

DR. DIYABALANAGE: Yeah, yeah.

DR. ROSS: And so, then we would be able to see that. Then maybe we'll be able to dig down a bit deeper on that.

DR. DIYABALANAGE: Yeah. Yeah, we can, yeah.

DR. BERGFELD: Would you put an asterisk and put a footnote in?

DR. DIYABALANAGE: Exactly. Yeah, probably something like that.

DR. COHEN: Or you can even put in the Discussion that there are lots of reports on the individual constituents. But I'm not sure it's going to change our final determination on this.

DR. ROSS: No. As I said, it's got a lot of good data in here. And I think the major use, the flower, that's pretty close to clearing. It's just whether or not we can answer that DART question one way or another. Now the other team, tomorrow, might think, well, you know, there's no DART question to be answered here, so that discussion should be had.

DR. COHEN: Because Susan wanted absorption, which I agreed with, but then what are you measuring? We have this real DART issue.

DR. ROSS: Well, if it weren't the DART issue with the seed extract, I don't think it would have been flagged, or really rise to the top of the concerns. But because there is, I think you have to ask the question. At least, we need to have the discussion.

DR. COHEN: Okay, all right.

DR. TILTON: David is correct, that if you look at the constituents, they certainly aren't identical, but there is considerable overlap.

DR. ROSS: Yeah.

DR. TILTON: Of course these are coming from multiple types of extractions. They're summarized across multiple studies. So they're not specific to the constituents that might be in the extracts for cosmetic purposes, but we don't have that data to know.

DR. COHEN: Okay.

DR. BERGFELD: David, you want to summarize where you are with this then?

DR. COHEN: All right. We have an IDA for concentration of use of the nine of the fourteen ingredients, particularly seed extract and flour because of DART issue. We want the DART on the flower extract and the extract. We want method of manufacturing for the cosmetic materials, irritation, sensitization on those we don't have. We have flour, and we have germ. Did I leave anything out?

DR. ROSS: I would just mention when you have the method of manufacture to specify that you want the details of the extraction solvent.

DR. COHEN: Okay.

DR. ROSS: I mean, are you presenting this tomorrow? Oh, no, it's Don.

DR. COHEN: No, it's Don.

DR. ROSS: Well, I guess you'll get a sense of it then. But on the DART issue with the flower, I mean, I think the intro is because we have the DART issues with the seed, and we have some overlap in the constituents, we wanted a discussion of whether we needed DART issue with the flower.

DR. COHEN: It depends on what they say, but I intend to open the issue if it's not opened.

DR. ROSS: Yeah, that would just be a good discussion. I'd like to hear what they say about it.

DR. COHEN: Okay, two down 13 to go. We will not run this past 9:00 p.m. today, don't worry.

DR. ROSS: These are fast, these next ones.

DR. COHEN: I don't know, we'll see. We always say that, but.

Full Panel – December 3, 2024

NELUMBO NUCIFERA

DR. BELSITO: Yeah. Okay.

DR. BERGFELD: This is a biggie.

DR. COHEN: Yeah.

DR. BELSITO: So Nelumbo Nucifera. This is a report on safety of 14 of the derived ingredients from this plant. Among them is a flower oil, is not included in the web-based dictionary, but there are reported uses so it's been included in this report as well. The root water is said to function as a fragrance ingredient but it hasn't been reviewed by RIFM nor is it on their docket, so we're including that in this report as well.

We did receive a good amount of data, but despite that data we thought that the report was still insufficient. Let me see if I can find those. Composition, we got a lot of composition data but it was basically data that didn't really tell us what was in any of these plant parts. It was sort of a breakdown on flavonoids and other types of ingredients in these plants. So we really had no sense as to what was in these products.

And for some reason I just lost my insufficiencies here. So concentration of use, method of manufacturing we had for most of these but we did not have for whole plant, flower, leaf, stem or Phytoplacenta. The fact that some of these were GRAS ingredients -- Hold on, I may just have this in another PDF here. Yeah -- no.

DR. COHEN: I Can go through some of our -- we agree with your idea, we can go through some of ours too.

DR. BELSITO: Yeah, David, for some reason it dropped my insufficiencies here.

DR. COHEN: No, no, it's no problem, it's happened to me.

DR. SNYDER: Do you want me to cover them, Don, I wrote them down. But go ahead -- go ahead, David.

DR. BELSITO: Yeah, yeah, go ahead, Paul.

DR. SNYDER: So we had insufficient for composition data, insufficient for a method of manufacturer and impurities, excluding those that are food use, clear those. For the root we wanted systemic endpoints, and whole plant a 28-day dermal. We wanted in vitro genotox, dermal sensitization, irritation, UV absorption data, in vitro ocular, and then the pesticides and heavy metals.

And regarding some of these Don had, and I think was captured by the writer, the specific parts that we needed, those specific endpoints for.

DR. BELSITO: I got it now, Paul. So we needed composition on all, manufacturer and impurities on the whole plant, flower, leaf, stem and phytoplacenta. We had food use for flower, flower leaf, stem, germ, leaf, rhizomes and seeds, so we could clear

those for the systemic endpoints, but we needed data for the whole plant, callus, Phytoplacenta and stamen. We needed either a 28-day dermal or tox data if absorbed.

We needed in vitro genotox on all except the flower and germ, and in vivo genotox on all. Dermal sensitization and irritation on the callus, Phytoplacenta and stamen, and UV absorption on all except the germ, leaf seed, and in vitro ocular on all except the flower.

DR. BERGFELD: That's quite a laundry list.

DR. COHEN: Yeah, I know. It's a great list. Just one question for me personally for clarification. If absorbed, you want further data, what are you measuring for the absorption?

DR. BELSITO: That's a good point since it's a botanical. What specific material?

DR. COHEN: Yeah.

DR. BELSITO: So how do we get around that?

DR. BERGFELD: You have to ask for the systemic toxicity studies.

DR. COHEN: Yeah.

DR. ROSS: That's -- yeah.

DR. COHEN: That is it. So we wanted -- I think a lot of this is overlapping. There's just such a long list. I'm sorry to the writers about this. So we wanted concentration of use for 9 out of the 14 ingredients, particularly seed extract and flower because of the DART issues. Want the dart for flower extract and total extract? You already mentioned the method of manufacturing.

DR. BELSITO: Can we just go back to your DART? The flower and the seeds have food use.

DR. COHEN: Hold on, let's go back.

DR. ROSS: Don, did you say they had GRAS status?

DR. BELSITO: Well, I mean, it's not in the document. It doesn't say GRAS, it just says use as foods.

DR. ROSS: Yeah, I saw that.

DR. COHEN: Wouldn't we normally ask for GRAS status on that as opposed to just being reported as a food? We did that in a few other things.

DR. HELDRETH: The problem a lot of times with foods, if it's been in use in the US for say more than 50 years, they're not going to mark it with a GRAS status in the code, it's just kind of understood that we haven't seen reported issues with the consumption of that material. So you won't find a GRAS status in the FDA for it.

DR. COHEN: Yeah, but for non-cosmetic use, I don't think this is one that's been used for over 50 years. I mean, I don't know that for sure but is this sufficient?

Don brings up a good point about the DART, but this is just commentary about it without much corroboration, right?

DR. ROSS: I mean the discussion around DART in our team meeting went something like this. That there were some concerns with the seed at fairly low doses, about 7.5 megs per keg. And then when we compared the alkaloids and flavonoids in the seed extract, with the flower extract, which is in Table 4, I believe, they're obviously different. There are a lot of differences, but there are quite a few similarities.

And so that's where we came back to requesting the DART data for the flower extract also. So that was the summary of our discussion on DART. But we wanted your opinions on it basically.

DR. COHEN: I just think we've had higher standards than just using it as food, we usually wanted more.

DR. HELDRETH: We've done the historical food use in many reports. I mean look to the brown algae report. There's numerous ingredients there that are clear based on historical food use just because there's not going to be -- you know, FDA is not going to invest time in determining that, you know, oranges are GRAS. We're not going to find it, unfortunately.

DR. BERGFELD: Is that an item for the Discussion, the historical food use? Anyone?

DR. COHEN: It could -- I just recall those tables for the algae that it said GRAS or we had other toxicology. It wasn't just a single mention of it as a food. And we've deliberated over the food use and GRAS quite a bit, right?

DR. BELSITO: There was another category, I don't remember what it was called.

DR. COHEN: You're talking about in that table, right?

DR. BELSITO: Yeah, maybe Priya can tell us. I forget what that category was called. It wasn't GRAS. It was something else that we asked the people from Europe exactly what it meant.

MS. CHERIAN: It was QPS.

DR. COHEN: Yeah, yeah, yeah, right.

MS. CHERIAN: QPS status is what you're thinking of.

DR. BELSITO: Yeah. Okay.

DR. COHEN: So how about DART for flower and the extract or this verification of the food.

DR. BELSITO: I mean, it's insufficient. I'm fine with whatever you want to add on at this point. I mean, we'll deal with it when we look at it again. There's a huge insufficiency list for these ingredients.

DR. COHEN: Yeah. We also had irritation and sensitization on those that we don't have right now because we don't have the total extract. We have it on flower extract and germ extract, but we don't have it on other things, correct?

DR. BELSITO: Let me take a look here. We have human dermal -- we have dermal irritation. We don't have it on the flower. We don't have it on the callus. We don't have it on the Phytoplacenta and we don't have it on the stamen. So we're missing irritation for those parts. And then for sensitization, we don't have on the whole plant, we don't have on the flower, we don't have on the flower leaf stem.

DR. COHEN: We have flower extract, don't we?

DR. BELSITO: Yeah.

DR. DIYABALANAGE: Yes, yes, we have for flower.

DR. BELSITO: For flower?

DR. COHEN: For the flower extract.

DR. BELSITO: We have sensitization?

DR. COHEN: Yeah, there's a HRIPT on the flower extract at 1 percent.

DR. BELSITO: What page is that?

DR. COHEN: I got to go into the PDF, I have it just opened.

DR. HELDRETH: 28.

DR. BELSITO: I didn't check it off on my list.

DR. ROSS: I think the effective concentration was lower.

It was .15 percent. We also made a comment --

DR. COHEN: Oh yeah, yeah, .15 percent David. That's right.

DR. ROSS: Yeah. We also made a comment --

DR. COHEN: Yeah. And we were going to editorially change that as well.

DR. ROSS: We'd like these sentences lead with the effect of concentration, rather than the concentration that was tested, because it was hard to pull those out. But yeah, effective was .15 percent. You have an HRIPT there.

DR. BELSITO: Okay. So we have irritation, sensitization.

We have on germ. We have an in vitro DPRA and KeratinoSens. And again, germ, we have sensitization in five Guinea pigs. And then the flower. yeah, we have -- you're right. Human, we have a flower extract with an HRIPT.

DR. COHEN: Don, I think for the flower, anyway, it's got coumarin in it as one of the constituents. So it still may wind up with a safe when formulated to be non-sensitizing, right, if it has the coumarin in it?

DR. BELSITO: Yeah. I mean, none of these studies were overwhelming and would certainly meet the standard criteria. I mean, the HRIPT was 53 and 56 for the germ extract, not 100. The Guinea pig test was in 5 Guinea pigs, normally you want at least 10. And there were no controls as far as I can tell. So, I mean --

DR. COHEN: We're asking for it. We're asking for the irritation on that, so.

DR. BELSITO: Yeah, I mean just -- that's fine.

DR. COHEN: So I think the two together, we have the motion sort of lined up.

DR. BERGFELD: Well, it's insufficient. That is the motion. And the list I'm all confused about. Priya, do you know where we are with this? We have two teams.

DR. BELSITO: This is Thushara.

DR. DIYABALANAGE: Yeah, it's clear. Yeah. It's a long list but yeah, it's clear.

DR. BERGFELD: You've got to clear? Okay.

DR. DIYABALANAGE: It's good.

DR. BERGFELD: You think you want to repeat it?

DR. DIYABALANAGE: No, I think we will get the transcript of your conversations too, like, so then we can sort it out.

DR. BERGFELD: Okay. All right. Any other comments?

DR. COHEN: And we'll have it in our returns.

DR. BERGFELD: Bart?

DR. HELDRETH: Priya was kind enough to dig up the regs on foods that have been in use for many years. According to the USFDA, foods such as soybeans -- this is from the soybeans report -- that have been ingested as food and food products, prior to January 1, 1958, are considered GRAS through experience based on common use in food. And that's 21 CFR 170.30.

So, if these materials have been in use prior to January 1, 1958, and they are grandfathered in as GRAS.

DR. ROSS: I think, Bart, you may have -- some of these data we've asked for in the archives of various industries or places. And so, I think requesting it might shake those out a little. So, yeah.

DR. HELDRETH: Yeah, I'm not objecting to any of that.

I'm just stating how the GRAS works.

DR. COHEN: I think, though, if you went into the local ShopRite and asked for the soy and the wheat, you'd find them. If I went in and asked for the Nelumbo Nucifera aisle, no one would know what I'm talking about. So I don't think that is necessarily a 50-year, well-known food product. I think we need more evidence of its routine use. I need more convincing.

DR. BERGFELD: It's in Asia.

DR. DIYABALANAGE: So there are a lot of Lotus products, actually. It goes by the word Lotus.

DR. SNYDER: Nonetheless, we can just change our wording to say the Panel understands these food uses and therefore, you know, has no concern.

DR. BERGFELD: Correct. That can go into discussion as well.

DR. ROSS: If we decide to go that way, yeah.

DR. BERGFELD: All right, we have everyone agreeing about insufficient. We have a list, that has been stated by Thushara that he can put together, of what everyone has said, but he's not repeating it right now because everyone will feed into him for their documents.

Is there anything else to discuss?

DR. ROSS: Yes, I had a just a couple of points. And Thushara and us -- we talked about this in our team meetings.

DR. BERGFELD: Okay.

DR. ROSS: One was some clarity around the extracts in Table 4, were the water extract, ethanol extracts, either. And I realize that's hard to do, but the flower extract in its method of manufacturer is a water extract. Much of the data is as an ethanol extract.

DR. DIYABALANAGE: Yeah, yeah, yeah, yeah.

DR. ROSS: So it's all a bit mixed up. And then we wanted the data summary table right up front to be split out by ingredient.

DR. DIYABALANAGE: Okay.

DR. BERGFELD: Anything else? Any other comments?

DR. BELSITO: Yeah, in the document itself, there's a section that is labeled as atopic dermatitis, which is not atopic dermatitis at all. It PDF Page 25, inhibitory effects on atopic dermatitis formation and inflammation.

This is sensitization, not atopic dermatitis. The effects of orally-administered -- this is nucifera leaf extract on the severity of 2,4-Dinitrochlorobenzene induced allergic contact dermatitis, not atopic dermatitis.

The classic sensitization protocol that's discussed.

DR. DIYABALANAGE: Yeah.

DR. COHEN: It's often used as a surrogate for preclinical work in drug development sometimes, but you're right, it's not AD.

DR. BERGFELD: Okay, editorial. Anything else? All right, I'm going to call – Don, to have something else.

DR. BELSITO: No.

DR. BERGFELD: You're just mumbling. All right, going to call the question. It's insufficient. The list will come out. All those opposed? Abstaining? Approved. It'll go out as insufficient data announcement with a long laundry list.

Safety Assessment of *Nelumbo nucifera*-Derived Ingredients as Used in Cosmetics

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ABBREVIATIONS

ALT	alanine aminotransferase
AST	aspartate transferase
cAMP	cyclic adenosine monophosphate
AST	aspartate transferase
BCOP	bovine cornea opacity and permeability test
C3GE	cyanidin 3-*O*-glucoside equivalent
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPK	creatine phosphokinase
CPSC	Consumer Product Safety Commission
CREB	cAMP-response element-binding protein
DAPI	4',6-diamidino-2-phenylindole, dihydrochloride
DAPK1	death-associated protein kinase 1
Dictionary	web-based (wINCI) *International Cosmetic Ingredient Dictionary and Handbook*
DMSO	dimethyl sulfoxide
DNCB	dinitrochlorobenzene
DNPH	2,4-dinitrophenylhydrazine
DOPA	4-dihydroxyphenylalanine
DPRA	direct peptide reactivity assay
DW	dry weight
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
G-6-PSD	glucose-6-phosphate dehydrogenase
GAE	gallic acid equivalents
HET-CAM	hen's egg test on the chorioallantoic membrane
HPLC	high-performance liquid chromatography
HPLC-DAD	high-performance liquid chromatography with diode array detector
HRIPT	human repeated-insult patch test
3β-HSD	3β-hydroxysteroid dehydrogenase
IC_{50}	half-maximal inhibitory concentration
INCI	International Nomenclature Cosmetic Ingredient
LD_{50}	median lethal dose
α-MSH	α-melanocyte stimulating hormone
MITF	microphthalmia-associated transcription factor
MED	minimal erythema dose
MoCRA	Modernization of Cosmetics Regulation Act
N/A	not applicable
Na-CMC	carboxymethyl cellulose
ND	not detected
NOAEL	no-observed-adverse-effect level
NR	not reported
NRU	neutral red uptake
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PEG	polyethylene glycol
PI	propidium iodide
pKA	protein kinase A
PVP	polyvinylpyrrolidone
QE	quercetin equivalents
RIFM	Research Institute for Fragrance Materials
RLD	Registration and Listing Data
TAE	tannic acid equivalents
TG	test guideline
TNF-α	tumor necrosis factor α
TRP-1	tyrosinase-related protein-1
US	United States

UVB	ultraviolet B
USP	*United States Pharmacopeia*
VCRP	Voluntary Cosmetic Registration Program
WHO	World Health Organization

DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 14 *Nelumbo nucifera*-derives ingredients are used in cosmetic formulations, most of which are reported to function in cosmetics as skin-conditioning agents and/or antioxidants. 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 …[to be determined]...

INTRODUCTION

This assessment reviews the safety of 14 *Nelumbo nucifera*-derived ingredients as used in cosmetic formulations:

Nelumbo Nucifera Callus Culture Extract
Nelumbo Nucifera Extract
Nelumbo Nucifera Flower Extract
Nelumbo Nucifera Flower/Leaf/Stem Juice
Nelumbo Nucifera Flower Oil
Nelumbo Nucifera Flower Water
Nelumbo Nucifera Germ Extract
Nelumbo Nucifera Leaf Extract
Nelumbo Nucifera Phytoplacenta Culture Extract
Nelumbo Nucifera Root Extract
Nelumbo Nucifera Root Water
Nelumbo Nucifera Seed Extract
Nelumbo Nucifera Seed Powder
Nelumbo Nucifera Stamen Extract

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), most of these ingredients are reported to function in cosmetics as skin-conditioning agents and/or antioxidants (Table 1).[1] Nelumbo Nucifera Flower Oil is not included in the *Dictionary*; however, it had reported uses in 2023 in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database and in RLD for 2024, and thus included in this review. A few of these ingredients have other reported functions; e.g., Nelumbo Nucifera Flower Water and Nelumbo Nucifera Seed Extract are reported to function as cosmetic astringents, and Nelumbo Nucifera Seed Powder is reported to function as an abrasive. Additionally, Nelumbo Nucifera Root Water is only reported to function as a fragrance ingredient. The Expert Panel for Cosmetic Ingredient Safety (Panel) does not typically review ingredients that function only as fragrance ingredients, because, as fragrances, the evaluation of the safety of these ingredients is the purview of the Research Institute for Fragrance Materials (RIFM). A RIFM safety monograph is not available at this time; therefore, this ingredient is included in this safety assessment.

These ingredients are all derived from the same species and have therefore been grouped together in this assessment. Botanicals, such as *Nelumbo nucifera*-derived ingredients, may contain hundreds of constituents. In this assessment, the Panel is reviewing the potential toxicity of each of these *Nelumbo nucifera*-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 January 2025. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics will be followed (i.e., *Nelumbo nucifera*). Often in the published literature, the general name "lotus" 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 (e.g., lotus petal extract). However, if it is known that the substance is a cosmetic ingredient, the *Dictionary* nomenclature (e.g., Nelumbo Nucifera Flower Extract) will be used.

CHEMISTRY

Definition and Plant Identification

According to the *Dictionary*, most of the *Nelumbo nucifera*-derived ingredients named in this assessment have the generic CAS No. 85085-51-4.[1] The definitions of these *Nelumbo nucifera*-derived ingredients are presented in Table 1.[1] *Nelumbo nucifera* belongs to the family Nelumbonaceae and is commonly known as Indian lotus, Chinese water lily, and sacred lotus.[2] The *Nelumbo nucifera* plant is native to China, Japan, and India and is a large, perennial rhizomatous aquatic herb which grows in ponds, jheels, ditches and pools.[3-5]

Generic definitions of the parts of plants which pertain to the ingredients reviewed in this report are presented in Table 2.[1] The roots of *Nelumbo nucifera* are planted in the soil of a muddy pond or river bottom.[6] The *Nelumbo nucifera* plant can grow up to 1.5 m in height and can have a horizontal spread of up to 3 m. Flowers grow solitary on stems (3 – 6 ft in length)

arising from the leaves, are white to pink in color, fragrant, and have a diameter of 4 – 10 in. The leaves float on the water surface, are shiny, round, and can have a diameter of 1 to 3 ft. Additionally, lotus leaves have unique water adhesion properties which make them hydrophobic.[7] *Nelumbo nucifera* seeds are 1 cm in diameter and are contained in a woody seed receptacle which looks like a showerhead.[8] Stamens are yellow and are comprised of many ripe carpels (10 mm long) which surround the seed receptacle.[6]

Chemical Properties

An aqueous *Nelumbo nucifera* flower extract was described as a dark, yellowish liquid with a specific gravity of 0.98 – 1.04.[9] Chemical properties for a *Nelumbo nucifera* flower extract,[9] Nelumbo Nucifera Flower Extract (extracted in isostearyl isostearate),[10] Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin),[11] and a *Nelumbo nucifera* lotus seed flour [12] can be found in Table 3.[9,12]

Method of Manufacture

Most of the methods described below are general to the processing of *Nelumbo nucifera*-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.

Nelumbo nucifera plant part extracts

Descriptions of the method of manufacture of a whole plant extract of *Nelumbo nucifera* were not found; however, descriptions of the manufacture of extracts with some plant parts were available. Accordingly, because Nelumbo Nucifera Extract is the extract of the whole plant, this information is provided.

In a preparation of a crude fruit extract, *Nelumbo nucifera* fruits (6 kg) were washed, separated from the seed pods, chopped, and shade-dried for 6 d.[13] The dried fruit was ground into a fine powder and macerated in 98% ethanol for 30 d with occasional shaking. The solvent was filtered, and the resulting *Nelumbo nucifera* fruit extract was evaporated under reduced pressure in a rotary evaporator and freeze-dried.

Nelumbo Nucifera Callus Culture Extract

For the preparation of a *Nelumbo nucifera* callus culture extract, sterilized *Nelumbo nucifera* seeds were grown under water to promote the germination of leaves.[14] Upon being transferred to an agar plate and with appropriate growth medium, these leaf segments began to induce callus formation. A callus suspension culture was initiated by adding 7 g callus inoculum to a 70 ml Murashige and Skoog liquid medium containing 30 g/l sucrose. The culture was incubated for approximately 2 - 3 wk. Dried or lyophilized callus (2 g/l) was added to distilled water in an Erlenmeyer flask, which was heated in a 40°C water bath for 4 h. The extract was then filtered twice, using a strainer and a 0.22 µm filter.

In a study seeking to establish a reliable method for lotus callus induction, tissue from lotus leaves, immature cotyledons, immature embryos and rhizome tips were cultured separately in Murashige and Skoog medium that was supplemented with 3 mg/l 2,4-dichlorophenoxyacetic acid and 1 mg/l zeatin.[15] Immature cotyledons (leaf origins in the seed) taken 9 d after pollination showed the earliest signs of callus formation 5 d after culture, followed by sections of immature seed embryos which formed calluses 18 d after pollination and 7 d post-culture.

Nelumbo Nucifera Flower Extract

An aqueous *Nelumbo nucifera* flower extract was prepared by extracting freeze-dried and ground *Nelumbo nucifera* flowers.[9] For the first extraction, 50 g of ground flowers were heated with 2 l of distilled water at 100°C until the solution volume was reduced by half. Another portion of 2 l fresh water was added and heated again until the total solution volume became 50% (second extraction). The third extraction was performed under the same conditions and the final solution was cooled to room temperature and preservatives were added. The preservatives used included 20% propylene glycol and 0.5% of a trade name mixture containing phenoxyethanol, methylparaben, ethylparaben, propylparaben, butylparaben, and isobutylparaben. The resultant solution was filtered with a 200-mesh (0.75 µm) filter, refrigerated for 24 h, and filtered again with mixed cellulose ester filter.

Nelumbo Nucifera Flower/Leaf/Stem Juice

According to the *Dictionary*, Nelumbo Nucifera Flower/Leaf/Stem Juice is the juice expressed from the flowers, leaves, and stems of *Nelumbo nucifera*.[1] No further information regarding method of manufacture was found or submitted.

Nelumbo Nucifera Flower Water

According to the *Dictionary*, Nelumbo Nucifera Flower Water is the aqueous extract of the steam distillate obtained from the flowers of *Nelumbo nucifera*.[1] No further information regarding method of manufacture was found or submitted.

Nelumbo Nucifera Germ Extract

According to an industry submission describing a method of manufacture for a trade name mixture containing 0.5-1.5 w/v% Nelumbo Nucifera Germ Extract as used in cosmetics, raw dried material was extracted with an ethanolic solution, filtered and concentrated.[16] This was dissolved in (50% volume)1,3-butylene glycol solution and allowed sedimentation. The resultant product was packaged after filtration and adjustment.

Nelumbo nucifera germs (200 g) were extracted with 50% ethanol under reflux for 2 h.[17] The resulting mixture was filtered through diatomite, and this filtrate was concentrated under reduced pressure at 60°C. The residue was freeze-dried, and 23.1 g of a *Nelumbo nucifera* germ extract was obtained.

Nelumbo Nucifera Leaf Extract

According to an industry submission, a trade name mixture containing a maximum of 1.2% Nelumbo Nucifera Leaf Extract is prepared by solubilization of *Nelumbo nucifera* leaf powder in a mix of water/butylene glycol (50/50).[18] The soluble and insoluble phases were separated, the soluble phase was filtered and then using sterilized membrane filtration.

An aqueous *Nelumbo nucifera* leaf extract was prepared by freeze-drying and grinding leaves (50 g) and performing 3 extractions with 2 l of water heated to 100°C until the solution volume reduced to half.[9] The final extract was cooled and preservatives were added. The preservatives used included 20% propylene glycol and 0.5% of a trade name mixture containing phenoxyethanol, methylparaben, ethylparaben, propylparaben, butylparaben, and isobutylparaben. The resultant solution was filtered with a 200-mesh (0.75 µm) filter, refrigerated for 24 h, and filtered again with a mixed cellulose ester filter.

Another aqueous *Nelumbo nucifera* leaf extract was reported to be prepared from *Nelumbo nucifera* leaves that were washed with distilled water, air-dried at 50°C, and ground into powder.[19] Distilled water (5 l) was used to resuspend 200 g of the leaf powder for 24 h at 4°C. The precipitate was removed via filtration and the supernatant was condensed using a vacuum concentrator. The condensed solution was then lyophilized as a *Nelumbo nucifera* leaf extract.

Nelumbo Nucifera Root Extract

An aqueous *Nelumbo nucifera* root extract was prepared by freeze-drying and grinding the root (50 g) and performing an extraction 3 times with 2 l of water heated to 100°C until the solution volume reduced to half.[9] The final extract was cooled and preservatives were added. The preservatives used included 20% propylene glycol and 0.5% of a trade name mixture containing phenoxyethanol, methylparaben, ethylparaben, propylparaben, butylparaben, and isobutylparaben. The resultant solution was filtered with a 200-mesh (0.75 µm) filter, refrigerated for 24 h, and filtered again with mixed cellulose ester filter.

In another study, fresh lotus roots were ground into powder using a mortar and pestle.[20] Ground samples of *Nelumbo nucifera* lotus root were weighed to 20 g and added to either distilled water, anhydrous ethanol, methanol, 20, 40, 60 or 80% ethanol, or 20, 40, 60, or 80% methanol, at a material-to-liquid ratio of 1:10 (g:ml). The resulting *Nelumbo nucifera* lotus root extracts were obtained via ultrasonic extraction at an extraction temperature of 50°C for 1 h, concentrated with a rotary evaporator, dried into a lyophilized powder using a vacuum freeze dryer, and stored at – 20°C.

Nelumbo Nucifera Seed Extract

A crude *Nelumbo nucifera* seed extract was prepared by drying, grinding, and extracting *Nelumbo nucifera* seeds in a Soxhlet extractor with petroleum ether.[21] The resultant extract was dried by the removal of solvent under vacuum.

An aqueous *Nelumbo nucifera* seed extract was prepared by freeze-drying and grinding the seeds (50 g) and performing an extraction 3 times with 2 l of water heated to 100°C until the solution volume reduced to half.[9] The final extract was cooled and the preservatives were added. The preservatives used included 20% propylene glycol and 0.5% of a trade name mixture containing phenoxyethanol, methylparaben, ethylparaben, propylparaben, butylparaben, and isobutylparaben. The resultant solution was filtered with a 200-mesh (0.75 µm) filter, refrigerated for 24 h, and filtered again with a mixed cellulose ester filter.

For a study, *Nelumbo nucifera* seeds were dried, powdered, and then extracted with 50% ethanol in a Soxhlet apparatus.[22] The resulting ethanolic extract was filtered and then evaporated under reduced pressure. A *Nelumbo nucifera* lotus seed tea was prepared by removing the seed coat, roasting the seeds until brown, and then extracting the roasted seeds with hot water.[23]

Nelumbo Nucifera Seed Powder

In a preparation of *Nelumbo nucifera* seed powder, fresh lotus seeds were washed and the seed coat was separated from the seed.[12] The seeds were then dried in a tray dryer at 60°C, ground into flour, and sieved through 72 µm mesh. Another *Nelumbo nucifera* seed powder was obtained using dry lotus seeds.[24] Seed kernels were obtained by breaking with a hammer and were immediately ground using a mortar and pestle. The resulting *Nelumbo nucifera* seed powder was sieved through a fine cloth to obtain uniform particle size.

Nelumbo Nucifera Stamen Extract

Dried powder of *Nelumbo nucifera* stamens (5 kg) was extracted with 95% ethanol by percolation at room temperature over 2 wk.[25] The extract was then filtered and the combined filtrate was evaporated to remove ethanol under reduced pressure and lyophilized to yield an ethanolic *Nelumbo nucifera* stamen extract.

Dried *Nelumbo nucifera* stamens (100 g) were extracted in an ultrasonic bath using 90% ethanol.[26] The resulting solution was centrifuged and filtered through 0.45µm nylon syringe membranes to obtain an ethanolic *Nelumbo nucifera* stamen extract.

Composition and Impurities

The main chemical classes of compounds present in the *Nelumbo nucifera* plant are proteins, amino acids, and steroids (present mostly in the seeds), carbohydrates (present mostly in the leaves and seeds), alkaloids and flavonoids (present mostly in the flowers, leaves, and seeds), and terpenoids (present mostly in the leaves).[27] Alkaloids are the prominent bioactive chemical class of constituents present in *Nelumbo nucifera.* Among them, the high representation of biosynthetic sub classes of aporphine alkaloids, benzylisoquinoline alkaloids, and bisbenzylisoquinoline alkaloids is significant.[28-31] Nuciferine is the main aporphine alkaloid, and neferine and liensinine are the main bioactive bisbenzylisolquinoline alkaloids present in the *Nelumbo nucifera* plant.[30] A list of major constituents, organized by chemical class, and presence in *Nelumbo nucifera* plant parts (embryo, flower, leaf, seed, and stamen) is provided in Table 4.

Nelumbo Nucifera Extract

The mineral and heavy metal content of *Nelumbo nucifera* has been considered.[32] A *Nelumbo nucifera* plant was described as containing iron (171.38 ppm), zinc (45 ppm), copper (8.43 ppm), nickel (4.16 ppm), lead (0.728 ppm), chromium (0.27 ppm), arsenic (0.178 ppm), mercury (0.065 ppm), and cadmium (0.022 ppm).

Nelumbo Nucifera Flower Extract

According to an industry submission, Nelumbo Nucifera Flower Extract (1 - 5%) extracted in isostearyl isostearate (95 – 99%) complies with aflatoxin limits set in the *United States Pharmacopeia* (USP) and pesticide and residual solvent limits set in the *European Pharmacopoeia*.[10] Heavy metal content was not analyzed; however, according to the raw materials used and the manufacturing process, the eventual presence of total heavy metals in this product would be technically unavoidable and lower than 10 ppm.

According to an industry submission, a trade name mixture of Nelumbo Nucifera Flower Extract (0.5 – 1%) extracted in propanediol (70 -90%) and glycerin (10 – 30%) with 0.5 – 1% Nymphaea Caerulea Flower Extract also comprised 70 – 90% propanediol and 10 – 30% glycerin.[11] According to gas chromatography-mass spectrometry analysis, benzyl alcohol was present at 3.4 – 13 ppm (average value of 6.7 ppm); all other European fragrance allergens were below the limit of detection (< 2 ppm). Heavy metal content was not analyzed, however, according to the raw materials used and the manufacturing process, the eventual presence of total heavy metals in this product would be technically unavoidable and lower than 10 ppm.

The total flavonoid content in whole *Nelumbo nucifera* flowers and *Nelumbo nucifera* petals, using ultrasound extraction with ethanol and flavonoid enrichment, was determined to be 40.08 ± 1.94 and 38.67 ± 0.70 mg/g dry weight (DW), respectively.[26] Separate aqueous and ethanolic extracts of white and red *Nelumbo nucifera* petals were evaluated for total phenolic, tannin, flavonoid, and monomeric anthocyanin content.[33] For both aqueous extracts, the average total phenolic content was 22.41 gallic acid equivalents (GAE)/g DW, the average total tannin content was 18.84 tannic acid equivalents (TAE)/g DW, the average total flavonoid content was 9.22 quercetin equivalents (QE)/g DW, and the total monomeric anthocyanin content for the aqueous red petal extract was 49.75 µg cyanidin 3-*O*-glucoside equivalents (C3GE)/g DW. For both ethanolic extracts, the average total phenolic content was 0.52 GAE/g DW, the average total tannin content was 1.24 TAE/g DW, and the average total flavonoid content was 1.24 QE/g DW. In another ethanolic *Nelumbo nucifera* flower extract, the average total flavonoid content was reported to be 15.98 mg/100 g of dry extract, while the total phenolic content was reported to be 10.68 mg/100 g of dry extract.[34]

A hydroalcoholic *Nelumbo nucifera* flower extract was determined to contain alkaloids, proteins and amino acids, flavonoids, tannins, and phytosterols (amounts not specified).[35] Phenolic substances (total, 10.20 µg/100 g), protein (34 µg/100 g), vitamin C (0.36 µg/100 g), vitamin E (0.42 µg/100g), tannins (4.30 µg/100g), and carbohydrates (672 µg/100 g) were also identified.

An ethyl alcohol *Nelumbo nucifera* lotus petal extract was shown to have a higher total phenolic content (351 mg GAE/g dry extract) compared to an ethyl acetate lotus petal extract (208 mg GAE/g dry extract) when analyzed via the Folin-Ciocalteau method.[36] A quantitative comparison of reference standard compounds in both lotus petal extracts identified in a high-performance liquid chromatography with diode array detector (HPLC-DAD) analysis is presented in Table 5.

A 70% ethanolic *Nelumbo nucifera* petal extract was analyzed.[37] Total phenolic content (18.56 GAE)/g), total flavonoid content (6.77QE/g), total alkaloid content (4.55 piperidine equivalents), and total tannins (23.14 GAE/g) were measured.

In another phytochemical study, the alkaloids present in a methanolic *Nelumbo nucifera* flower bud extract were identified.[38] A crude alkaloid fraction of 0.9 kg methanolic *Nelumbo nucifera* flower bud extract contained nuciferine (183 mg), nornuciferine (121 mg), *N*-methylasimilobine (36 mg), (-)-lirinidine (3 mg), lysicamine (38.2 mg), pronuciferine (23 mg), and β-sitosterol (1.8 mg).

One aqueous extract of *Nelumbo nucifera* flower was reported to contain 10 ppm heavy metals, 2 ppm arsenic, and 100 cfu/ml microbes.[9] Quantification of phenolic, flavonoid, and anthocyanin content in the flower and leaf stalk, leaf, petal,

seed embryo, and stamen of the *Nelumbo nucifera* plant is presented in Table 6.[39] Total phenolic content (GAE/g DW) was highest in the leaf (39.09 ± 0.79 GAE/g DW) and total flavonoid content was highest in the petal (approximately 5054.72 mg/100 g DW). Minimal anthocyanins (C3GE/g DW) were detected in the stamen (0.23 ± 0.02) and petal (0.05 ± 0.00).

Nelumbo Nucifera Germ Extract

According to an industry submission, Nelumbo Nucifera Germ Extract is composed of tannins and flavonoids or tannins and saccharides.[16] The presence of heavy metals were not more than 20 ppm and arsenic was not present at more than 2 ppm.[16]

Several flavonoids and alkaloids such as neferine, and polyphenols, such as orientin, isoorientin, vitexin, isovitexin, vicenin-3, vicenin-1, and schaftoside were identified (amounts not specified) in a *Nelumbo nucifera* germ extract prepared with 50% ethanol.[40] Quantification of phenolic, flavonoid, and anthocyanin content in a *Nelumbo nucifera* seed embryo is presented in Table 6.[39]

Nelumbo Nucifera Leaf Extract

According to an industry submission, the composition of a trade name mixture containing 0.5 – 1.2% Nelumbo Nucifera Leaf in a 50/50 mix of water/butylene glycol was as follows: sugars (51.1%), mineral ashes 28.0%, proteins 28%, and polyphenols 7.6%.[18] The presence of heavy metals antimony, arsenic, cadmium, chromium, cobalt, mercury, nickel, lead and vanadium was below the threshold (≤ 0.5 ppm).

The total phenolic content for an aqueous and a methanolic extract of *Nelumbo nucifera* leaves was 85.01 ± 2.32 mg GAE/g DW and 147.63 ± 2.23 mg GAE/g DW, respectively; the total flavonoid content was determined to be 35.38 ± 1.32 mg QE/g DW in the aqueous extract and 41.86 ± 1.07 mg QE/g DW in the methanolic extract.[41] In another phytochemical study, the following compounds were identified in the ethyl acetate fraction of a methanolic *Nelumbo nucifera* leaf extract (36.9 g): *N*-methylasimilobine *N*-oxide (3.3 mg), nuciferine (67.3 mg), nuciferine *N*-oxide (40.7 mg), *N*-nornuciferine (2.3 mg), dehydronuciferine (3.9 mg), ± (41.8 mg), quercetin 3-*O*-β-d-galactopyranoside (7.5 mg), and (+)-catechine (40.5 mg).[38] Quantification of phenolic, flavonoid, and anthocyanin content in a *Nelumbo nucifera* old leaf and leaf stalk are presented in Table 6.[39]

Nelumbo Nucifera Root Extract

A phytochemical screening of an ethanolic extract of *Nelumbo nucifera* roots was performed.[42] The *Nelumbo nucifera* root extract was found to contain carbohydrates, alkaloids, glycosides, flavonoids, and proteins and amino acids (amounts not specified).

Nelumbo Nucifera Seed Extract

Nelumbo nucifera seeds, extracted with a hydroalcoholic solvent, were analyzed for phenolic content.[43] The total phenolic content of the hydroalcoholic *Nelumbo nucifera* seed extract was determined to be 7.61 ± 0.04% (w/w). In another phytochemical study, *Nelumbo nucifera* lotus seed proteins were fractionated according to their solubility in various solvents.[44] The major phytochemicals present in the seeds of *Nelumbo nucifera* are the alkaloids dauricine, nuciferine, pronuciferine, liensinine, isoliensinine, rosmerine and neferine.

The essential and non-essential amino acid composition of a lotus seed protein and its fractions (water-soluble albumin, salt-soluble globulin, alcohol-soluble prolamine, and alkali-soluble glutelin) is presented in Table 7. Total essential amino acid content in the seed protein was 322.82 g/kg (crude protein, DW), while the total non-essential amino acid content was 553.06 g/kg. The essential and non-essential amino acid contents were highest in the globulin fraction. Palmitic acid (33.27%) and linoleic acid (19.9%) were the 2 most prevalent constituents in a fatty acid composition of a whole *Nelumbo nucifera* seed oil (obtained via extraction of seed powder with 2:1 v/v chloroform: methanol solution). The fatty acid profile from this analysis is presented in Table 8.[45]

Nelumbo Nucifera Seed Powder

A nutritive analysis of *Nelumbo nucifera* seeds demonstrated that it contains 1.93% crude fat, 2.7% crude fiber, 4.5% ash, 10.6% protein, 10.5% moisture content, and 72.17% carbohydrate.[46] The composition of the mineral content in *Nelumbo nucifera* seeds was reported as potassium (28.5%), calcium (22.1%), magnesium 9.2%, sodium 1%, and negligible percentages of chromium, copper, manganese, iron, and zinc.

The nutritional composition of a *Nelumbo nucifera* lotus seed flour (per 100 g) was analyzed.[12] A nutritive analysis of *Nelumbo nucifera* seeds suggested a by-weight content of 72.17% carbohydrates, 10.16% proteins, 2.7% crude fiber, and 1.93% crude fat. Pyrolysis resulted in 4.5% residual ash and release of 10.5% moisture.

Nelumbo Nucifera Stamen Extract

The total phenolic content in a *Nelumbo nucifera* stamen was determined to be 36.37 ± 0.73 mg GAE/100 g DW.[39] Flavonoids such as myricetin (7.63 ± 0.35 mg/100 g DW), luteolin (amount not determined), quercetin (43.94 ± 2.08 mg/100 g DW), naringenin (2185.84 ± 24.21 mg/100 g DW), kaempferol (160.71 ± 13.66 mg/100 g DW), isorhamnetin (192.09 ± 15.70 mg/100 g DW) , cyanidin (115.79 ± 10.21 mg/100 g DW), and delphinidin (211.63 ± 17.21 mg/100 g DW) were also identified. In another phytochemical study, total flavonoid content was higher in an ethanolic *Nelumbo nucifera* stamen

extract (68.11 ± 3.53 mg/g DW), compared to ethanolic *Nelumbo nucifera* whole flower and petal extracts (40.08 ± 1.94 and 38.67 ± 0.70 mg/g DW, respectively).[26]

Phytochemical investigations on *Nelumbo nucifera* stamens have been able to identify the benzylisoquinoline alkaloids annaine, dehydroanonaine, armepavine, asimilobine, demthycoclaurine, lirinidine, dehydronuciferine, liriodenine, dehydroemerine, nornuciferine, N-methylasimilobine, N-methylcoclaurine, N-methylisococlaurine, N-norarmepavine and romarin.[47] In addition, the bis-benzylisoquinolic alkaloids iosliensinine and lisensinine have also been reported from the stamens of *Nelumbo nucifera*.

Seven flavonoids were identified in the ethanolic *Nelumbo nucifera* stamen extract via reversed-phase high-performance liquid chromatography (HPLC), recorded at 320 nm: isorhamnetin-3-*O*-glucose, kaempferol-3-*O*-glucose, kaempferol 3-*O*-glucuronic acid, kaempferol-3-*O*-robinobioside, myricetin-3-*O*-glucose, quercetin-3-*O*-glucuronic acid, and rutin (amounts not determined). Quantification of phenolic, flavonoid, and anthocyanin content in a *Nelumbo nucifera* stamen is presented in Table 6.[39]

UV Absorption

Nelumbo Nucifera Germ Extract

The ultraviolet (UV) absorption of Nelumbo Nucifera Germ Extract in water and butylene glycol was determined.[48] According to an industry submission, three trade name mixtures that consisted of Nelumbo Nucifera Germ Extract in water and butylene glycol (concentrations not stated) have absorption maxima of 272.1, 273.0 and 273.0 nm.

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 *Nelumbo nucifera*-derived ingredients in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was 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 (i.e., RLD). An exception is made for small businesses, which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h.[49] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

Nelumbo Nucifera Flower Extract had the highest number of reported uses, with 544 uses (211 of which are for face and neck cleansing products) are reported in the RLD in 2024[50] and in 2023, 200 fuses reported in the VCRP in 2023[51] (Table 9). The results of the concentration of use survey conducted by the Council in 2022 and 2024 indicate that Nelumbo Nucifera Root Extract has the highest maximum reported concentration of use; it is reported to be used at up to 0.2% in foundations.[52,53]

Cosmetic products containing *Nelumbo nucifera*-derived ingredients may incidentally come in contact with the eyes (e.g., Nelumbo Nucifera Flower Extract at 0.0015% in eye lotions), and could be incidentally ingested or come in contact with mucous membranes (e.g., Nelumbo Nucifera Flower Extract at 0.1% in lipstick). Use in baby products is also reported (e.g., Nelumbo Nucifera Flower Extract is used at up to 0.00055% in baby shampoos).

Additionally, *Nelumbo nucifera*-derived ingredients are used in cosmetics that can possibly be inhaled; for example, Nelumbo Nucifera Flower Oil is reported to be used in perfumes (concentration of use not reported) and Nelumbo Nucifera Flower Extract is reported to be used at 0.1% 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 cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Some products containing *Nelumbo nucifera*-derived ingredients may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. Some of the reported product categories for these ingredients

as listed in the RLD do require designation if airbrush application is used, and this type of application was reported for Nelumbo Nucifera Flower Extract in leg and body paints. Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

All of the *Nelumbo nucifera*-derived ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[54]

Non-Cosmetic

Nelumbo nucifera flowers, leaves, rhizomes, stems and seeds are all edible and widely used in traditional medicine. *Nelumbo nucifera* flowers are ornamental and the species is of religious significance in South East Asia.[55] *Nelumbo nucifera* seeds are used in East Asian cuisine and are sometimes sold as a snack food.[56] *Nelumbo nucifera* seed powder is used in baked goods, and *Nelumbo nucifera* seeds are used to produce milk and other food products.[57,58] *Nelumbo nucifera* seeds have also been used in the production of biofuels.[56]

TOXICOKINETIC STUDIES

No relevant toxicokinetic studies on *Nelumbo nucifera*-derived ingredients were found in the published literature, and unpublished data were not submitted. In general, toxicokinetic data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Nelumbo Nucifera Germ Extract

In a study to determine acute toxicity, groups of 4 male and 4 female mice were given a trade name mixture containing 0.5 -1.5 w/v% Nelumbo Nucifera Germ Extract (composed of tannins and flavonoids) [16] The LD_{50} was > 2 g/kg. (Additional details were not provided.)

Oral

Details on the acute oral toxicity studies summarized below can be found in Table 10.

No signs of toxicity or mortality were observed in mice that received a single oral dose (up to 99.9 g/kg bw) of an herbal mixture capsule containing 33% *Nelumbo nucifera* Gaertn.[59] The acute oral toxicity of several ethanolic extracts of *Nelumbo nucifera* plant parts were evaluated using rats.[42] The acute oral LD_{50} values of a *Nelumbo nucifera* leaf, flower, and root extract, a *Nelumbo nucifera* leaf and root extract, and a *Nelumbo nucifera* flower extract were > 2 g/kg, which was the maximum dose tested for each test article. No mortality was observed in rats administered a single oral dose of a hydroalcoholic *Nelumbo nucifera* flower extract at 2 g/kg.[35] A hydroalcoholic *Nelumbo nucifera* seed extract, in 0.3% sodium carboxymethyl cellulose, had an acute oral LD_{50} > 1 g/kg in mice.[43] The acute oral LD_{50} values for an ethanolic *Nelumbo nucifera* lotus root extract and a *Nelumbo nucifera* stamen extract-polyvinylpyrrolidone (PVP)-10 complex were both > 5 g/kg in mice and rats, respectively.[25,60]

Short-Term, Subchronic, and Chronic Toxicity Studies

Details on the repeated dose oral toxicity studies summarized below can be found in Table 11.

An herbal mixture capsule containing 33% *Nelumbo nucifera* Gaertn. was dissolved in water and orally administered at doses of 0, 1.44, or 4.32 g/kg/d to Wistar rats (10/group; sex not specified) for 4 wk.[59] Statistically significant increases in body weight were observed in 1.44 g/kg/d rats after 2 wk of treatment, compared to controls. No gross lesions or size changes were observed in the heart, liver, lungs, or kidneys and no significant histopathological differences were observed in rats treated for 4 wk, compared to controls. In a 6-mo study, a *Nelumbo nucifera* lotus seed tea was administered as the drinking fluid to male SKH-1 hairless mice (10/group).[23] No significant differences in food or liquid consumption or body weight were observed between treated mice and controls. In another oral toxicity study, Sprague-Dawley rats (5/sex/group) were orally dosed with 0, 500, 1000, or 2000 mg/kg/d Nelumbinis semen (*Nelumbo nucifera* seeds) for 13 wk.[61] No mortality, body weight, or ophthalmic changes were observed in treated animals, compared to controls. Statistically significant lower food consumption was observed in males at weeks 7 and 12 for the 500 and 2000 mg/kg/d groups and at weeks 7, 9, 10, and 12 for 1000 mg/kg/d males, compared to controls. Lower right adrenal gland weight in 500 and 1000 mg/kg males was neither dose-dependent or sex-matched and was, thus, not considered treatment-related. The no-observed-adverse-effect-level (NOAEL) was determined to be 2000 mg/kg/d for both sexes (combined). Beagle dogs (1/sex/group)

were orally dosed with 0, 500, 1000, 2000, or 4000 mg/kg/d Nelumbinis semen for 28 d.[61] No mortality was observed. Vomiting in the 2000 mg/kg male, low specific gravity of the urine in all treated females, and white blood cell reactions in all the treated males and the 2000 mg/kg female were not considered systemically or toxicologically significant. The NOAEL was determined to be 4000 mg/kg/d. In a 90-d oral toxicity study, Sprague-Dawley rats (6/sex/group) were orally administered 0, 50, 100, or 200 mg/kg/d of a *Nelumbo nucifera* stamen extract-PVP complex in distilled water.[25] Statistically significant decreases in the body weights of 200 mg/kg females and reduced relative heart, liver, and kidney weights were not considered treatment-related because the values were within normal laboratory range. No gross or histopathological abnormalities were noted. The NOAEL for both male and female rats was determined to be > 200 mg/kg/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details on the in vitro and oral reproductive toxicity studies summarized below can be found in Table 12.

In an in vitro reproductive toxicity study, rat sperm was tested with an aqueous *Nelumbo nucifera* petal extract at 0, 0.22, 0.44, 0.88, 1.76, or 3.52 mg/ml.[33] A statistically significant increase in sperm viability was observed from exposure to the 0.22 - 1.76 mg/ml concentrations; differences in sperm viability from the 3.52 mg/ml group and controls were not significant. In an animal study, male Wistar albino rats (10/group) were orally administered 7.5 mg/kg bw of a petroleum ether *Nelumbo nucifera* seed extract every other day for 15 d.[21] Statistically significant decreases in testis, epididymis, and adrenal gland weights, body growth rate, sperm count and motility, and 3β-hydroxysteroid dehydrogenase (3β-HSD) and glucose-6-phosphate dehydrogenase (G-6-PSD) levels in treated animals, compared to controls, were considered possibly due to inhibition of testicular steroidogenesis. In a similar study, female Wistar rats (12/group) were orally dosed with up to 7.5 mg/kg of a petroleum ether *Nelumbo nucifera* seed extract every other day for 15 d.[21] Statistically significant inhibition of the vaginal opening and first estrus and decreases in body weights, ovary weights, and uterus weights were observed in treated animals, compared to controls. The researchers considered the suppressed activity of 3β-HSD and G-6-PSD to possibly indicate an inhibition of ovarian steroidogenesis. The potential effects of an ethanolic *Nelumbo nucifera* seed extract were evaluated in female Wistar albino rats.[22] Groups of female Wistar albino rats (10/group) were orally dosed with 0 or 800 mg/kg bw of an ethanolic *Nelumbo nucifera* seed extract for 40 d. Statistically significant decreases in ovary, uterus, and vagina weights were observed in treated animals, compared to controls. Estrous cycles were prolonged in treated animals, which was accompanied by a statistically significant increase in the diestrus phase of the estrous cycle in treated animals, compared to controls. Groups of male Wistar rats (10/group) were dosed with an ethanolic *Nelumbo nucifera* seed extract at 0, 50, 100, or 200 mg/kg bw/d, via gavage, for 60 d.[62] Decreases in the testes, epididymis, seminal vesicle, and ventral prostate weights of treated animals were observed in a dose-dependent manner. A statistically significant decrease in sperm motility was observed in all treated groups. Dose-dependent and statistically significant decreases in testicular and caudal epididymal sperm and serum testosterone levels were observed, compared to controls.

GENOTOXICITY STUDIES

In Vitro

Nelumbo Nucifera Flower Extract

An Ames test was performed in accord with the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 471 to evaluate the mutagenic potential of a trade name mixture of Nelumbo Nucifera Flower Extract (0.5 – 1%, extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract).[11] *Salmonella typhimurium* strains TA1535, TA1537, TA8, TA-100, and TA102 were tested in the presence and absence of metabolic activation. The test substance was not mutagenic.

Methanolic extracts of *Nelumbo nucifera* plumule and blossom were not mutagenic when tested at 0.5, 1, or 2.5 mg/plate, with or without metabolic activation, using *Salmonella typhimurium* TA98 and TA100 strains in an Ames test.[63] In another Ames test, dichloromethane, methanol, and aqueous *Nelumbo nucifera* flower extracts were not mutagenic towards *S. typhimurium* strains TA98 and TA100 without metabolic activation.[64] No further details were provided.

Nelumbo Nucifera Germ Extract

The mutagenicity of trade name mixtures containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (composed of tannins and flavonoids and of tannins and saccharides) was determined by reverse mutation testing using *S. typhimurium* strains TA100, TA1535, TA98, and TA 1537 and *Escherichia coli* WP2*uvrA*.[16] The concentration of each test solution was 5000 µg/plate. Negative results were observed for both trade name mixtures.

CARCINOGENICITY STUDIES

No relevant carcinogenicity studies on the *Nelumbo nucifera*-derived ingredients evaluated in this report were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

Several *Nelumbo nucifera*-derived ingredients exhibit anti-carcinogenic properties. Aqueous and methanolic *Nelumbo nucifera* leaf extracts have been shown to inhibit angiogenesis in normal and breast cancer cells.[65-67] (Human breast cancer MDA-MB-231 cells were treated with a *Nelumbo nucifera* leaf extract at 0.5, 1, 2, 3, 4, and 5 mg/ml concentrations.) A methanolic *Nelumbo nucifera* floral receptacle extract and an ethanolic *Nelumbo nucifera* petal extract were shown to have cytotoxic effects against breast and cervical cancer cell lines (PC_{50} of 10.5 µg/ml), respectively.[67,68] An aqueous *Nelumbo nucifera* rhizome extract exhibited antiproliferative effects in both epidermoid and breast cancer cells[69] and an ethanolic *Nelumbo nucifera* stamen extract was shown to induce apoptosis in human colon cancer cells.[70]

OTHER RELEVANT STUDIES

Effects on Pigmentation

The skin lightening effects of aqueous *Nelumbo nucifera* leaf, root, flower, stem, and seed extracts were evaluated, separately, at doses of 10, 50, 100, or 200 µg/ml, in both a tyrosinase inhibition assay and a 4-dihydroxyphenylalanine (DOPA)-oxidase inhibition assay.[9] Arbutin was used as the positive control (at the same concentration as the test substances). Statistically significant tyrosinase inhibition was exhibited by the *Nelumbo nucifera*-derived extracts, compared to that of arbutin. In the DOPA-oxidase assay, the inhibitory effect at the 100 µg/ml concentration was 59% for a *Nelumbo nucifera* leaf extract, 57% for a *Nelumbo nucifera* seed extract, and 50% for a *Nelumbo nucifera* flower extract, compared to the 44% inhibitory effect of arbutin. Based on skin-lightening effects seen in the study, the researchers concluded that inhibition of one of these pathways was sufficient to affect melanin synthesis.

A phosphodiesterase inhibitor, theophylline, was utilized to stimulate melanogenesis in murine B16 melanoma 4A5 cells, which were subsequently treated with methanolic *Nelumbo nucifera* flower bud, stamen, seed, and leaf extracts (at up to 100 µg/ml).[38] The methanolic *Nelumbo nucifera* flower bud extract significantly inhibited melanogenesis with a half-maximal inhibitory concentration (IC_{50}) value of 20 µg/ml. The *Nelumbo nucifera* leaf extract exhibited a moderate effect, while the inhibitory activity of the stamen and seed extracts were weak. *Nelumbo nucifera* flower bud, stamen, and seeds showed no cytotoxic effects and the leaf extract showed weak cytotoxicity at a high concentration of 100 µg/ml.

Nelumbo Nucifera Callus Culture Extract

The whitening effect of a *Nelumbo nucifera*-derived callus extract was evaluated in cultured B16F1 melanoma cells using a melanin synthesis inhibition test.[14] Cells were treated with 0.025, 0.050, or 0.1% of a *Nelumbo nucifera*-derived callus extract. α-melanin stimulating hormone (10 nM) was used as the negative control and kojic acid was used as the positive control; negative and positive controls produced expected results. A dose-dependent, inhibitory effect on melanin synthesis of cells treated with the *Nelumbo nucifera*-derived callus extract was observed at approximately 26.65% at the low dose, 36.02% at the medium dose, and 78.89% at the high dose, on average. Kojic acid used as a positive control showed a suppression rate of 54.52% at 200 ppm.

Nelumbo Nucifera Leaf Extract

The potential for an aqueous *Nelumbo nucifera* leaf extract to inhibit melanogenesis was evaluated in B16F1 melanoma cells obtained from mice.[19] Cells were treated with 10 µM α-melanocyte stimulating hormone (α-MSH) and either aqueous *Nelumbo nucifera* leaf extract (0.1, 0.2, 0.3, 0.4, or 0.5 mg/ml) or gallic acid, a constituent of the leaf extract, (60, 70, 80, 90, 100 µM) for 24, 48, or 72 h. Melanin content was measured by normalizing total melanin values with protein content (µg of melanin/mg of protein) and levels of proteins associated with melanogenesis were measured using an immunoblotting assay. Overall, the *Nelumbo nucifera* leaf extract exhibited better efficacy in inhibiting melanogenesis stimulated by α-MSH compared to gallic acid, which the authors surmised was due to the synergistic effect of the extract. Furthermore, the *Nelumbo nucifera* leaf extract significantly inhibited the expression of tyrosinase, microphthalmia-associated transcription factor (MITF) and tyrosinase-related protein-1 (TRP-1) in a dose-dependent manner, indicating that the *Nelumbo nucifera* leaf extract reduced melanin content via downregulation of MITF and tyrosinase family proteins. Congruently, treatment with *Nelumbo nucifera* leaf extract also exhibited inhibition of cyclic adenosine monophosphate (cAMP) response element-binding (CREB) protein, and protein kinase A (pKA) phosphorylation under both basal and stimulated conditions.

The effects of an aqueous *Nelumbo nucifera* leaf extract upon melanogenesis and epidermal hyperplasia induced by ultraviolet B (UVB) radiation were evaluated in guinea pigs.[19] Four female Dunkin-Hartley guinea pigs had a 1.5 cm^2 area of the back exposed to 280 – 305 nm UVB radiation 3 times/wk for 2 wk, for a total UVB dose of 500 mJ/cm^2 per exposure. The animals received a topical gel application of 1 or 2 % *Nelumbo nucifera* leaf extract mixed with polyethylene glycol (PEG-40) to irradiated skin the following day. Skin biopsies were collected, stained, and measured for melanin content. Results revealed that treatment with the *Nelumbo nucifera* leaf extract reversed UVB-induced epidermal hyperplasia and melanin content in the epidermis of irradiated guinea pigs. Western blot analysis demonstrated that the *Nelumbo nucifera* leaf extract downregulated the expression of proteins involved in melanogenesis under UVB-stimulated conditions (tyrosinase, TRP-1, β-actin, extracellular signal-regulated kinase (ERK), phospho-ERK) and modulated cAMP mediated PKA signaling and ERK activity, confirming mechanistic involvement in the depigmentation of guinea pig skin under study conditions.

Photoprotective Effects

Nelumbo Nucifera Leaf Extract

The protective effects of an ethanolic *Nelumbo nucifera* leaf extract against UVB radiation were evaluated using mitochondria isolated from the livers of female Sprague-Dawley rats.[71] The reaction models comprised 0.5 ml mitochondrial protein, with either 10, 100, or 1000 µg/ml *Nelumbo nucifera* leaf extract in 70% v/v ethanol added as the test material. Butylated hydroxytoluene and gallic acid served as positive controls, while 70% v/v ethanol solution without test extracts served as a model group; the blank control group was identical to the model group, without irradiation. Each mixture was irradiated for 4 h with a 20 W UVB lamp; the irradiation dose was measured to be 0.88 J/cm^2. In a thiobarbituric acid assay, the overall absorbance at 532 nm was lower in groups treated with the leaf extract and positive controls, compared to the model group. However, only the 100 µg/ml and 1000 µg/ml *Nelumbo nucifera* leaf extract groups showed a statistically significant inhibition capacity against UVB-induced oxidation.

The protective effects of the same *Nelumbo* nucifera leaf extract against UVB-induced phototoxicity were evaluated in vivo using male BALB/C mice.[71] Groups of 6 mice were divided into non-irradiated controls, a radiation-only model group, 3 groups receiving 0.1% sodium carboxymethyl cellulose solvent with 50, 250, or 5000 mg/kg bw ethanolic *Nelumbo nucifera* leaf extract, or positive control group receiving 250 mg/kg bw gallic acid. The animals were irradiated for 1 h daily for the first 5 d (irradiation dose = 0.22 J/cm^2) and then maintained for 2 h up till the tenth day (irradiation dose = 0.44 J/cm^2). All mice were treated with a topical dose of corresponding solvent on the dorsal surface 30 min prior to irradiation. Effects resulting from UVB irradiation were significantly reversed with treatment with the *Nelumbo nucifera* leaf extracts and gallic acid. The group treated with 50 mg/kg leaf extract showed significantly reduced malondialdehyde levels and superoxide dismutase activity compared to the UVB-model group. Additionally, glutathione peroxidase, catalase, and hydroxyproline levels were significantly higher in the groups treated with the 250 and 500 mg/kg bw *Nelumbo nucifera* leaf extracts than that of the UVB model group.

Nelumbo Nucifera Seed Extract

The potential for the oral administration of an aqueous *Nelumbo nucifera* lotus seed tea to protect against the effects of UVB-irradiation was examined in hairless male SKH-1 mice.[23] The lotus seed tea was made by roasting *Nelumbo nucifera* seeds until browned and extracting with hot water. Animals were randomly divided into 2 groups (n = 10) which either received the lotus seed tea or water (controls) as drinking fluid for 6 mo. After the 6 mo-treatment period, each group was further divided into 2 groups each (n = 5), 2 of which received UVB-irradiation and 2 of which were not irradiated (water group, water-UVB group, lotus seed tea group, and lotus seed tea-UVB group). The backs of the mice were irradiated with UVB at a dose of 1.8 mW/s and 50 mJ/cm^2 3 times per wk; the dose of irradiation was increased by 20% every wk for 15 wk. The moisture content of skin was measured using a Corneometer. A 1 cm^2 cross-section was obtained from the center of the dorsal side, stained with hematoxylin-eosin dye, and observed for histopathological changes in the skin; 5 random locations on a skin tissue were selected and average values were used. The skin homogenate samples were treated with either hydrochloric acid (control) or 2,4-dinitrophenylhydrazine (DNPH) and the respective absorbance of each sample was measured at 370 nm. The difference in the spectrum of the DNPH-treated sample and the hydrochloride control was determined and the protein carbonyl content of tissue samples was calculated using the molar absorption coefficient. There were no significant differences in the final weight, food intake, water intake, body weight gain, or food efficiency of mice in either group treated for 6 mo, or across the treatment groups after the 3 mo-irradiation period. There were no significant differences in the moisture content of animal skin prior to radiation exposure. Moisture content measured in the skin 2 mo after UVB irradiation was 32.60 ± 6.95% in mice treated with the *Nelumbo nucifera* lotus seed tea, compared to 22.67 ± 1.25% for the water controls ($p < 0.05$). Tissues of mice that were irradiated had an abnormally enlarged epidermis and horny layers, but the tissue samples from mice treated with *Nelumbo nucifera* lotus seed tea had a relatively thinner horny layer, suggesting a protective effect. Protein carbonyl values of skin tissues in the water-UVB group were higher than those of the *Nelumbo nucifera* lotus seed tea, with no significance.

Inhibitory Effect on Atopic Dermatitis Formation and Inflammation

Nelumbo Nucifera Leaf Extract

The effect of an orally administered aqueous *Nelumbo nucifera* leaf extract upon the severity of 2,4-dinitrochloro-benzene (DNCB)-induced atopic dermatitis and inflammation was evaluated in NC/Nga mice.[72] A 200 µl-application of 1% DNCB (w/w) in olive oil/acetone was made to shaved dorsal skin of the mice (7/group) to evoke sensitization. Four days later, mice received 3 challenge applications of 200 µl 0.4% DNCB (w/v) per week over 4 wk. The aqueous *Nelumbo nucifera* leaf extract (5, 25, or 50 mg/mouse/d) was fed to the mice, via gavage, from the day of sensitization until 4 wk. Controls received distilled water and were also sensitized with DNCB. Dermatitis symptoms on the face, ears, and dorsal part of the body (erythema/hemorrhage, pruritis and dry skin, edema, excoriation/erosion, and lichenification) were scored blindly on a scale of 1-3 every week for 4 wk; the sum of these individual scores was considered the skin severity score (maximum score: 15). Skin severity scores across groups were similar up to 14 d from the day of sensitization; however, from day 14 to day 28 after sensitization, there were significantly lower dermatitis scores in treated animals, compared to controls. The epidermal thickness of dorsal skin of mice treated with the 50 mg/mouse/d *Nelumbo nucifera* leaf extract was 61.3 ± 21 µm compared to 88.7 ± 15 µm in controls. Thus, the effects seen in controls, including hyperkeratosis,

parakeratosis, acanthosis with varying degrees of spongiosis, exocytosis of mononuclear cells in the epidermis, and infiltration of inflammatory cells into the upper dermis, were suppressed in treated animals. The suppression of DNCB-induced elevated immunoglobulin E levels was statistically significant in animals treated with 25 and 50 mg/mouse/d *Nelumbo nucifera* leaf extract compared to controls.

Immunomodulatory Effects

Nelumbo Nucifera Seed Extract

The potential immunomodulatory effects of an ethanolic *Nelumbo nucifera* seed extract and an ethanolic *Nelumbo nucifera* rhizome extract were evaluated in Swiss albino mice.[73] Groups of mice (6/sex/group) were orally dosed with either saline (negative control), 100 or 300 mg/kg of the seed or rhizome extract, or dexamethasone (positive control). Blood was collected 14 d after dosing and analyzed for immunologic markers. A statistically significant, dose-dependent increase in leukocyte count was seen in the serum of mice treated with both extracts, which was more significant for the *Nelumbo nucifera* seed extract groups. Neutrophil and basophil counts were significantly decreased for cells treated with both extracts, but monocyte counts were not significantly changed compared to controls. A statistically significant increase in the percentage of neutrophil adhesion was observed in cells from mice treated with *Nelumbo nucifera* rhizome extract; no significant changes in neutrophil adhesion were observed in cells from mice treated with *Nelumbo nucifera* seed extract, compared to controls.

Anti-Inflammatory Effects

Nelumbo Nucifera Flower Extract

The anti-inflammatory effects of *Nelumbo nucifera* lotus petals extracted (separately) with ethyl acetate and ethyl alcohol were examined in human monocyte-derived macrophages stimulated with lipopolysaccharide.[36] Cells were treated with 500 µl of 5% (low) and 10% (high) concentrations of *Nelumbo nucifera* lotus petal extracts for 6 h, either prior to or after stimulation of an inflammatory response with 10 ng/ml lipopolysaccharide for 6 h. Aspirin and dexamethasone were utilized as positive controls. Results from an enzyme-linked immunosorbent assay (ELISA) showed that pre-treating and post-treating human macrophages with both *Nelumbo nucifera* lotus petal extracts significantly decreased tumor necrosis factor-alpha (TNF-α) secretion; by comparison, ethyl acetate and ethyl alcohol *Nelumbo nucifera* lotus petal extracts were more effective than the positive controls in suppressing TNF-α secretion when applied after exposure to lipopolysaccharide.

Cytotoxicity

Nelumbo Nucifera Flower Extract

An in vitro 3T3neutral red uptake (NRU) cytotoxicity assay was performed in accord with OECD TG 129 to estimate the basal cytotoxicity of 10 – 100 mg/ml Nelumbo Nucifera Flower Extract (0.5 – 1%, extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract) in Balb/c 3T3 fibroblasts.[11] Dose-dependent cytotoxicity was observed; the IC_{50} was 14.71 mg/ml and the test substance was classified as a non-toxic substance.

Anti-Aging in Fibroblasts

Nelumbo Nucifera Germ Extract

The effect of *Nelumbo nucifera* lotus germ extract (50 µg/ml) upon mitochondrial function was evaluated in human diploid fibroblast cell lines, NB1RGB and IMR90.[17] Exposure to the *Nelumbo nucifera* lotus germ extract increased mitochondrial transmembrane potential in aging IMR90 cells. Additionally, treatment with the *Nelumbo nucifera* lotus germ extract upregulated death-associated protein kinase 1 (DAPK1), by stimulating the acetylation of histones and inducing autophagy through activation of the DAPK1-Beclin1 signaling pathway, compared to dimethyl sulfoxide (DMSO) controls. Furthermore, treatment of young and aging NB1RGB cells with *Nelumbo nucifera* lotus germ extract for 72 h stimulated collagen production and cell proliferation in a 3-dimensional gel culture. The researchers posited that *Nelumbo nucifera* lotus germ extract rejuvenates aging fibroblasts via the DAPK1-Beclin1 pathway, clearing abnormal proteins and agglutinates that are characteristic of aging via autophagy.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details on the in dermal irritation and sensitization studies summarized below can be found in Table 13.

Neither a trade name mixture containing 0.5 – 1% Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract)[11] nor a trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides) indicated potential for dermal irritation in in vitro studies, and a trade name mixture containing 1 - 5% Nelumbo Nucifera Flower Extract (extracted in isostearyl isostearate) was not an irritating to rabbit skin.[16] In clinical patch tests, no irritation was observed with trade name mixtures containing 1 - 5% Nelumbo Nucifera Flower Extract (extracted in isostearyl isostearate; tested at 25% in mineral oil);[10] 0.5 – 1%, Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract; tested at 15%);[11] 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids; tested at 50%);[16] or 0.5 - 1.2% Nelumbo Nucifera Leaf Extract (tested at 25%).[18] Use tests (28-d) with foundations containing 0.2% Nelumbo Nucifera Flower Water[75] or 0.2%

Nelumbo Nucifera Root Water[77] reported very good tolerance and no comedogenicity. Irritation was not observed in studies that examined the irritation potential of extracts of several plant parts.[9]

A direct peptide reactivity assay (DPRA) and a KeratinoSens assay of a trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides) were both negative, and a trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids) was not a sensitizer in guinea pigs (induction with 5 and 100%; challenge at 10 and 100%).[16] No irritation or sensitization was reported in HRIPTs with trade name mixtures containing 0.5 – 1% Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract; tested at 15%),[11] 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tested at up to 30%),[16] or 0.5 - 1.2% Nelumbo Nucifera Leaf Extract (tested at 25%);[18] with an emulsion containing 0.0001% Nelumbo Nucifera Germ Extract (as supplied);[76] or with foundations (as supplied) containing 0.00001% Nelumbo Nucifera Flower Extract,[74] 0.2% Nelumbo Nucifera Flower Water,[75] or 0.2% Nelumbo Nucifera Root Water.[77]

A trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract did not indicate phototoxic potential in vitro, and was not phototoxic or a photosensitizer in guinea pigs (tested at up to 30%.)[16] Foundations (as supplied) containing 0.2% Nelumbo Nucifera Flower Water[75] or Nelumbo Nucifera Root Water[77] were not phototoxic or photosensitizing in clinical studies with 28 or 26 subjects, respectively.

OCULAR IRRITATION STUDIES

Details on the ocular irritation and sensitization studies summarized below can be found in Table 14.

In vitro ocular irritation studies were performed with trade name mixtures containing Nelumbo Nucifera Flower Extract at 1 – 5% extracted in isostearyl isostearate[10] or at 0.5 – 1% extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract,[11] a trade name mixture containing a maximum of 0.5 - 1.2% Nelumbo Nucifera Leaf Extract,[18] and with a foundation containing ~0.2% Nelumbo Nucifera Flower Water.[75] Results were primarily negative in all studies.

SUMMARY

This assessment reviews the safety of 14 *Nelumbo* nucifera-derived ingredients; 1 ingredient, Nelumbo Nucifera Flower Oil, is not included in the *Dictionary* but is listed in use in the VCRP and RLD, si it is included in this report, According to the *Dictionary*, the 13 *Nelumbo nucifera*-derived ingredients named in the *Dictionary* and reviewed in this safety assessment are mostly reported to function as skin-conditioning agents or antioxidants.

The main chemical classes of compounds present in the *Nelumbo nucifera* plant are proteins, amino acids, and steroids (present mostly in the seeds), carbohydrates (present mostly in the leaves and seeds), alkaloids and flavonoids (present mostly in the flowers, leaves, and seeds), and terpenoids (present mostly in the leaves). Alkaloids are the prominent bioactive chemical class of constituents.

Nelumbo Nucifera Flower Extract had the highest number of reported uses, with 544 uses reported in the RLD in 2024 and 200 uses reported in the VCRP in 2023. According to the Council survey, Nelumbo Nucifera Root Extract had the maximum reported concentration of use, at up to 0.2% in foundations.

A trade name mixture containing 0.5 -1.5 w/v% Nelumbo Nucifera Germ Extract (composed of tannins and flavonoids) had a dermal LD_{50} > 2 g/kg in mice. No signs of toxicity or mortality were observed in mice that received a single oral dose of an herbal mixture capsule (up to 99.9 g/kg bw) containing 33% *Nelumbo nucifera* Gaertn. The acute oral LD_{50} values were > 2 g/kg, in rats, for several ethanolic *Nelumbo nucifera* leaf, flower, and root, *Nelumbo nucifera* leaf and root, and *Nelumbo nucifera* flower extracts. No mortality or toxicity was observed in rats administered a single oral dose of an hydroalcoholic *Nelumbo nucifera* flower extract at 2 g/kg. A hydroalcoholic *Nelumbo nucifera* seed extract, in 0.3% sodium carboxymethylcellulose, had an acute oral LD_{50} of > 1 g/kg in mice. The acute oral LD_{50} values for an ethanolic *Nelumbo nucifera* lotus root extract and a *Nelumbo nucifera* stamen extract-PVP-10 complex were both > 5 g/kg in mice and rats, respectively.

Groups of 10 Wistar rats were orally administered up to 4.32 g/kg/d of an herbal mixture capsule containing 33% *Nelumbo nucifera* Gaertn., dissolved in water, for 4 wk. A statistically significant increase in body weights was observed in 1.44 g/kg/d rats after 2 wk of treatment, compared to controls; no other significant gross or histopathological differences were observed, compared to controls. No significant differences in food or liquid consumption were observed between male SKH-1 hairless mice that received a *Nelumbo nucifera* lotus seed tea as drinking water for 6 mo compared to controls. Groups of 5 Sprague-Dawley rats were orally dosed with up to 2000 mg/kg/d Nelumbinis semen for 13 wk; the NOAEL for both sexes was determined to be 2000 mg/kg/d. Nelumbinis semen was orally administered to Beagle dogs at up to 4000 mg/kg/d a for 28 d; the NOAEL was determined to be 4000 mg/kg/d. The NOAEL for a *Nelumbo nucifera* stamen extract-PVP-10 complex was determined to be > 200 mg/kg/d for both male and female rats in a 90-d oral toxicity study.

Rat sperm was tested with an aqueous *Nelumbo nucifera* petal extract at 0, 0.22, 0.44, 0.88, 1.76, or 3.52 mg/ml in an in vitro reproductive toxicity study. A statistically significant increase in sperm viability was observed in the 0.22 – 1.76 mg/ml groups; no significant differences were observed between the 3.52 mg/ml group and controls. Male Wistar albino rats (10/group) were orally administered 7.5 mg/kg bw of a petroleum ether *Nelumbo nucifera* seed extract every other day for

15 d. Statistically significant decreases in the weight of the testis, epididymis, adrenal glands, body growth rate, sperm count and motility, 3β-HSD and G-6-PSD levels in treated animals, compared to controls have been observed. In a related study, female Wistar rats were orally administered up to 7.5 mg/kg bw of a petroleum ether *Nelumbo nucifera* seed extract every other day for 15 d. Statistically significant decreases in body, ovary, and uterus weights, 3β-HSD and G-6-PSD levels, as well as inhibition of the vaginal opening and first estrus were observed in treated animals compared to controls. In another study, female Wistar albino rats that were orally dosed with 800 mg/kg bw of an ethanolic *Nelumbo nucifera* seed extract for 40 d; statistically significant decreases in ovary, uterus, and vagina weights were observed, compared to controls. Estrous cycles were also prolonged in treated animals, which was accompanied by a statistically significant increase in the diestrous phase of the estrous cycle in treated animals, compared to controls. Dose-dependent and statistically significant decreases in testicular and caudal epididymal sperm and serum testosterone levels were observed in male Wistar rats dosed with up to 200 mg/kg bw/d of an ethanolic *Nelumbo* nucifera seed extract for via gavage for 60 d, compared to controls.

Nelumbo Nucifera Flower Extract (0.5 – 1%, extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract) was not mutagenic in an Ames test. Methanolic extracts of *Nelumbo nucifera* plumule and blossom were not mutagenic at up to 2.5 mg/plate, with or without metabolic activation in an Ames test using *S. typhimurium* TA98 and TA100 strains. In another Ames test, several *Nelumbo nucifera* flower extracts were not mutagenic towards *S. typhimurium* TA98 and TA100, without metabolic activation. Trade name mixtures containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (composed of tannins and flavonoids and of tannins and saccharides) were not mutagenic in an Ames test. Additionally, aqueous and methanolic *Nelumbo nucifera* leaf extracts, a *Nelumbo nucifera* flower receptacle extract, a *Nelumbo nucifera* petal extract, a *Nelumbo nucifera* rhizome extract, and a *Nelumbo nucifera* stamen extract have been shown to exhibit anti-carcinogenic effects in various cancer cell lines.

The skin lightening effects of aqueous *Nelumbo nucifera* leaf, root, flower, stem, and seed extracts were evaluated at up to 200 µg/ml in a tyrosinase inhibition and DOPA-oxidase assay. DOPA-oxidase was inhibited by 59% after treatment with a *Nelumbo nucifera* leaf extract, 57% was inhibited after treatment with a *Nelumbo nucifera* seed extract, and 50% was inhibited after treatment with a *Nelumbo nucifera* flower extract, in comparison to the 44% inhibitory effect of the positive control (arbutin). In a melanogenesis inhibition assay, a methanolic *Nelumbo nucifera* flower bud extract significantly inhibited melanogenesis in murine B16 melanoma 4A5 cells, with an IC_{50} value of 20 µg/ml; methanolic *Nelumbo* nucifera leaf extract and stamen extract exhibited a moderate and a weak effect, respectively. Dose-dependent increases in inhibition were seen in cultured B16F1 melanoma cells treated with up to 0.1% *Nelumbo nucifera* callus culture extract in a melanin synthesis inhibition test. In another melanogenesis inhibition test, B16F1 melanoma cells were treated with up to 0.5 mg/ml of a *Nelumbo nucifera* leaf extract; overall, the *Nelumbo nucifera* leaf extract significantly inhibited the expression of tyrosinase, MITF, and TRP-1 in a dose-dependent manner and also inhibited cAMP protein and pKA phosphorylation under both basal and stimulated conditions. In a study evaluating the effect of an aqueous *Nelumbo nucifera* leaf extract upon melanogenesis and epidermal hyperplasia induced by UVB exposure, topical treatment with 1 or 2% *Nelumbo nucifera* leaf extract reversed UVB-induced epidermal hyperplasia and melanin content in the epidermis of irradiated guinea pigs.

The effect of an orally administered aqueous *Nelumbo nucifera* leaf extract (up to 50 mg/mouse/d) upon the severity of DNCB-induced atopic dermatitis and inflammation was evaluated in NC/Nga mice over 4 wk. The epidermal thickness of dorsal skin of mice treated with the 50 mg/mouse/d *Nelumbo nucifera* leaf extract was 61 ± 21 µm compared to 89 ± 15 µm in controls. The suppression of DNCB-induced elevated immunoglobulin E levels was statistically significant in animals treated with 25 mg and 50 mg/mice/d *Nelumbo nucifera* leaf extract compared to controls.

The potential immunomodulatory effects of an orally administered ethanolic *Nelumbo nucifera* seed extract and an *Nelumbo nucifera* rhizome extract (100 or 300 mg/kg) were evaluated in Swiss albino mice. A statistically significant, dose-dependent increase in leukocyte count was seen in the serum of rats treated with both extracts, which was more significant for the *Nelumbo* nucifera seed extract groups. Neutrophil and basophil counts were significantly decreased for cells treated with both extracts, but monocyte counts were not significantly changed compared to controls; neutrophil adhesion was only significant in the cells of mice treated with the *Nelumbo nucifera* rhizome extract.

The protective effects of an ethanolic *Nelumbo nucifera* leaf extract (10, 100, or 1000 µg/ml) against UVB radiation were evaluated using reaction models comprised of mitochondrial protein isolated from the livers of female Sprague-Dawley rats. Significant inhibition against UVB-induced oxidation was observed in the reaction models treated with 100 µg/ml and 1000 µg/ml *Nelumbo nucifera* leaf extract. In an in vivo phototoxicity study, the protective effects of an ethanolic *Nelumbo* nucifera leaf extract (50, 250, or 5000 mg/kg bw) against UVB-induced phototoxicity were evaluated using male BALB/C mice. The group treated with 50 mg/kg leaf extract showed significant protective activity in the contents of malondialdehyde and superoxide dismutase by a reduction of the level of their activity, compared to the UVB-model group. Additionally, glutathione peroxidase, catalase, and hydroxyproline levels were significantly higher in the groups treated with the 250 and 500 mg/kg bw *Nelumbo nucifera* leaf extracts than that of the UVB-model group. In another study, the potential for an aqueous *Nelumbo nucifera* lotus seed tea (administered as drinking fluid for 6 mo) to protect from the effects of UVB-irradiation was examined in hairless male SKH-1 mice. Moisture content measured in the skin 2 mo after UVB irradiation was 32.60 ± 6.95% in mice treated with the *Nelumbo nucifera* lotus seed tea, compared to 22.67 ± 1.25% for the water controls ($p < 0.05$). Tissues of mice that were irradiated had an abnormally enlarged epidermis and horny layers, but the

tissue samples from mice treated with *Nelumbo nucifera* lotus seed tea had a relatively thinner horny layer, suggesting a protective effect.

The anti-inflammatory effects of 6-h exposure to ethyl acetate or ethyl alcohol *Nelumbo nucifera* petal extracts were examined in human monocyte-derived macrophages treated either prior to or after stimulation with lipopolysaccharide. ELISA results showed that pre-treating and post-treating human macrophages with both *Nelumbo nucifera* petal extracts significantly decreased TNF-α secretion, especially when applied after exposure to lipopolysaccharide, when compared to positive controls.

The effect of *Nelumbo nucifera* germ extract upon mitochondrial function was evaluated in human diploid fibroblast cell lines, NB1RGB and IMR90. Treatment with 50 µg/ml of a *Nelumbo nucifera* germ extract increased mitochondrial transmembrane potential, stimulated collagen production and cell proliferation, and upregulated the DAPK1-Beclin1 signaling pathway. The researchers posited that the *Nelumbo nucifera* germ extract rejuvenates aging fibroblasts via activation of the DAPK1-Beclin1 pathway, in which autophagy clears age-related abnormal proteins and agglutinates.

Neither a trade name mixture containing 0.5 – 1% Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract) nor a trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides) indicated potential for dermal irritation in in vitro studies, and a trade name mixture containing 1 - 5% Nelumbo Nucifera Flower Extract (extracted in isostearyl isostearate) was not an irritating to rabbit skin. In clinical patch tests, no irritation was observed with trade name mixtures containing 1 - 5% Nelumbo Nucifera Flower Extract (extracted in isostearyl isostearate; tested at 25% in mineral oil); 0.5 – 1%, Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract; tested at 15%); 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids; tested at 50%); or 0.5 - 1.2% Nelumbo Nucifera Leaf Extract (tested at 25%). Use tests (28-d) with foundations containing 0.2% Nelumbo Nucifera Flower Water or 0.2% Nelumbo Nucifera Root Water reported very good tolerance and no comedogenicity. Irritation was not observed in clinical studies (20 subjects) that examined the irritation potential of extracts of several plant parts.

A DPRA and a KeratinoSens assay of a trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides) were both negative, and a trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids) was not a sensitizer in guinea pigs (induction with 5 and 100%; challenge at 10 and 100%). No irritation or sensitization was reported in HRIPTs with trade name mixtures containing 0.5 – 1% Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract; tested at 15%), 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tested at up to 30%), or 0.5 - 1.2% Nelumbo Nucifera Leaf Extract (tested at 25%); with an emulsion containing 0.0001% Nelumbo Nucifera Germ Extract (as supplied); or with foundations (as supplied) containing 0.00001% Nelumbo Nucifera Flower Extract, 0.2% Nelumbo Nucifera Flower Water, or 0.2% Nelumbo Nucifera Root Water.

A trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract did not indicate phototoxic potential in vitro, and was not phototoxic or a photosensitizer in guinea pigs (tested at up to 30%.) Foundations (as supplied) containing 0.2% Nelumbo Nucifera Flower Water or 0.2% Nelumbo Nucifera Root Water were not phototoxic or photosensitizing in clinical studies with 28 or 26 subjects, respectively.

In vitro ocular irritation studies were performed with trade name mixtures containing Nelumbo Nucifera Flower Extract either at 1 – 5% extracted in isostearyl isostearate or at 0.5 – 1% extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract, a trade name mixture containing a maximum of 0.5 - 1.2% Nelumbo Nucifera Leaf Extract, and with a foundation containing ~0.2% Nelumbo Nucifera Flower Water. Results were negative in all studies.

DRAFT DISCUSSION

This assessment reviews the safety of *Nelumbo nucifera*-derived ingredients as used in cosmetic formulations, in accordance with the product categories and concentrations of use identified in the Use section and Use table. The Panel reviewed the available data and concluded [TBD].

The Panel 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 also discussed the issue of incidental inhalation that could result from exposure to these ingredients; for example, Nelumbo Nucifera Flower Oil is reported to be used in perfumes (concentration of use not reported) and Nelumbo Nucifera Flower Extract is reported to be used at 0.1% in face powders, and could possibly be inhaled. Inhalation toxicity data were not available. However, coupled with the small actual exposure in the breathing zone and the low concentrations at which this ingredient is used (or is expected to be used) in potentially inhaled products, the available information indicates that the 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.

As stated in the Use section, products containing these ingredients may be marketed for use with airbrush delivery systems. While it may be known in some (but not all) instances whether or not there is use in airbrush applications, information regarding the consumer habits and practices data, product particle size data, and/or other relevant particle data (e.g., diameter) related to this use technology are absent, and thus the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions and functions of *Nelumbo nucifera*-derived ingredients[1*]

Ingredient/CAS No.	Definition	Function
Nelumbo Nucifera Callus Culture Extract 85085-51-4 (generic)	Nelumbo Nucifera Callus Culture Extract is the extract of a culture of the callus of *Nelumbo nucifera*.	antifungal agent; antimicrobial agent antioxidant; skin-conditioning agent - humectant
Nelumbo Nucifera Extract 85085-51-4 (generic)	Nelumbo Nucifera Extract is the extract of the whole plant, *Nelumbo nucifera*.	antioxidant; skin-conditioning agent - miscellaneous
Nelumbo Nucifera Flower Extract 85085-51-4 (generic)	Nelumbo Nucifera Flower Extract is the extract of the flower of *Nelumbo nucifera*.	skin-conditioning agent - miscellaneous
Nelumbo Nucifera Flower/Leaf/Stem Juice 85085-51-4 (generic)	Nelumbo Nucifera Flower/Leaf/Stem Juice is the juice expressed from the flowers, leaves, and stems of *Nelumbo nucifera*.	antioxidant
Nelumbo Nucifera Flower Water 85085-51-4 (generic)	Nelumbo Nucifera Flower Water is the aqueous extract of the steam distillate obtained from the flowers of *Nelumbo nucifera*.	antioxidant; cosmetic astringent; fragrance ingredient; skin-conditioning agent-miscellaneous
Nelumbo Nucifera Germ Extract 85085-51-4 (generic)	Nelumbo Nucifera Germ Extract is the extract of the germ of *Nelumbo nucifera*.	antioxidant; skin-conditioning agent - humectants
Nelumbo Nucifera Leaf Extract 85085-51-4 (generic)	Nelumbo Nucifera Leaf Extract is the extract of the leaves of *Nelumbo nucifera*.	skin-conditioning agent - miscellaneous
Nelumbo Nucifera Phytoplacenta Culture Extract 85085-51-4 (generic)	Nelumbo Nucifera Phytoplacenta Culture is the extract of a culture of the phytoplacenta of *Nelumbo nucifera*.	antioxidant; antimicrobial agent; hair-conditioning agent; skin-conditioning agent - humectant
Nelumbo Nucifera Root Extract 85085-51-4 (generic)	Nelumbo Nucifera Root Extract is the extract of the roots of *Nelumbo nucifera*.	skin-conditioning agent – miscellaneous
Nelumbo Nucifera Root Water 85085-51-4 (generic)	Nelumbo Nucifera Root Water is the aqueous solution of the steam distillate obtained from the roots of *Nelumbo nucifera*.	fragrance ingredient
Nelumbo Nucifera Seed Extract 85085-51-4 (generic)	Nelumbo Nucifera Seed Extract is the extract of the seeds of *Nelumbo nucifera*.	antifungal agent; antimicrobial agent; antioxidant; cosmetic astringent; hair conditioning agent; skin protectant; skin-conditioning agent – emollient; skin-conditioning agent - miscellaneous
Nelumbo Nucifera Seed Powder 85085-51-4 (generic)	Nelumbo Nucifera Seed Powder is the powder obtained from the dried, ground seeds of *Nelumbo nucifera*.	abrasives; antioxidants
Nelumbo Nucifera Stamen Extract 85085-51-4 (generic)	Nelumbo Nucifera Stamen Extract is the extract of the stamens of *Nelumbo nucifera*.	antioxidants; skin protectants

*Nelumbo Nucifera Flower Oil is not included in this table because it is not an INCI ingredient.

Table 2. Generic definitions of plant parts as they apply to *Nelumbo nucifera*-derived ingredients[1]

Plant Part	Definition
Callus	An undifferentiated mass of cells; a thickened area of an organ of a plant or scar tissue that covers a wound in a plant
Callus culture	An undifferentiated mass of cells produced through tissue culture
Flower	The reproductive shoot in flowering plants, usually with sepals, petals, stamens and pistil(s)
Germ	The embryo in a seed; the part of a seed that can develop into a new plant
Juice	The liquid contained in the vegetative parts or fruits of a plant
Leaf	Flattened photosynthetic organs that are attached to stems
Phytoplacenta	Novel word for placentas from plants, used in INCI Committee to indicate a plant-sourced placenta as opposed to animal-sourced
Root	Organ of a plant that absorbs and transports water and nutrients, lacks leaves and nodes, and is usually underground
Seed	A propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm, or seed coat
Stamen	The male reproductive organ in flowers, usually formed by a filament and anther (part of stamen that produces and contains pollen, and typically originates at the stalk/stem)
Stem	A slender or elongated structure that supports a plant, fungus, a plant part, or a plant organ

INCI – International Nomenclature Cosmetic Ingredient

Table 3. Chemical properties

Property	Value	Reference
Nelumbo Nucifera Flower Extract		
Physical Form	liquid	9
Color	dark, yellowish	9
pH	4 - 7	9
Specific Gravity	0.98 – 1.04	9
Nelumbo Nucifera Flower Extract (1 - 5%) extracted in isostearyl isostearate (95 – 99%)		
Physical Form	transparent liquid	10
Color	pale yellow-yellow	10
Density (g/ml; 20°C)	0.84 - 0.88	10
Solubility	soluble in oils	10
Nelumbo Nucifera Flower Extract (0.5 – 1%) extracted in propanediol (70 -90%) and glycerin (10 – 30%) with Nymphaea Caerulea Flower Extract		
Physical Form	transparent, slightly turbid liquid	11
Color	brown – dark brown	11
Nelumbo Nucifera Seed Powder		
Physical Form	fine ground flour	12
pH	7.43	12

Table 4. Main constituents in *Nelumbo nucifera*, organized by chemical class and presence in plant parts[27-31,41,43,47,68,78-82]

Constituent	Embryo	Flower	Leaf	Seed	Stamen
ALKALOIDS – *Aporphine alkaloids*					
anonaine			♦♦	♦♦	
anonaine-*N*-acetyl		♦			
asimilobine		♦♦	♦♦	♦♦	
caaverine			♦♦	♦♦	
cepharadione			♦		
dehydroanonaine			♦		
dehydroaporphine			♦		
dehydronuciferine			♦		
dehydroroemerine			♦		
2-hydroxy-1-methoxyaporphine			♦		
7-hydroxydehydronuciferine			♦		
glaziovine				♦	
lirindine			♦♦	♦♦	
liriodenine			♦		
lysicamine			♦		
methyl asimilobine			♦♦	♦♦	
nelumnucine			♦♦	♦♦	
N-methylasimilobine		♦♦	♦♦		
N-methylasimilobine-*N*-oxide			♦♦	♦♦	
nornuciferine		♦			
N-nornuciferine			♦♦	♦♦	
O-nornuciferine		♦♦	♦♦	♦♦	
nuciferine	♦♦	♦♦	♦♦	♦♦	
nuciferine-*N*-acetyl		♦			
nuciferine-*N*-methanol		♦			
nuciferine-*N*-oxide			♦♦	♦♦	
pronuciferine	♦♦	♦♦	♦♦	♦♦	
(6*R*, 6*ar*) roemerine-N_{β}-oxide			♦		
roemerine		♦♦	♦♦	♦♦	
roemerine-*N*-oxide			♦♦	♦♦	

Table 4. Main constituents in *Nelumbo nucifera*, organized by chemical class and presence in plant parts[27-31,41,43,47,68,78-82]

Constituent	Embryo	Flower	Leaf	Seed	Stamen
ALKALOIDS – *Benzylisoquinoline alkaloids*					
Constituent	**Embryo**	**Flower**	**Leaf**	**Seed**	**Stamen**
Anonaine					♦
Dehydroanonaine					♦
argemexerine			♦♦	♦♦	
armepavine		♦♦	♦♦	♦♦	♦
bromo methyl armepavine			♦♦	♦♦	
(+)-1(*R*)- coclaurine			♦		
coclaurine		♦♦	♦♦	♦♦	
demethylcoclaurine	♦				
6-demethyl-4-methyl-*N*-methylcoclaurine				♦	
isococlaurine		♦♦	♦♦		
(+)-juziphine		♦			
lotusine	♦♦	♦♦			
methoxymethyl lisoquinoline			♦♦	♦♦	
4'-methyl coclaurine			♦♦	♦♦	
methylhigenamine				♦	
methyl lotusine			♦		
4'-*N*-methylcoclaurine			♦♦	♦♦	
N-methylcoclaurine		♦♦	♦♦	♦♦	♦
N-methylisococlaurine		♦♦	♦♦		♦
Nornuciferine			♦		♦
norarmepavine		♦			
N-norarmepavine			♦		♦
nor-*O*-methylarmepavine				♦	
4'-*O*-methylarmepavine			♦		
norcoclaurine			♦♦	♦♦	
norcoclaurine-6-*O*-glucoside				♦	
(-)-1(*S*)-norcoclaurine			♦		
norjuziphine		♦			
Rosmerine			♦	♦	♦
ALKALOIDS – *Bisbenzylisoquinoline alkaloids*					
Constituent	**Embryo**	**Flower**	**Leaf**	**Seed**	**Stamen**
dauricine		♦♦		♦♦	
6-hydroxynorisoliensinine	♦♦	♦♦			
isoliensinine	♦♦	♦♦	♦♦	♦♦	♦
liensinine	♦♦	♦♦	♦♦	♦♦	♦
methyl neferine	♦				
neferine	♦♦	♦♦	♦♦	♦	
nelumboferine	♦♦		♦♦		
nelumborine		♦			
N-norisoliensinine	♦♦	♦♦			
FLAVONOIDS – *and Flavonoid glycosides*					
Constituent	**Embryo**	**Flower**	**Leaf**	**Seed**	**Stamen**
(-)-catechin			♦		
dihydrophaseic acid				♦	
dihydrophaseic acid 3'-*O*-*β*-D-glucopyranoside				♦	
hyperin	♦♦		♦♦		
isoquecetrin			♦		♦
isoschaftoside			♦		
kaempferol		♦♦		♦♦	♦
kaempferol 3-*O*-*β*-D-galactopyranoside					♦
kaempferol 3-*O*-*β*-D -glucopyranoside					♦
kaempferol 3 *O*-*β*-D-glucuronopyranoside					♦
kaempferol 3-*O*-*β*-D-glucuronopyranosyl methylester					♦
kaempferol 3-*O*-*α*-L -rhamnopyranosyl-(1→6)-β-D-glucopyranoside					♦
Luteolin		♦			
Luteolin glucoside		♦			♦

Table 4. Main constituents in *Nelumbo nucifera*, organized by chemical class and presence in plant parts[27-31,41,43,47,68,78-82]

Constituent	Embryo	Flower	Leaf	Seed	Stamen
myricetin 3',5'-dimethylether 3-*O*-*β*-D -glucopyranoside					♦
quercetin			♦		♦
quercetin 3-*O*-*β*-D-glucuronide			♦		
quercetin 3-*O*-*β*-D-xylopyranosyl-(1→2)-β-d-			♦		
rutin	♦♦		♦♦		
Megastigmanes, terpenoids & glucosides and other compounds					
Constituent	**Embryo**	**Flower**	**Leaf**	**Seed**	**Stamen**
annuionone D			♦		
boscialin			♦♦	♦♦	
betulinic acid				♦	
byzantionoside A			♦		
chrysoeriol 7-*O*-glucopyranoside			♦		
(+)-dehydrovomifoliol			♦		
dihydrophaseic acid				♦	
(*E*)-3-hydroxymegastigm-7-en-9-one			♦		
elephantorrhizol			♦		
epiloliolide			♦♦	♦♦	
epitaxifolin			♦		
5,6-epoxy-3-hydroxy-7-megastigmen-9-one			♦		
galactopyranoside			♦		
grasshopper ketone			♦		
icariside B_2			♦		
isohydnocarpin			♦		
lanosterol				♦	
luteolin				♦	
nelumnnucifoside A			♦♦	♦♦	
nelumnnucifoside B			♦♦	♦♦	
3-*O*-*β*-dxylopyranosyl-(1-2)-*β*-D-galactopyranoside			♦		
3-*O*-*β*-D-glucuronide			♦		
3-oxo-retro-α-ionol I taxifolin			♦		
5,7,3'5'-tetrahydroxyflavanone			♦		
vomifoliol			♦♦	♦♦	

♦ - present in single plant part; ♦♦ - present in multiple plant parts

Table 5. Comparison of standard phenolic acid and lactone compounds found in a HPLC-DAD analysis of two *Nelumbo nucifera* lotus petal extracts[36]

Compound	Ethyl acetate lotus petal extract (µg/ml)	Ethyl alcohol lotus petal extract (µg/ml)
chlorogenic acid	1.45 ± 0.120	3.10 ± 1.070
coumarin	1.72 ± 0.330	4.61 ± 0.590
ferulic acid	20.62 ± 1.560	51.27 ± 1.190
kaempferol	92.17 ± 0.850	31.84 ± 1.810
quercetin	43.34 ± 0.280	25.95 ± 0.730
rutin	2.42 ± 0.020	5.61 ± 3.150

HPLC-DAD - high-performance liquid chromatography with diode array detector

Table 6. Phenolic, flavonoid, and anthocyanin contents in parts of a *Nelumbo nucifera* plant (mg/100 g DW)[39]

	Plant parts					
	flower stalk	**leaf stalk**	**old leaf**	**petal**	**seed embryo**	**stamen**
Phenolic acids						
ferulic acid	ND	ND	ND	ND	24.71 ± 2.03	ND
gallic acid	ND	163.09 ± 8.58	49.38 ± 4.83	277.84 ± 6.36	ND	ND
p-coumaric acid	ND	ND	ND	ND	105.34 ± 2.93	10.78 ± 0.38
Flavonoids						
cyanidin	12.02 ± 0.09	7.15 ± 0.74	184.82 ± 11.38	349.98 ± 24.28	1901.52 ± 14.15	115.79 ± 10.21
delphinidin	20.70 ± 0.24	6.15 ± 1.05	39.46 ± 2.42	1837.27 ± 52.67	691.58 ± 9.84	211.63 ± 17.21
isorhamnetin	3.51 ± 0.28	6.80 ± 0.35	2.67 ± 0.09	237.85 ± 13.86	11.56 ± 0.85	192.09 ± 15.70
kaempferol	6.40 ± 0.64	ND	3.87 ± 0.31	197.83 ± 19.81	4.92 ± 0.41	160.71 ± 13.66
luteolin	4.89 ± 0.35	12.43 ± 0.77	ND	ND	37.50 ± 1.87	ND
myricetin	8.89 ± 0.83	ND	ND	8.55 ± 0.29	ND	7.63 ± 0.35
naringenin	2213.41 ± 11.35	1918.10 ± 37.81	1064.17 ± 75.38	2226.9 ± 13.66	2241.51 ± 18.41	2185.84 ± 24.21
quercetin	59.91 ± 5.64	35.95 ± 1.94	458.56 ± 33.45	196.34 ± 19.03	81.79 ± 3.57	43.94 ± 2.08
Total phenolic contents (mg GAE/g DW)	4.33 ± 0.11	2.72 ± 0.10	39.09 ± 0.79	12.25 ± 0.36	12.84 ± 0.22	36.37 ± 0.73
Total anthocyanidin contents (mg C3GE/g DW)	ND	ND	ND	0.05 ± 0.00	ND	0.23 ± 0.02

C3GE – cyanidin 3-*O*-glucoside equivalent; DW – dry weight; GAE – gallic acid equivalent; ND – not detected

Table 7. Amino acid profile of a *Nelumbo nucifera* lotus seed protein and its protein fractions (g/kg crude protein on a DW basis)[44]

	Protein fraction					
	Seed protein	**Albumin**	**Globulin**	**Prolamine**	**Glutelin**	**Soybean***
Essential amino acids (EAA)						
isoleucine	32.73	31.7	32.4	4.98	26.33	46.2
leucine	64.04	58.02	59.24	8.35	49.73	77.2
lysine	56.94	44.15	41.88	11	36.56	60.8
methionine	24.5	23.52	23.13	8.3	23.12	12.2
phenylalanine	44.81	42.34	45.13	10.53	38.51	48.4
threonine	35.31	28.91	29.20	7.17	25.56	37.6
tryptophan	21.66	24.14	29.71	3.04	9.37	33.9
valine	42.83	38.75	40.84	10.77	34.48	45.9
Total essential amino acids	**322.82**	**291.53**	**301.53**	**64.14**	**243.66**	**362.2**
Non-essential amino acids (NEAA)						
alanine	43.34	36.19	36	4.75	31.86	42.3
arginine	72	78.97	80.17	8.52	53.83	71.3
aspartic acid	98.68	91.74	93.32	16.91	69.78	113
cystine	8.12	6.82	7.81	3.9	6.21	17
glutamic acid	171.32	157.98	154.46	30.32	111.93	169
glycine	44.28	36.44	36.73	6.25	30.97	40.1
histidine	23.66	22.57	22.47	3.57	18.34	25
proline	18.09	17	18.55	3.7	16.99	48.6
serine	58.44	55.08	56.02	10.03	41.91	56.7
tyrosine	15.13	18.47	14.04	6.04	14.41	12.4
Total non-essential amino acids	**553.06**	**521.26**	**519.57**	**93.99**	**396.23**	**595.4**
Hydrophobic amino acids	314.62	283.96	304.89	81.68	251.99	360.9
Hydrophilic amino acids	270	109.3	107.07	27.14	88.09	123.7
Basic amino acids	152.6	145.69	144.52	23.09	108.73	157.1
Acidic amino acids	53.67	249.72	247.78	47.23	181.71	282
Total amino acids (EAA + NEAA)	**875.88**	**812.79**	**821.10**	**158.13**	**639.89**	**957.6**

*soybean protein was used as the reference

Table 8. Fatty acid composition of a whole *Nelumbo nucifera* seed oil[45]

Acid	Amount (%)
arachidic acid	5.5
capric acid	2.09
lauric acid	2.04
linoleic acid	19.9
linolenic acid	3.4
mygaric acid	0.2
myristic acid	3.21
oleic acid	11.7
palmitic acid	33.27
palmitoleic acid	5.7
stearic acid	3
unknown	10

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
	Nelumbo Nucifera Callus Culture Extract			Nelumbo Nucifera Extract			Nelumbo Nucifera Flower Extract		
Totals*	**40**	**8**	**NR**	**64**	**7**	**NR**	**544**	**200**	**0.00025 – 0.13**
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*8*	*NR*	***	*5*	*NR*	***	*151*	*0.00025 – 0.13*
Rinse-Off	***	*NR*	*NR*	***	*2*	*NR*	***	*49*	*0.00025 – 0.00055*
Diluted for (Bath) Use	***	*NR*	*NR*	***	*NR*	*NR*	***	*NR*	*NR*
Exposure Type									
Eye Area	***	NR	NR	***	1	NR	***	4	0.00025 – 0.0015
Incidental Ingestion	***	NR	NR	***	NR	NR	***	1	0.1
Incidental Inhalation-Spray	***	5[a]; 3[b]	NR	***	2[a]	NR	***	1; 79[a]; 35[b]	NR
Incidental Inhalation-Powder	***	3[b]	NR	***	NR	NR	***	1; 35[b]; 5[c]	0.1; 0.001 – 0.05[c]
Dermal Contact	***	8	NR	***	5	NR	***	182	0.00025 – 0.1
Deodorant (underarm)	***	NR	NR	***	NR	NR	***	NR	NR
Hair - Non-Coloring	***	NR	NR	***	2	NR	***	17	0.00055
Hair-Coloring	***	NR	NR	***	NR	NR	***	NR	NR
Nail	***	NR	NR	***	NR	NR	***	NR	0.13
Mucous Membrane	***	NR	NR	***	NR	NR	***	17	0.00025 – 0.1
Baby Products	***	NR	NR	***	NR	NR	***	11	0.00055
as reported by product category									
Baby Products							***1***		
Baby Shampoos							1	2	0.00055
Baby Lotions/Oils/Powders/Creams							NR	5	NR
Baby Wipes									
Other Baby Products							NR	4	NR
Bath Preparations							***1***		
Other Bath Preparations							1	NR	NR
Eye Makeup Preparations (not children's)							***4***		
Eye Shadow							NR	1	0.00025
Eye Lotion				NR	1	NR	2	1	0.0015
Eye Makeup Remover							2	NR	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)									
Other Eye Makeup Preparations							NR	2	NR
Fragrance Preparations							***2***		
Cologne and Toilet Water									
Perfumes							NR	1	NR
Powders (dusting/talcum, excl aftershave talc)									
Other Fragrance Preparation							2	NR	NR
Hair Preparations (non-coloring)	***6***						***80***		
Hair Conditioners							4 (l.o.); 23 (r.o.)	3	NR
Hair Sprays (aerosol fixatives)									
Rinses (non-coloring)							1	1	NR
Shampoos (non-coloring)	1 (r.o.)	NR	NR				1 (l.o.); 34 (r.o.)	5	NR
Tonics, Dressings, and Other Hair Grooming Aids							4	4	NR
Other Hair Preparations				NR	2	NR	9 (l.o.); 5 (r.o.)	2	NR

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
Hair Coloring Preparations									
Hair Dyes and Colors (all types requiring caution statements and patch tests)									
Hair Rinses (coloring)									
Other Hair Coloring Preparation									
Makeup Preparations (not eye; not children's)				***3***			***120***		
Blushers and Rouges (all types)				3	NR	NR	24	NR	NR
Face Powders							5	1	0.1
Foundations				3 (tradition application)	NR	NR	31 (traditional application)	1	NR
Leg and Body Paints							1 (airbrush application)	NR	NR
Lipsticks and Lip Glosses							57	1	0.1
Makeup Bases				3 (traditional application)	NR	NR	6 (traditional application)	1	NR
Makeup Fixatives									
Other Makeup Preparations							2 (l.o.)	4	NR
Personal Cleanliness				***6***			***17***		
Bath Soaps and Body Washes				5	NR	NR	13	10	0.00025
Sprays									
Feminine Deodorants							NR	1	NR
Other Personal Cleanliness Products							4 (r.o.)	5	NR
Shaving Preparations				***1***					
Other Shaving Preparations				1	NR	NR			
Skin Care Preparations	***39***			***53***			***316***		
Cleansing	4	NR	NR	3	2	NR	43	19	NR
Face and Neck (excluding shaving preps)	21 (l.o.); 1 (r.o.)	3	NR	26 (l.o.); 3 (r.o.)	NR	0.01% (not spray 0.01% (l.o); 0.02% (r.o)	211 (l.o.); 29 (r.o.)	28	0.001 (not spray)
Body and Hand (excluding shaving preps)	2 (l.o.)	NR	NR	7 (l.o.)	NR	0.001%	7 (l.o.); 3 (r.o.)	6	0.01 – 0.05 (not spray)
Moisturizing	10	3	NR	13	2	NR	87	70	0.0015 (not spray)
Night	NR	2	NR	2	NR	NR	1	2	NR
Paste Masks (mud packs)				1	NR	NR	5	3	NR
Skin Fresheners				1	NR	NR	9	3	NR
Other Skin Care Preparations	2 (l.o.)	NR	NR	8 (l.o.); 2 (r.o.)	NR	NR	14 (l.o.); 6 (r.o.)	13	NR
Suntan Preparations									
Indoor Tanning Preparations									
Other Suntan Preparations									
Other Preparations (i.e., those that do not fit another category)				***1***	NA	NA	***8***	NA	NA

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
	Nelumbo Nucifera Flower/Leaf/Steam Juice			Nelumbo Nucifera Flower Oil			Nelumbo Nucifera Flower Water		
Totals*	**NR**	**1**	**0.000023 – 0.0034**	**17**	**8**	**NR**	**74**	**13**	**0.001**
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*1*	*0.0034*	***	*5*	*NR*	***	*11*	*0.001*
Rinse-Off	***	*NR*	*0.000023*	***	*3*	*NR*	***	*2*	*NR*
Diluted for (Bath) Use	***	*NR*	*NR*	***	*NR*	*NR*	***	*NR*	*NR*
Exposure Type									
Eye Area	***	NR	NR	***	NR	NR	***	1	NR
Incidental Ingestion	***	NR	NR	***	NR	NR	***	NR	NR
Incidental Inhalation-Spray	***	1[b]	NR	***	5	NR	***	5[a]; 1[b]	NR
Incidental Inhalation-Powder	***	1[b]	0.0034[c]	***	NR	NR	***	1[b]	0.001[c]
Dermal Contact	***	1	0.0034	***	8	NR	***	13	0.001
Deodorant (underarm)	***	NR	NR	***	NR	NR	***	NR	NR
Hair - Non-Coloring	***	NR	0.000023	***	NR	NR	***	NR	NR
Hair-Coloring	***	NR	NR	***	NR	NR	***	NR	NR
Nail	***	NR	NR	***	NR	NR	***	NR	NR
Mucous Membrane	***	NR	NR	***	2	NR	***	NR	NR
Baby Products	***	NR	NR	***	NR	NR	***	NR	NR
as reported by product category									
Baby Products							***3***		
Baby Shampoos							1	NR	NR
Baby Lotions/Oils/Powders/Creams							1	NR	NR
Baby Wipes									
Other Baby Products							1 (l.o.); 2 (r.o.)	NR	NR
Bath Preparations (diluted for use)									
Other Bath Preparations									
Eye Makeup Preparations									
Eye Shadow									
Eye Lotion									
Eye Makeup Remover									
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)									
Other Eye Makeup Preparations							NR	1	NR
Fragrance Preparations				***1***			*4*		
Perfumes				NR	5	NR			
Other Fragrance Preparation				1	NR	NR	4	NR	NR
Hair Preparations (non-coloring)				***1***			***7***		
Hair Conditioner	NR	NR	0.000023				1 (l.o.)	NR	NR
Hair Spray (aerosol fixatives)							1	NR	NR
Rinses (non-coloring)							2	NR	NR
Shampoos (non-coloring)							1 (r.o.)	NR	NR
Tonics, Dressings, and Other Hair Grooming Aids							2	NR	NR
Other Hair Preparations				1 (l.o.)	NR	NR			
Hair Coloring Preparations							***7***		
Hair Dyes and Colors (all types requiring caution statements and patch tests)									
Hair Rinses (coloring)							7 (r.o.)	NR	NR

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
Other Hair Coloring Preparation									
Makeup Preparations (not eye; not children's)				***3***			*4*		
Blushers and Rouges (all types)									
Face Powders									
Foundations				3 (traditional application)	NR	NR			
Leg and Body Paints									
Lipsticks and Lip Glosses									
Makeup Bases							2 (traditional application)	NR	NR
Makeup Fixatives							1	NR	NR
Other Makeup Preparations							1 (l.o.)	NR	NR
Personal Cleanliness Products				***2***			*1*		
Bath Soaps and Body Washes				1	2	NR			
Sprays									
Feminine Deodorants									
Other Personal Cleanliness Products				1 (l.o.)	NR	NR	1 (r.o.)	NR	NR
Shaving Preparations									
Other Shaving Preparations									
Skin Care Preparations				***9***			*47*		
Cleansing				1	1	NR	5	NR	NR
Face and Neck (excluding shaving preps)	NR	1	0.0034 (not spray)	7 (l.o.); 1 (r.o.)	NR	NR	26 (l.o.)	1	0.001 (not spray)
Body and Hand (excluding shaving preps)							1 (l.o.)	NR	NR
Moisturizing				2	NR	NR	11	4	NR
Night									
Paste Masks (mud packs)							4	2	NR
Skin Fresheners							2	1	NR
Other Skin Care Preparations							NR	4	NR
Suntan Preparations							***3***		
Indoor Tanning Preparations							3 (traditional application)	NR	NR
Other Suntan Preparations							1	NR	NR
Other Preparations (i.e., those that do not fit another category)				***1***	NA	NA			

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
	Nelumbo Nucifera Germ Extract			Nelumbo Nucifera Leaf Extract			Nelumbo Nucifera Phytoplacenta Culture Extract		
Totals*	**34**	**8**	**NR**	**63**	**20**	**0.00025**	**NR**	**1**	**NR (2024)[53]**
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*8*	*NR*	***	*17*	*NR*	***	*NR*	**NR**
Rinse-Off	***	*NR*	*NR*	***	*3*	*0.00025*	***	*NR*	**NR**
Diluted for (Bath) Use	***	*NR*	*NR*	***	*NR*	*NR*	***	*NR*	**NR**
Exposure Type									
Eye Area	***	2	NR	***	NR	NR	***	NR	**NR**
Incidental Ingestion	***	NR	NR	***	NR	NR	***	NR	**NR**
Incidental Inhalation-Spray	***	5[a]	NR	***	7[a]; 8[b]	NR	***	NR	**NR**
Incidental Inhalation-Powder	***	NR	NR	***	1; 8[b]	NR	***	NR	**NR**
Dermal Contact	***	8	NR	***	20	0.00025	***	1	**NR**
Deodorant (underarm)	***	NR	NR	***	NR	NR	***	NR	**NR**
Hair - Non-Coloring	***	NR	NR	***	NR	NR	***	NR	**NR**
Hair-Coloring	***	NR	NR	***	NR	NR	***	NR	**NR**
Nail	***	NR	NR	***	NR	NR	***	NR	**NR**
Mucous Membrane	***	NR	NR	***	1	0.00025	***	NR	**NR**
Baby Products	***	NR	NR	***	NR	NR	***	NR	**NR**
as reported by product category									
Baby Products				***1***					
Baby Shampoos									
Baby Lotions/Oils/Powders/Creams				1	NR	NR			
Baby Wipes									
Other Baby Products									
Bath Preparations									
Other Bath Preparations									
Eye Makeup Preparations (not children's)	***2***			***1***					
Eye Shadow									
Eye Lotion	2	1	NR						
Eye Makeup Remover	NR	1	NR						
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)									
Other Eye Makeup Preparations				1	NR	NR			
Fragrance Preparations									
Perfumes									
Other Fragrance Preparation									
Hair Preparations (non-coloring)				***1***					
Hair Conditioners									
Hair Sprays (aerosol fixatives)									
Rinses (non-coloring)									
Shampoos (non-coloring)									
Tonics, Dressings, and Other Hair Grooming Aids									
Other Hair Preparations				1 (r.o.)	NR	NR			

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
Hair Coloring Preparations									
Hair Dyes and Colors (all types requiring caution statements and patch tests)									
Hair Rinses (coloring)									
Other Hair Coloring Preparation									
Makeup Preparations (not eye; not children's)				***1***					
Blushers and Rouges (all types)									
Face Powders				NR	1	NR			
Foundations									
Leg and Body Paints									
Lipsticks and Lip Glosses									
Makeup Bases									
Makeup Fixatives				1	NR	NR			
Other Makeup Preparations									
Personal Cleanliness	***1***			***5***					
Bath Soaps and Body Washes	1	NR	NR	3	1	0.00025			
Sprays				1	NR	NR			
Feminine Deodorants				1 (l.o.)	NR	NR			
Other Personal Cleanliness Products				1 (r.o.)	NR	NR			
Shaving Preparations									
Other Shaving Preparations									
Skin Care Preparations	***31***			***55***					
Cleansing	2	NR	NR	7	2	NR			
Face and Neck (excluding shaving preps)	18 (l.o.); 1 (r.o.)	NR	NR	31 (l.o.); 5 (r.o.)	3	NR			
Body and Hand (excluding shaving preps)				7 (l.o.)	5	NR			
Moisturizing	28	5	NR	11	6	NR			
Night									
Paste Masks (mud packs)									
Skin Fresheners	8	NR	NR	5	NR	NR			
Other Skin Care Preparations	NR	1	NR	3 (l.o.); 1 (r.o.)	1	NR	NR	1	NR
Suntan Preparations									
Indoor Tanning Preparations									
Other Suntan Preparations									
Other Preparations (i.e., those that do not fit another category)				***1***	NA	NA			

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
	Nelumbo Nucifera Root Extract			Nelumbo Nucifera Root Water			Nelumbo Nucifera Seed Extract		
Totals*	**190**	**15**	**0.2**	**21**	**1**	**NR**	**72**	**25**	**NR**
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*8*	*0.2*	***	*NR*	*NR*	***	*20*	*NR*
Rinse-Off	***	*7*	*NR*	***	*1*	*NR*	***	*5*	*NR*
Diluted for (Bath) Use	***	*NR*	*NR*	***	*NR*	*NR*	***	*NR*	*NR*
Exposure Type									
Eye Area	***	NR	NR	***	NR	NR	***	NR	NR
Incidental Ingestion	***	NR	NR	***	NR	NR	***	NR	NR
Incidental Inhalation-Spray	***	4[a]; 3[b]	NR	***	NR	NR	***	8[a]; 5[b]	NR
Incidental Inhalation-Powder	***	3[b]	NR	***	NR	NR	***	5[b]	NR
Dermal Contact	***	8	0.2	***	1	NR	***	21	NR
Deodorant (underarm)	***	NR	NR	***	NR	NR	***	NR	NR
Hair - Non-Coloring	***	5	NR	***	NR	NR	***	4	NR
Hair-Coloring	***	2	NR	***	NR	NR	***	NR	NR
Nail	***	NR	NR	***	NR	NR	***	NR	NR
Mucous Membrane	***	1	NR	***	NR	NR	***	1	NR
Baby Products	***	NR	NR	***	NR	NR	***	NR	NR
as reported by product category									
Baby Products	***1***						***3***		
Baby Shampoos							2	NR	NR
Baby Lotions/Oils/Powders/Creams							1	NR	NR
Baby Wipes	1	NA	NA						
Other Baby Products									
Bath Preparations (diluted for use)									
Other Bath Preparations									
Eye Makeup Preparations							***2***		
Eye Shadow									
Eye Lotion							1	NR	NR
Eye Makeup Remover									
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)							1	NA	NA
Other Eye Makeup Preparations									
Fragrance Preparations									
Perfumes									
Other Fragrance Preparation									
Hair Preparations (non-coloring)	***23***						***12***		
Hair Conditioner	2 (l.o.); 12 (r.o.)	1	NR				5 (r.o.)	1	NR
Hair Spray (aerosol fixatives)									
Rinses (non-coloring)									
Shampoos (non-coloring)	9 (r.o.)	2	NR				6 (r.o.)	1	NR
Tonics, Dressings, and Other Hair Grooming Aids	NR	2	NR				2	NR	NR
Other Hair Preparations									
Hair Coloring Preparations									
Hair Dyes and Colors (all types requiring caution statements and patch tests)	NR	2	NR						

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
Other Hair Coloring Preparation							NR	2	NR
Makeup Preparations (not eye; not children's)	***13***			***15***					
Blushers and Rouges (all types)									
Face Powders	NR	NR	0.2	15	NR	NR			
Foundations	**NR**	NR	0.2				NR	2	NR
Leg and Body Paints									
Lipsticks and Lip Glosses	10	NR	NR						
Makeup Bases	3 (traditional application)	NR	NR						
Makeup Fixatives									
Other Makeup Preparations									
Personal Cleanliness Products	***4***			***2***			***1***		
Bath Soaps and Body Washes	4	NR	NR	1	NR	NR	1	1	NR
Sprays									
Feminine Deodorants									
Other Personal Cleanliness Products	NR	1	NR						
Shaving Preparations									
Other Shaving Preparations									
Skin Care Preparations	***148***			***4***			*54*		
Cleansing	14	1	NR	2	1	NR	2	1	NR
Face and Neck (excluding shaving preps)	114 (l.o.); 15 (r.o.)	3	NR	2 (l.o.)	NR	NR	NR	5	NR
Body and Hand (excluding shaving preps)	9 (l.o.)								
Moisturizing	83	2	NR				27	7	NR
Night									
Paste Masks (mud packs)	3	NR	NR				1	1	NR
Skin Fresheners	9	NR	NR				5	1	NR
Other Skin Care Preparations	1 (l.o.)	1	NR				2 (l.o.)	1	NR
Suntan Preparations									
Indoor Tanning Preparations									
Other Suntan Preparations									
Other Preparations (i.e., those that do not fit another category)	***1***	NA	NA						

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
	Nelumbo Nucifera Seed Powder			Nelumbo Nucifera Stamen Extract					
Totals*	**13**	**1**	**NR**	**6**					
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*1*	*NR*	***	*1*	*NR*			
Rinse-Off	***	*NR*	*NR*	***	*NR*	*NR*			
Diluted for (Bath) Use	***	*NR*	*NR*	***	*NR*	*NR*			
Exposure Type									
Eye Area	***	NR	NR	***	NR	NR			
Incidental Ingestion	***	NR	NR	***	NR	NR			
Incidental Inhalation-Spray	***	NR	NR	***	1[b]	NR			
Incidental Inhalation-Powder	***	NR	NR	***	1[b]	NR			
Dermal Contact	***	1	NR	***	1	NR			
Deodorant (underarm)	***	NR	NR	***	NR	NR			
Hair - Non-Coloring	***	NR	NR	***	NR	NR			
Hair-Coloring	***	NR	NR	***	NR	NR			
Nail	***	NR	NR	***	NR	NR			
Mucous Membrane	***	NR	NR	***	NR	NR			
Baby Products	***	NR	NR	***	NR	NR			
as reported by product category									
Baby Products									
Baby Shampoos									
Baby Lotions/Oils/Powders/Creams									
Baby Wipes									
Other Baby Products									
Bath Preparations									
Other Bath Preparations									
Eye Makeup Preparations (not children's)									
Eye Shadow									
Eye Lotion									
Eye Makeup Remover									
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)									
Other Eye Makeup Preparations									
Fragrance Preparations									
Perfumes									
Other Fragrance Preparation									
Hair Preparations (non-coloring)									
Hair Conditioners									
Hair Sprays (aerosol fixatives)									
Rinses (non-coloring)									
Shampoos (non-coloring)									
Tonics, Dressings, and Other Hair Grooming Aids									
Other Hair Preparations									
Hair Coloring Preparations									
Hair Dyes and Colors (all types requiring caution statements and patch tests)									
Hair Rinses (coloring)									

Table 9. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[50,51]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]	RLD (2024)[50]	VCRP (2023)[51]	% (2022)[52]
Other Hair Coloring Preparation									
Makeup Preparations (not eye; not children's)									
Blushers and Rouges (all types)									
Face Powders									
Foundations									
Leg and Body Paints									
Lipsticks and Lip Glosses									
Makeup Bases									
Makeup Fixatives									
Other Makeup Preparations									
Personal Cleanliness	***1***								
Bath Soaps and Body Washes									
Sprays									
Feminine Deodorants									
Other Personal Cleanliness Products	1 (r.o.)	NR	NR						
Shaving Preparations									
Other Shaving Preparations									
Skin Care Preparations	***12***			***6***					
Cleansing									
Face and Neck (excluding shaving preps)	10 (l.o.). 2 (r.o.)	NR	NR	5 (l.o.)	1	NR			
Body and Hand (excluding shaving preps)									
Moisturizing	9	NR	NR	1	NR	NR			
Night									
Paste Masks (mud packs)									
Skin Fresheners	1	NR	NR						
Other Skin Care Preparations	NR	1	NR						
Suntan Preparations									
Indoor Tanning Preparations									
Other Suntan 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)
PCPC concentration of use survey is underway, but results have not yet been received.
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)
*** In the RLD 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] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 10 . Acute oral toxicity studies

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/Results	Reference
Nelumbo nucifera Gaertn., 0.5 g in a capsule (33% of contents)*	N/A	Swiss mice (10/group; sex not specified)	59.9, 79.9, or 99.9 g capsule materials/kg bw	Contents of the capsule was dissolved in distilled water and administered orally ; 7-d observation	No signs of toxicity and no mortality were observed.	59
Nelumbo nucifera leaf, flower, and root extract (ethanol)	N/A	Wistar albino rats (n = 3; of sex not specified)	2 g/kg	OECD TG 425; via gavage; 24-h observation	LD_{50} > 2 g/kg No deaths occurred.	42
Nelumbo nucifera leaf and root extract (ethanol)	N/A	Wistar albino rats (n = 3;sex not specified)	2 g/kg	OECD TG 425; via gavage; 24-h observation	LD_{50} >2 g/kg No deaths occurred.	42
Nelumbo nucifera flower extract (ethanol)	N/A	Wistar albino rats (n = 3; of sex not specified)	2 g/kg	OECD TG 425; via gavage; 24-h observation	LD_{50} > 2 g/kg No deaths occurred.	42
Nelumbo nucifera flower extract (water, in ethanol)	N/A	Male Wistar albino rats (3/sex/group)	2 g/kg	OECD TG 420; via gavage; 14-d observation	The test substance was considered non-toxic at up to 2 g/kg. No mortality occurred.	35
Nelumbo nucifera lotus root extract (ethanol)	N/A	ICR mice (12/sex/group)	0, 2, or 5 g/kg	Animals were dosed orally; 14-d observation	LD_{50} > 5 g/kg	60
Nelumbo nucifera seed extract (water, in ethanol)	0.3% w/v Na-CMC, in distilled water	Male Swiss albino mice (6/group)	0, 0.2, 0.4, 0.6, 0.8, or 1 g/kg bw	Animals were dosed orally; 24-h observation	LD_{50} > 1 g/kg No signs of toxicity were observed.	43
Nelumbo nucifera stamen extract-PVP complex**	distilled water	Sprague-Dawley rats (5/sex/group)	0 or 5 g/kg	OECD TG 420; via gavage; 14-d observation	LD_{5}> 5 g/kg	25

N/A – not applicable; Na-CMC – sodium carboxymethyl cellulose; OECD – Organisation for Economic Co-operation and Development;PVP-10 - polyvinylpyrrolidone-10; TG – test guideline; WHO – World Health Organization

*each capsule contained 0.5 g *Nelumbo nucifera* Gaertn., 0.5 g *Codonopsis pilosula (Franch)* Nannf, 0.15 g *Lactuca indica* L., 0.1 g *Curcuma longa* L., 0.1 g *Zingiber officinale* Rosc., 0.075 g *Saussurea lappa* Clarke, and 0.075 g *Atractylodes macrocephela* Koidz.

**Ethanol was used in the initial extraction of the *Nelumbo nucifera* stamen extract-PVP complex and was subsequently removed during the preparation process.

Table 11. Repeated dose oral toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Nelumbo nucifera Gaertn., in a capsule,	distilled water	Wistar rats (10/group; sex not specified) Swiss mice	4 wk	0, 1440, or 4320 mg/kg/d, in a capsule, Nelumbo nucifera 0.5g is only 33% of contents of the capsule)*	orally dosed; body weight changes, hematology, and serum biochemistry values (AST, ALT, total bilirubin, albumin, total cholesterol, and creatine levels) were evaluated before treatment, and after 2 and 4 wk of treatment. For acute toxicity study, a group of mice (10 per group) were fasted for 12-16 h and administered the test mixture orally in ascending doses that the mice could tolerate. The general symptoms of toxicity and the mortality in each group was observed for 72 h. The animals that survived were observed for another 7 d for delayed toxicity.	Statistically significant increases in body weight were observed in rats in the 1.44 g/kg/d group after 2 wk of treatment, compared to controls. No significant differences in red blood cell counts, hematocrit, hemoglobin level, platelet count, total white blood cell count and white blood cells, AST, total bilirubin, albumin concentration, and total cholesterol concentration were observed between treated animals and controls. After 4 wk of treatment, a statistically significant increase in ALT levels was observed in the 4.32 g/kg/d group compared to controls; however, these values were at the normal range for rats and no significant differences were observed compared to baseline values. No gross lesions or changes in size were observed in heart, liver, lungs, or kidney and abdominal cavities in treated rats, as compared to controls, upon necropsy. No significant differences were observed upon histopathological examination of the liver and kidneys of rats treated for 4 wk compared to controls; serum creatinine levels in both treated groups were also not significantly different from controls.	59

Table 11. Repeated dose oral toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Nelumbo nucifera lotus seed tea (produced by roasting uncoated seeds and extracting with hot water)	N/A	Male SKH-1 hairless mice (10/group)	6 mo	not specified	administered as the drinking fluid; mice received either *Nelumbo nucifera* lotus seed tea (test animals) or tap water (controls). Both groups received a chow diet. The animals were subsequently used for testing in a phototoxicity study.	No significant differences in food or liquid consumption or body weight were observed between test animals and controls.	23
Nelumbinis semen (*Nelumbo nucifera* seeds)	N/A	Sprague-Dawley rats (5/sex/group)	13 wk	0, 500, 1000, or 2000 mg/kg/d	Administered by gavage, mortality, clinical signs, body weight changes, food and water consumption, urinalysis, hematology and serum biochemistry, and necropsy findings and relative organ weights were recorded.	No mortality, body weight, or ophthalmic changes were observed in treated animals, compared to controls. Food consumption was lower, compared to controls, at weeks 7 and 12 for males in the 500 and 2000 mg/kg/d groups, and at weeks 7, 9, 10, and 12 for males dosed with 1000 mg/kg/d. A significant increase in hemoglobin concentration distribution (all test groups) and red blood cell distribution (500 and 2000 mg/kg/d groups) in males were not considered test article-related. Higher AST and ALT levels in all treated females and lower CPK levels in both treated sexes were not statistically significant. Lower right adrenal gland weight (with respect to body mass) in male rats from the 500 and 1000 mg/kg/d groups, in comparison to controls was neither dose-dependent or sex-matched, and, thus, was not considered treatment-related. No gross pathological abnormalities were observed. The NOAEL was determined to be 2000 mg/kg/d for both sexes combined.	61
Nelumbinis semen (*Nelumbo nucifera* seeds)	N/A	Beagle dogs (1/sex/group)	28 d	0, 500, 1000, 2000, or 4000 mg/kg/d	orally administered; body weights and average food consumption were recorded weekly. Serum biochemical values were obtained both before and after dosing. Animals were observed daily for changes in behavior, food intake, and urine output.	No mortality was observed. Vomiting was observed in the male dog that received the 2000 mg/kg dose, which could have been induced by gastro-intestinal stimuli. In the urinalysis, proteinuria was observed in controls and 500 and 1000 mg/kg males and in 50, 100, and 4000 mg/kg females. Low specific gravity of the urine was observed in all treated females. Urine occult blood was seen for the 2000 and 4000 mg/kg male and female, respectively. However, these effects were observed before treatment and none of these effects were dose-dependent or accompanied with other corresponding changes. No systemic and toxicologically significant changes related to treatment with Nelumbinis semen were observed. The NOAEL was determined to be 4000 mg/kg/d.	61

Table 11. Repeated dose oral toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Nelumbo nucifera stamen extract-PVP complex**	distilled water	Sprague-Dawley rats (6/sex/group)	90 d	0, 50, 100, or 200 mg/kg/d	OECD TG 408; orally dosed; body weights were recorded on day 0, 90, and at necropsy. Controls received 80% PVP-10 (w/w) in distilled water. A 200 mg/kg treatment satellite group and a control satellite group were observed for 28 d post-dosing for reversibility, persistence, or delayed toxicity occurrence. Any rat that died during the study underwent pathological examination.	No deaths or treatment-related signs were observed in treated animals during the study or recovery period. There was a slight but statistically significant decrease in the body weight of 200 mg/kg/d females compared to controls on day 90. However, weight changes of both groups showed no significant difference and the % weight changes of both groups were similar. Additionally, no statistically significant differences were observed in male and female satellite rats compared to controls at any dose. A few statistically significant differences were observed in the hematologic and biochemical parameters of 200 mg/kg rats treated for 90 d compared to controls. However, these minimal differences were not considered pathologically significant or treatment-related. Absolute kidney weights were slightly lower in 200 mg/kg/d rats for both sexes at day 90 and for treated females after 118 d, compared to controls. Relative liver weights were lower than controls for both sexes on day 90 and in treated males on day 118; relative heart, liver, and kidney weights were also lower than controls in treated females at day 90. However, these results were not considered treatment-related because values were within normal laboratory range and no abnormality was noted with respect to gross or histopathological examination of all organs. The NOAEL for both male and female rats was determined to be > 200 mg/kg/d.	25

ALT – alanine aminotransferase; AST – aspartate transferase; CPK – creatine phosphokinase; N/A – not applicable; NOAEL – no-observed-adverse-effect level; OECD – Organisation for Economic Cooperation and Development; PVP- polyvinylpyrrolidone; TG – test guideline; WHO – World Health Organization

*each capsule contained 0.5 g *Nelumbo nucifera* Gaertn., 0.5 g *Codonopsis pilosula (Franch)* Nannf, 0.15 g *Lactuca indica* L., 0.1 g *Curcuma longa* L., 0.1 g *Zingiber officinale* Rosc., 0.075 g *Saussurea lappa* Clarke, and 0.075 g *Atractylodes macrocephela* Koidz.

**Ethanol was used in the initial extraction of the *Nelumbo nucifera* stamen extract-PVP complex and was subsequently removed during the preparation process.

Table 12. Reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
IN VITRO						
Nelumbo nucifera petal extract (aqueous)	N/A	Rat sperm	0, 0.22, 0.44, 0.88, 1.76, or 3.52 mg/ml	Sperm dosed with extracts of *Nelumbo nucifera* petals (from red and white flowers) were first stained with DAPI, followed by staining with PI. Sperm which stained red with PI was considered dead, but sperm that remained unstained with PI was considered viable.	Increases in sperm viability were statistically significant at the 0.22 - 1.76 mg/ml exposure concentrations, when compared to controls. No statistically significant differences were seen between the viability of sperm from the highest dose group (3.52 mg/ml) and controls.	33
ORAL						
Nelumbo nucifera seed extract (petroleum ether)	peanut oil	Male Wistar albino rats (10/group)	7.5 mg/kg bw	orally administered; rats were dosed every other day for a 15-d period. An untreated group received saline (5 mg/kg) and vehicle controls were given refined groundnut oil (10 ml/kg); body weights were measured before and after the treatment period; 8 rats/group were sacrificed 24 h after the last dose. Testis, cauda epididymis, and adrenal glands were dissected out and weighed; sperm was obtained from the cauda epididymis; sperm count and mobility, cholesterol, ascorbic acid content, 3β-HSD and G-6-PD activity were measured in the testis.	Statistically significant decreases in the weights of testis, epididymis, and adrenal gland, the rate of body growth, sperm count, and motility were observed in treated rats, compared to controls. The researchers considered the statistically significant decrease in 3β-HSD and G-6-PD activity to possibly be due to inhibition of testicular steroidogenesis.	21
Nelumbo nucifera seed extract (petroleum ether)	peanut oil	Female Wistar albino rats (12/group)	0, 2.5, 5, or 7.5 mg/kg bw	orally administered; rats were dosed on alternate days for 15 d. An untreated group received saline (5 mg/kg) and vehicle controls were given refined groundnut oil (10 ml/kg). Body weights were measured before and after the treatment period. Rats were inspected daily for vaginal opening and a daily vaginal lavage was taken to determine the age at first estrus. Eight rats/group were sacrificed 24 h after the last dose. Ovaries and uteri were dissected and weighed; cholesterol, ascorbic acid content, 3β-HSD and G-6-PD activity was measured in the ovaries.	Delayed onset of sexual maturity was indicated by the age of vaginal opening and appearance of first estrus. Statistically significant inhibition of vaginal opening (38%) and first estrus (32%) were observed in 7.5 mg/kg bw rats, compared to vehicle controls. Statistically significant decreases in body weights (16.3%), ovary weights (57.3%), and uterus weights (80.8%) were observed in rats treated with the highest dose, compared to vehicle controls. Ovarian cholesterol content also increased by 99% and ascorbic acid increased by 29% in the 7.5 mg/kg bw group, compared to vehicle controls. The researchers considered that suppressed activity of 3β-HSD (21%) and G-6-PD (23%) in treated rat ovaries may be due to reduced ovarian steroidogenesis.	21
Nelumbo nucifera seed extract (50% ethanol)	N/A	Female Wistar albino rats (10/group)	0 or 800 mg/kg bw	orally administered for 40 d; animals were killed on day 41. Body weights were measured at the end of the experiment. Ovaries, uteri, and vaginas were dissected out, weighed and examined; blood was also collected for hematological studies.	Statistically significant decreases in ovary, uterus, and vagina weights were observed in treated animals, compared to controls; changes in body weights of the experimental animals were not significant. Total erythrocyte count, total leucocyte count, hemoglobin, blood sugar, and hematocrit values were within normal range when compared to controls. Statistically significant decreases in serum protein and glycogen levels and an increase in serum cholesterol were observed in treated animals, compared to controls. Prolonged length of the estrous cycle and an increase in the diestrous phase of the cycle in treated animals, compared to controls, was statistically significant.	22

Table 12. Reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
Nelumbo nucifera seed extract (50% ethanol)	N/A	Male Wistar rats (10/group)	0, 50, 100, or 200 mg/kg bw/d	dosed via gavage for 60 d; initial and final body weights were recorded; blood was collected for hematological analysis; upon necropsy, reproductive and accessory sex organs (testes, epididymis, seminal vesicle, ventral prostate, and vas deferens) along with the liver were weighed; cauda epididymal sperm motility and density was assessed; serum testosterone was measured using ELISA.	No statistically significant changes in body weights, blood sugar and serum levels of protein, cholesterol, triglycerides, and phospholipids were observed, compared to controls. Statistically significant decreases in testes, epididymis, seminal vesicle, and ventral prostate weights were observed in a dose-dependent manner. Reduced sperm motility was statistically significant in all treated groups. Concentrations of testicular and caudal epididymal sperm reduced by 25.04 and 30.70% in the 50 mg/kg group, 56.4 and 71.68% in the 100 mg/kg group, and 63.55 and 84.14% in the 200 mg/kg group, respectively. Fertility reduced up to 100% after treatment with the *Nelumbo nucifera* seed extract. Decreases in serum testosterone were also statistically significant in a dose-dependent manner, compared to controls.	62

DAPI – 4',6-diamidino-2-phenylindole, dihydrochloride; ELISA – enzyme linked immunosorbent assay; G-6-PSD – glucose-6-phosphate dehydrogenase; 3β-HSD – 3β-hydroxysteroid dehydrogenase; N/A – not applicable; PI – propidium iodide

Table 13. Dermal irritation and sensitization studies

Test Article	Vehicle	Test Concentration/Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
IN VITRO						
trade name mixture containing 0.5 – 1% Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract)	not specified	10 – 100 mg/ml	Balb/c 3T3 fibroblasts	3T3 NRU cytotoxicity assay	IC_{50} = 14.71 mg/ml (14,710 µg/ml). non-toxic	11
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides)	none	undiluted	reconstructed human epidermis	skin irritation test (OECD TG 439); additional details not provided	non-irritant	16
ANIMAL						
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids)	not specified	10 and 100% doses (effective test concentration: 0.05 – 0.15% and 0.5 – 1.5% Nelumbo Nucifera Germ Extract)	3 rabbits	Details not provided	non-irritant	16
HUMAN						
trade name mixture containing 1 - 5% Nelumbo Nucifera Flower Extract (extracted in isostearyl isostearate)	mineral oil	25% (effective test concentration: 0.25-1.25% Nelumbo Nucifera Flower Extract) 0.02 ml was applied to a 50 mm^2 area	10 subjects	0.02 ml was applied to a 50 mm^2 area on the back of each subject, Test sites were evaluated 30 min after patch removal, evaluated following a 48-h occlusive application	The primary cutaneous irritation index was 0.20, and cutaneous compatibility was deemed "good."	10

Table 13. Dermal irritation and sensitization studies

Test Article	Vehicle	Test Concentration/Dose	Test Population/System	Protocol	Results	Reference
trade name mixture containing 0.5 – 1% Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract)	not specified	15% (effective test concentration: 0.075 – 0.15% Nelumbo Nucifera Flower Extract)	11 subjects	0.02 ml was applied to a 50 mm^2 area on the back as a 48-h occlusive patch. Test sites were evaluated 15 min after patch removal	non-irritating	11
foundation containing 0.2% Nelumbo Nucifera Flower Water	none	details not provided	28 subjects	28-d use test (details not provided)	c	75
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids)	not specified	50% (effective test concentration: 0.25 – 0.75%)	46 subjects	patch test; occlusive patch	negative	16
trade name mixture containing a maximum of 0.5 - 1.2% Nelumbo Nucifera Leaf Extract	water	25% (effective test concentration: 0.125 - 0.3% Nelumbo Nucifera Leaf Extract)	11 subjects	patch test (details not provided)	non-irritating	18
foundation containing 0.2% Nelumbo Nucifera Root Water	none	details not provided	33 subjects	28-d use test (details not provided)	very good tolerance, no comedogenicity	77
Nelumbo Nucifera Extract (aq.), leaf Extract, Root Extract, Seed Extract and Stem Extract		1% of individual extract	20 subjects	Several patch tests were performed to evaluate the irritation potential of each extract. patches containing 1% of the individual extracts placed on the forearm using a Haye's test chamber for 24 h; blank patches were used for comparison.	No signs of skin irritation were observed for up to 3 d after patch removal.	9
Water cream containing 1% each of an aqueous *Nelumbo nucifera* leaf extract, *Nelumbo nucifera* flower extract, *Nelumbo nucifera* root extract, and *Nelumbo nucifera* stem extract, and 4% combined extract (identity not specified),			20 subjects		no skin irritation observed	9
SENSITIZATION						
IN CHEMICO/IN VITRO						
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides)	none	100 mM	Details not provided	(DPRA	negative	16
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides)	not stated	0.04% (effective test concentration: 0.0002 – 0.0006% Nelumbo Nucifera Germ Extract)	Details not provided	KeratinoSens assay performed according to OECD TG 442D	negative	16
ANIMAL						
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids)	not specified	The first and second induction concentrations were 50 and 100%, respectively, and challenge was performed at 10 and 100%.	5 guinea pigs/group	skin sensitization study (details not provided)	not a sensitizer	16

Table 13. Dermal irritation and sensitization studies

Test Article	Vehicle	Test Concentration/Dose	Test Population/System	Protocol	Results	Reference
			HUMAN			
trade name mixture containing 0.5 – 1%, Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract)	not specified	Tested concentration 15%, (effective test concentration, 0.075 – 0.15% Nelumbo Nucifera Flower Extract; vehicle not specified).	53 subjects	HRIPT was completed. Patches (48-h) were applied 3x/wk for 3 wk. After a 2-wk non-treatment period, one 48-h challenge patch was applied	not an irritant or a sensitizer	11
a foundation containing 0.00001% Nelumbo Nucifera Flower Extract	none	0.2 ml tested neat (~0.05 ml/cm^2)	50 subjects	HRIPT; 3 (24-h) occlusive patches applied each wk for 3 wk ; challenge was performed following a 2-wk non-treatment period	not an irritant or sensitizer	74
foundation containing 0.2% Nelumbo Nucifera Flower Water	none	20 µl tested neat, (50 mm^2)	100 subjects	HRIPT (details not provided)	not an irritant or sensitizer	75
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids)	not specified	20% (no other details provided) (effective test concentration – 0.10 – 0.30%)	56 subjects	HRIPT (No other details provided)	not an irritant or sensitizer	16
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides)	not specified	30%, (no other details provided) (effective test concentration – 0.15 – 0.45%)	57 subjects	HRIPT (No other details provided)	not an irritant or sensitizer	16
Nelumbo Nucifera Germ Extract (emulsion containing 0.0001%)	none	0.1 - 0.15 g of the test material (as received (~25 -38 mg/ cm^2)	52 subjects	HRIPT; 3 (24-h) occlusive patches applied each wk for 3 wk ; challenge was performed following a 2-wk non-treatment period	not an irritant or sensitizer	76
trade name mixture containing a maximum of 0.5 - 1.2% Nelumbo Nucifera Leaf Extract	water	25% (effective test concentration: 0.125 - 0.3% Nelumbo Nucifera Leaf Extract)	56 subjects	HRIPT (details not provided)	not an irritant or sensitizer	18
foundation containing 0.2% Nelumbo Nucifera Root Water	none	40 µl tested undiluted, (110 mm^2)	103 subjects	HRIPT (details not provided)	not an irritant or sensitizer	77
			PHOTOTOXICITY			
			IN VITRO			
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides)	not specified	1000 µg/ml	no details provided	OECD TG 432 (3T3 NRU phototoxicity test)	no phototoxicity	16
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and saccharides)	not specified	50 µg/ml	no details provided	ROS assay (photosafety)	negative	16
			ANIMAL			
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids)	not specified	10 and 30% (effective test concentration: 0.05 – 0.15% and 0.15 – 0.45%, respectively)	5 guinea pigs/group	phototoxicity study (detail not provided)	negative	16

Table 13. Dermal irritation and sensitization studies

Test Article	Vehicle	Test Concentration/Dose	Test Population/System	Protocol	Results	Reference
trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract (tannins and flavonoids)	not specified	photoinduction: 30% (effective test concentration: 0.15 – 0.45%) photochallenge: 3, 6, and 10% (effective test concentrations: 0.015 – 0.045%, 0.03 – 0.135%, and 0.05 – 0.15%, respectively)	5 guinea pigs/group	photosensitization study (detail not provided)	negative	16
			HUMAN			
foundation containing 0.2% Nelumbo Nucifera Flower Water	none	applied neat; 50 µl over a 110 mm^2 surface	28 subjects	phototoxicity study: UVB and UVA (290 - 390 nm); dose equal to 0.75 MED or with UVA only (315 - 390 nm); dose equal to 20 J/cm^2)	not phototoxic	75
foundation containing 0.2% Nelumbo Nucifera Flower Water	none	applied neat; 50 µl over a 110 mm^2 surface	28 subjects	photosensitization study induction: UVB and UVA (290 - 390 nm); immediately after clinical examinations, dose levels equal to 1.5 times the MED challenge: UVA only (315 - 390 nm); dose equal to 5 J/cm^2 UVA	not photosensitizing	75
foundation containing 0.2% Nelumbo Nucifera Root Water	none	applied neat; 50 µl over a 110 mm^2 surface	26 subjects	phototoxicity study: UVB and UVA (290 - 390 nm; dose equal to 0.75 MED) or with UVA only (315 - 390 nm); dose equal to 20 J/cm^2	not phototoxic	77
foundation containing 0.2% Nelumbo Nucifera Root Water	none	applied neat; 50 µl over a 110 mm^2 surface	26 subjects	photosensitization study induction: UVB and UVA (290 - 390 nm); immediately after clinical examinations, dose levels equal to 1.5 times the MED challenge: UVA only (315 - 390 nm); dose equal to 4 J/cm^2 UVA	not photosensitizing	77

Table 14. Ocular Irritation Studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
IN VITRO						
trade name mixture containing 1 - 5% Nelumbo Nucifera Flower Extract (extracted in isostearyl isostearate)	mineral oil	25% in mineral oil (effective test concentration 0.25-1.25%)	Fresh fertile White Leghorn PA12 eggs	HET-CAM assay	non-irritant mean irritation index – 2.3	10
trade name mixture containing 0.5 – 1% Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract)	not specified	15% (effective test concentration 0.075-0.15%)	Fresh fertile White Leghorn eggs	HET-CAM assay	slightly irritating the mean irritation index - 2.25	11
trade name mixture containing 0.5 – 1% Nelumbo Nucifera Flower Extract (extracted in propanediol and glycerin with 0.5 – 1% Nymphaea Caerulea Flower Extract)	none	tested neat	isolated bovine corneas	BCOP test	very well tolerated corneal score (30 min) – 0.1 corneal score (4) – 0.0	11
foundation containing ~0.2% Nelumbo Nucifera Flower Water	not specified	not specified	not specified	Neutral red release assay	negligible cytotoxicity	75
foundation containing ~0.2% Nelumbo Nucifera Flower Water	not specified	not specified	not specified	HET-CAM	practically non-irritant	75
trade name mixture containing a maximum of 0.5 - 1.2% Nelumbo Nucifera Leaf Extract	none	tested neat	not specified	Neutral red release assay	non-cytotoxic	18

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 17, 2025

SUBJECT: Concentration of Use by FDA Product Category: Nelumbo Nucifera Phytoplacenta Extract

Nelumbo Nucifere Phytoplacenta Extract was included in the October 2024 PCPC concentration of use survey. No uses of this ingredients were reported.

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: January 2, 2025

SUBJECT: Nelumbo Nucifera Germ Extract

Anonymous. 2025. Summary Information – UV absorption of Nelumbo Nucifera Germ Extract in water and butylene glycol.

UV Absorption of Nelumbo Nucifera Germ Extract in Water and Butylene Glycol

Absorption was studied over a range of 200 to 400 nm for three trade name mixtures that consisted of Nelumbo Nucifera Germ Extract in water and butylene glycol (concentrations not stated).

The following absorption maxima were reported.

Absorption maximum
272.1 nm
273.0 nm
273.0 nm

December 2024

Summary Information – Trade name mixture containing a maximum of 1.2% Nelumbo Nucifera Leaf Extract

This trade name mixture is a hydroglycolic solution composed of 1,2% (maximum percentage) Nelumbo Nucifera Leaf Extract :

1. Method of manufacture, composition, and impurities data for these ingredients as used in cosmetics

Manufacture : solubilization of powder of leaf of Nelumbo nucifera in mix water/butylene glycol (50/50) -> Separation of soluble and insoluble phases -> Filtration of soluble phase -> membrane sterilization

Composition of Nelumbo Nucifera Leaf Extract included in the trade name mixture containing 0.5%-1.2% in a in mix of water/butylene glycol (50/50)

Sugars	51.1%
Mineral ashes	28.0 %
Proteins	13.3%
Polyphenols	7.6%

Impurities:

Heavy metals	N°CAS	Threshold (ppm)
Antimony	7440-36-0	≤0.5
Arsenic	7440-38-2	≤0.5
Cadmium	7440-43-9	≤0.5
Chromium	7440-47-3	≤0.5
Cobalt	7440-48-4	≤0.5
Mercury	7439-97-6	≤0.5
Nickel	7440-02-0	≤0.5
Lead	7439-92-1	≤0.5
Vanadium	7440-62-2	≤0.5

2. Dermal irritation and sensitization data, at or above the maximum reported concentration of use

- Patch test (11 subjects) made on an aqueous solution with 25% of the trade name mixture containing 0.5-1.2% Nelumbo Nucifera Leaf Extract => Non irritating
- Sensitization (HRIPT – 56 subjects) made on an aqueous solution with 25% of the trade name mixture containing 0.5-1.2% Nelumbo Nucifera Leaf Extract => non irritating and non sensitizing

3. Ocular irritation data

   Neutral red release assay (Method of Neutral Red Release (Official method for evaluating irritant potential : appendix VI of the J.O (Journal Officiel/National Register) N°302 of December 30,1999). Was completed on the trade name mixture containing 0.5-1.2% Nelumbo Nucifera Leaf extract (pure) => non cytotoxic

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: December 19, 2024

SUBJECT: Nelumbo Nucifera Leaf Water and Nelumbo Nucifera Root Water

Anonymous. 2024. Summary Information – Studies completed on a foundation containing 0.2% Nelumbo Nucifera Flower Water.

Anonymous. 2024. Summary Information – Studies completed on a foundation containing 0.2% Nelumbo Nucifera Root Water.

December 2024

Summary Information – Studies completed on a foundation containing 0.2% Nelumbo Nucifera Flower Water

Dermal irritation and sensitization data

NELUMBO NUCIFERA FLOWER WATER 0.2% in foundation (product tested undiluted)

HRIPT (100 subjects): Nonirritant, Not sensitizing

Occlusive Patch: 20µl on surface: 50 mm^2

Use-test (28 days, 30 subjects): Very good tolerance, no comedogenicity

Phototoxicity and Photosensitization

(28 subjects) Photo toxicity & Photosensitization: Non phototoxic, Not photosensitizing

Product application (foundation tested undiluted): 50µl over a 110 mm^2 surface

PHOTO-TOXICITY:

Solar exposure

U.V.-B & U.V.-A (290 to 390 nm, to a dose equal to 0.75 M.E.D) or with U.V.-A alone (315 to 390 nm, to a dose equal to 20 Joules/cm^2)

PHOTO-SENSITIZATION:

Induction phase U.V. -B & U.V. -A: 290 to 390 nm; immediately after clinical examinations, whose dose levels are equal to 1.5 times the M.E.D. for each subject.

"challenge" phase: U.V.-A spectrum alone: 315 to 390 nm, immediately after cutaneous examinations, whose administered dose level is equal to 5 Joules/cm^2 of U.V-A.

Ocular irritation data

NELUMBO NUCIFERA FLOWER WATER 0,1986% in foundation.

In vitro tests: NRR/ negligible cytotoxicity and HET-CAM/ practically non irritant

Summary Information – Studies completed on a foundation containing 0.2% Nelumbo Nucifera Root Water

Dermal irritation and sensitization

NELUMBO NUCIFERA ROOT WATER 0.2% in foundation (tested undiluted)

Occlusive Patch: 40µl on surface: 110 mm^2

HRIPT (103 subjects): Nonirritant, Not sensitizing

use-test (28days, 33 subjects): Very good tolerance, no comedogenicity

Phototoxicity and Photosensitization

(26 subjects) Photo toxicity & Photosensitization: Non phototoxic, Not photosensitizing

Product application: 50µl (tested undiluted) over a 110 mm^2 surface

PHOTO-TOXICITY:

Solar exposure

U.V.-B & U.V.-A (290 to 390 nm, to a dose equal to 0.75 M.E.D) or with U.V.-A alone (315 to 390 nm, to a dose equal to 20 Joules/cm^2)

PHOTO-SENSITIZATION:

. induction phase U.V. -B & U.V. -A: 290 to 390 nm; immediately after clinical examinations, whose dose levels are equal to 1.5 times the M.E.D. for each subject.

. "challenge" phase: U.V.-A spectrum alone: 315 to 390 nm, immediately after cutaneous examinations, whose administered dose level is equal to 4 Joules/cm^2 of U.V-A.

Note: "The Minimal Erythema Dose" (M.E.D.) in human skin is defined as the lowest U.V. dose that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of U.V. exposure, 16 to 24 hours after U.V. exposure" (COLIPA, SPF, Test Method Guidelines – May 2006).

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: January 27, 2025

SUBJECT: *Nelumbo nucifera*-Derived Ingredients

Anonymous. 2017. Clinical safety evaluation repeated insult patch test (foundation containing 0.00001% Nelumbo Nucifera Flower Extract tested as received).

Anonymous. 2009. Clinical safety evaluation repeated insult patch test (emulsion containing 0.0001% Nelumbo Nucifera Germ Extract tested as received).

[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

Test article was a foundation containing 0.00001% Nelumbo Nucifera Flower Extract
It was tested as received

[redacted]

Sponsor

[redacted]

Sponsor Representatives

[redacted]

Clinical Testing Facility

[redacted]

Sponsor Code: [redacted]

Date of Final Report

10-9-17

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted]

Study Director

9/28/2017

Date

[redacted]

Principal Investigator

9.27.17

Date

[redacted]

Medical Investigator

9/27/17

Date

[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

30 Sep 2017
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: July 26, 2017

Final evaluation: September 1, 2017

[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 April 24, 2017 and identified as follows:

[redacted] Entry No.	Test Article ID	Description
[redacted]	[redacted]	Light Green Viscous Liquid

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 0.2 mL) was placed onto a Parke-Davis Readi-Bandage® occlusive patch (approximately 0.05 mL/cm^2 of test material), which was 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]

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 (14 males and 41 females ranging in age from 19 to 70 years) were empanelled for the test procedure. Fifty (50/55) subjects satisfactorily completed the test procedure on Test Article: [redacted] Four (4/55) subjects discontinued for personal reasons unrelated to the conduct of the study. One (1/55) subject (Subject No. 31) was discontinued due to violation of the protocol; the subject had sunburn on the patch site. 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 50 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]	27	F	HS	30	[redacted]	29	M	CA
2		30	F	HS	31		48	M	CA
3		56	M	CA	32		59	F	CA
4		60	F	CA	33		23	F	CA
5		62	F	BA	34		70	M	CA
6		32	F	BA	35		62	F	CA
7		58	F	HS	36		34	M	HS
8		34	F	HS	37		62	F	CA
9		30	F	BA	38		63	M	CA
10		23	F	BA	39		38	F	CA
11		56	F	CA	40		57	M	CA
12		49	F	CA	41		57	F	CA
13		58	F	CA	42		26	F	CA
14		52	F	CA	43		26	F	HS
15		28	F	BH	44		34	F	HS
16		69	F	CA	45		62	F	CA
17		65	F	HS	46		21	M	HS
18		57	F	CA	47		55	F	HS
19		40	F	HS	48		27	M	CA
20		59	F	CA	49		67	F	CA
21		46	F	CA	50		61	F	HS
22		61	F	CA	51		33	F	HS
23		53	F	CA	52		29	F	CA
24		39	F	AS	53		32	M	CA
25		57	F	CA	54		34	M	HS
26		61	F	CA	55		19	F	CA
27		25	M	CA					
28		58	M	CA					
29		29	M	CA					

AS = Asian or Pacific Islander
BA = Black/African American
BH = Black Hispanic
CA = Caucasian
HS = Hispanic

Shaded area = Discontinued subject

[redacted]

[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	Discontinued									
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	Discontinued						
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	0	0	0	0	0	0	0	0	0	0
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	0	0	0	0	0	0	0	0	0	0
30	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)
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]

[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	Discontinued						
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	Discontinued			
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	Discontinued				
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)
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]

[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

Test article was an emulsion containing 0.0001% Nelumbo Nucifera Germ Extract
It was tested as received

[redacted]

Sponsor

[redacted]

Sponsor Representatives

[redacted]

Clinical Testing Facility

[redacted]

Sponsor Code: [redacted]

Date of Final Report

5-26-09

[redacted]

[redacted]

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted]
Study Director

22 May 2009
Date

[redacted]
Principal Investigator

20 May 2009
Date

[redacted]
Medical Investigator

5/22/09
Date

[redacted]

QUALITY ASSURANCE STATEMENT

This study was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in CFR Title 21, Parts 50, 56 and 312 and/or the Declaration of Helsinki, as appropriate.

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.

This study report has been reviewed to assure that it correctly describes the methods of testing and that the reported results accurately reflect the data obtained during the clinical study ([redacted]).

[redacted]

22 May 2009
Date

Manager, Quality Assurance

[redacted]

[redacted]

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[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

Principal Investigator:
Medical Investigator:
Study Director:

[redacted]

5.0 STUDY DATES

Study initiation: April 1, 2009

Final evaluation: May 8, 2009

[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 March 12, 2009 and identified as follows:

[redacted] Entry No.	Test Article I.D.	Description
[redacted]	[redacted]	Pale Pink 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

Approximately 50 male or female subjects ranging in age from 18 to 79 years were to be empaneled 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 dermatological condition that would have precluded application of the test article or determination of potential effects of the test article.

[redacted]

9.0 TEST PROCEDURE

The 9 Repeated Insult (occlusive) Patch Test (9-RIPT) 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.

[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 (15 males and 40 females ranging in age from 18 to 70 years) were empaneled for the testing 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 panelist 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
1	[redacted]	70	F	CA
2		19	M	HS
3		43	F	AS
4		29	F	CA
5		38	F	HS
6		56	F	BA
7		64	F	CA
8		18	F	CA
9		40	F	CA
10		52	F	CA
11		69	M	BA
12		20	F	HS
13		51	F	CA
14		20	M	OT
15		61	F	CA
16		48	F	BH
17		43	F	CA
18		45	F	CA
19		38	F	HS
20		51	M	CA
21		61	F	CA
22		19	M	HS
23		47	F	CA
24		46	F	CA
25		62	F	HS
26		65	M	HS
27		49	F	HS
28		61	F	CA

Subject No.	Initials	Age	Sex	Race
29	[redacted]	52	F	CA
30		19	F	CA
31		51	F	HS
32		69	F	HS
33		56	F	CA
34		59	F	CA
35		59	M	HS
36		58	F	CA
37		42	F	CA
38		67	F	CA
39		69	M	CA
40		53	F	HS
41		25	F	CA
42		49	F	CA
43		18	F	CA
44		63	M	HS
45		61	F	CA
46		48	F	CA
47		46	M	CA
48		20	M	BA
49		59	M	CA
50		29	F	HS
51		64	M	CA
52		18	F	CA
53		56	M	HS
54		53	F	BH
55		29	M	HS

AS = Asian or Pacific Islander
BA = Black/African American
BH = Black/Hispanica
CA = Caucasian
HS = Hispanic
OT = Other

Shaded area = Discontinued subject

[redacted]

[redacted]

TABLE 2

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	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	Discontinued										
19	Discontinued										
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	0	0	0	0	0	0	0	0	0	0
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	0	0	0	0	0	0	0	0	0	0
30	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)
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]

[redacted]

TABLE 2 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	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	Discontinued	
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
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)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
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[redacted]