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

Status:	Draft Final Report for Panel Review
Last Panel Review:	August 15, 2025
Release Date:	September 8-9, 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.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. 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, and Thushara Diyabalanage, Ph.D. Scientific Analyst/Writer, CIR.

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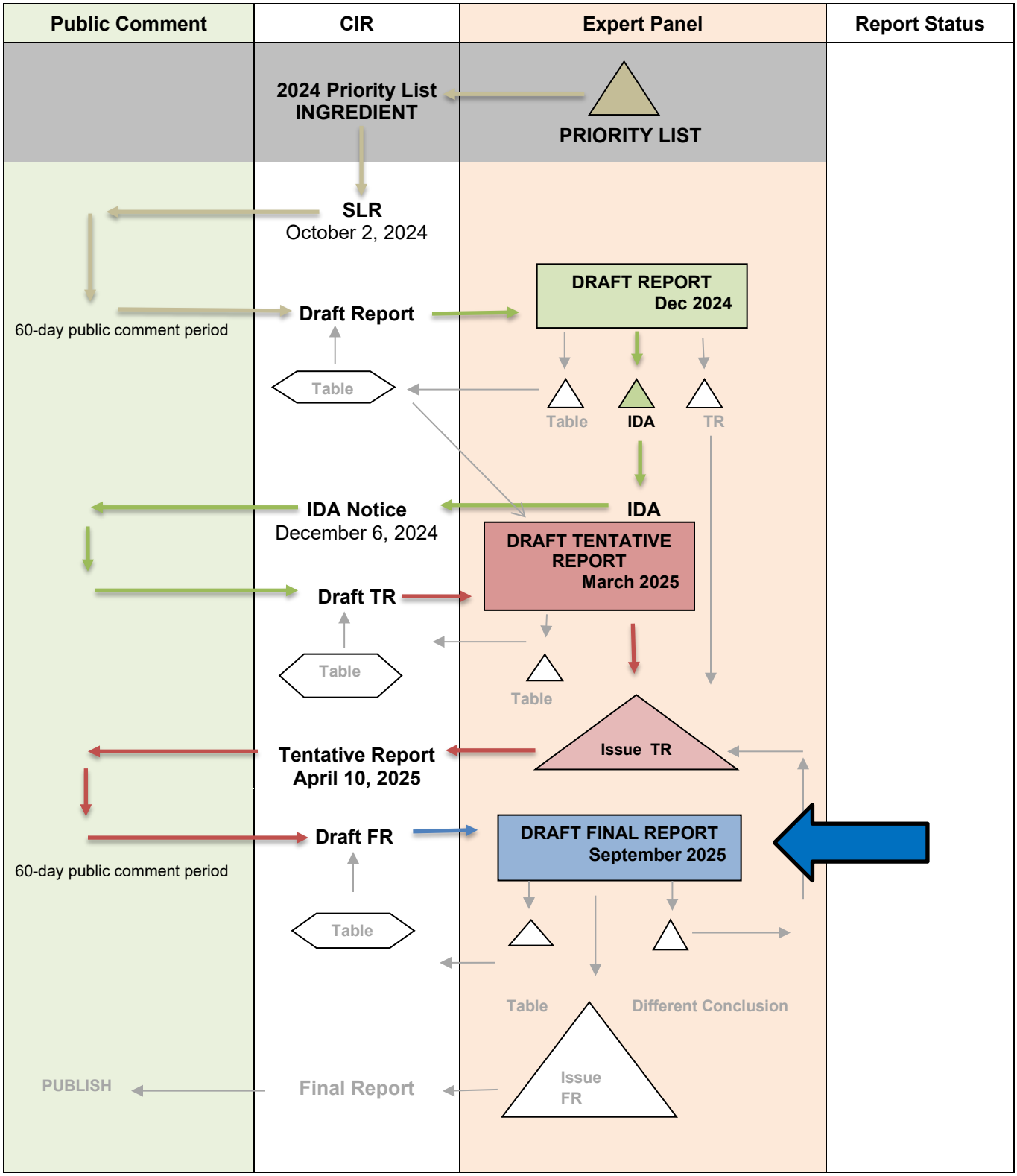
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Nelumbo nucifera* - Derived Ingredients

MEETING September 2025



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage, Ph.D.
Scientific Analyst/Writer, CIR
Date: August 15, 2025
Subject: Safety Assessment of *Nelumbo nucifera*-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Final Report on the Safety Assessment of *Nelumbo nucifera*-Derived Ingredients as Used in Cosmetics (It is identified as *report_NelumboNucifera_092025* in the pdf document). A Draft Report was submitted to the Panel in December 2024, for which the Panel issued an Insufficient Data Announcement (IDA). Subsequently, in March 2025, the Panel issued a Tentative Report concluding that the available data are insufficient to make a determination of safety for all 14 *Nelumbo nucifera*-derived ingredients. The Panel determined that the requirements listed in the IDA remained unmet and reiterated that following data are needed to arrive at a conclusion.

- For all ingredients
  - Composition and impurities
  - Methods of manufacturing
  - 28-d dermal toxicity data
    - if positive, additional data may be needed (e.g., development and reproductive toxicity data).
  - Ultraviolet (UV) absorption data (as well as more detailed information about the previously submitted UV spectra)
    - if absorbed, phototoxicity/photosensitization data are needed (additional protocol details are needed for the previously-submitted studies)
- For the callus-, phytoplacenta-, stamen-, and seed-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
- For flower- and whole plant-derived ingredients
  - Developmental and reproductive toxicity data
- For all except flower- and leaf-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*-derived ingredients, Correction received on April 23 (*data1_NelumboNucifera_092025*)
- P & K Skin Research Center Co., Ltd. 2011. Clinical safety evaluation study - repeated insult patch test of Nelumbo Nucifera Callus Culture Extract. (*data2_NelumboNucifera_092025*)
- Anonymous. 2023. Summary Information- HRIPT data for a serum containing 0.001% Nelumbo Nucifera Germ Extract (*data3_NelumboNucifera_092025*)
- Anonymous. 2025. Safety data of Nelumbo Nucifera Germ Extract short-time exposure (STE) test (OECD TG 491) (Raw material containing 1% Nelumbo Nucifera Germ Extract) (*data4_NelumboNucifera_092025*)
- Anonymous. 2025. Summary information- UV absorption of Nelumbo Nucifera Germ Extracts in water and butylene glycol. Corresponding UV spectra (with absorption maxima and solvents used) for the data submitted on January 2, 2025. (*data5_NelumboNucifera_092025*).

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

Comments received from the Council on the Draft Report prior to the last review and on the Tentative Report issued following the March meeting have been addressed (*PCPCcomments1_NelumboNucifera_092025* and *response-PCPCcomments1_NelumboNucifera_092025*, and (*PCPCcomments2_NelumboNucifera_092025 and response-PCPCcomments2_NelumboNucifera_092025*) respectively.

PCPC has also suggested clarifying as to why the Panel has not used the reported use of *Nelumbo nucifera* plant or parts as food to mitigate the potential systemic toxicity concerns, which is consistent with the strategy used in previous CIR reports involving edible plants. The Council requests that the Discussion include an explanation as to why the reported food use is not sufficient to address systemic toxicity concerns for of the flower-, germ-, leaf-, and root-derived ingredients.

The following supporting documents are also included in this package.

- search strategy (*search_NelumboNucifera_092025)*
- data profile (*dataprofile_NelumboNucifera_092025)*
- history *(history_NelumboNucifera_092025)*
- flow chart (*flow_NelumboNucifera_092025*)
- transcripts *(transcripts_NelumboNucifera_092025)*

The Panel should carefully consider and discuss the data (or lack thereof) and be prepared to issue a Final Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

	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
composition/impurities	N	N	N	N	R	N	N	N	N	N	N	N	N	N
method of manufacture	N	N	N	N	R	N	N	N	N	N	N	N	N	N
28-d dermal toxicity data	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UV absorption data; if positive, photosens/phototox	N	N	N	N	N	N	R	N	N	N	N	N	N	N
dermal irritation/sensitization	R						R		N			N	N	N
in vitro genotoxicity	N	N						N	N	N	N	N	N	N
DART		N	N	N	N	N								
in vitro ocular irritation	N	N					R		N	N	N	N	N	N

N – outstanding need; R – data were received/found; gray cell – not a data request for the ingredient

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).

March 2024- Insufficient data conclusion (IDA) for all 14 ingredients, Panel observed the data needs expressed in IDA was not fulfilled and re-iterated the same data requirements.

Data received:
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).
Personal Care Product Council. 2025. Concentration of use by FDA product category: *Nelumbo nucifera*-derived ingredients, Correction received on April 23.
P & K Skin Research Center Co., Ltd. 2011. Clinical safety evaluation study of three kinds of callus culture extracts by skin repeated insult patch test of Nelumbo Nucifera Callus Culture Extract.
Anonymous. 2023. Summary Information – HRIPT data for a serum containing 0.001% Nelumbo Nucifera Germ Extract
Anonymous. 2025. Safety data of Nelumbo Nucifera Germ Extract short-time exposure (STE) test (OECD TG 491) (Raw material containing 1% Nelumbo Nucifera Germ Extract)

Anonymous. 2025. Summary information- UV absorption of Nelumbo Nucifera Germ Extracts in water and butylene glycol. Corresponding UV spectra (showing absorption maxima) of the data submitted on January 2

Nelumbo nucifera -derived ingredients Data Profile* – September 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																			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	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	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] OR (nelumbo nucifera flower oil)

((((((((((((((((((((((((((((((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 (glycolysat 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/

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: March 4, 2025

SUBJECT: Draft Tentative Report: Safety Assessment of *Nelumbo nucifera*-Derived Ingredients as Used in Cosmetics (draft prepared for the March 13-14, 2025 meeting)

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

Key Issue

Cosmetic Use – Although the description of MoCRA in the Cosmetic Use section is better, it is still not very clear. The report currently states: "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."

We suggest the following changes (shown in red): "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was ~~terminated~~ discontinued in 2023, and as of 2024, manufacturers and processors ~~have been mandated~~ are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. ~~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, and the facilities that manufacture these products are not included in this exemption."

Additional Considerations

Cosmetic Use – Please correct: “200 fuses reported to the VCRP” (“fuses” should be “uses”)

Non-Cosmetic Use – Rather than saying that the various plant parts of *Nelumbo nucifera* are edible, perhaps it would be clearer to state that the various plant parts are used as food. This website on Thai cooking describes how some parts of the lotus are prepared https://shesimmers.com/2013/01/lotus-in-thai-cooking-culture.html . The following reference may also be useful.

Yang H, He S, Feng Q, et al. 2024. Lotus (Nelumbo nucifera): a multidisciplinary review of its cultural, ecological, and nutraceutical significance. Bioresources and Bioprocessing 11:18 https://doi.org/10.1186/s40643-024-00734-y .

Anti-Carcinogenicity – What concentrations/doses were associated with the effects in breast cancer cells and colon cancer cells?

Effects on Pigmentation – Units of µg/ml should be called concentrations rather than doses.

Photoprotective Effects, Nelumbo Nucifera Leaf Extract – In the description of reference 71, it is not clear what is meant by “maintained for 2 h up till the tenth day”. It would be clearer if “maintained” was replaced by “irradiated”.

Photoprotective Effects – Reference 23 states that the hairless mice were treated with a seed extract for 6-months before they were irradiated. Although they do not explicitly state that treatment continued during the additional 15-weeks during which they were irradiated, it appears that treatment continued. Rather than stating: “After the 6-mo treatment period”, it would be better to state it as it was stated in the paper: “After 6 months of treatment,”.

Dermal Irritation and Sensitization, Summary – Please correct: “was not an irritating to rabbit skin” (delete “an”).

More details of reference 9 (number of subjects and concentrations tested) should be included in the text.

Summary – Please correct “si it is included in this report” (“si” should be “so”)

Please revise: “(administered in drinking fluid for 6 mo)” to “(administered in drinking fluid for 6 mo before irradiation)”

Table 9, Nelumbo Nucifera Flower Extract – The high use concentration is listed as 0.13% and in the summary part of the table 0.13% is associated with “Nail”, but in the section by product category, no nail products are included (it should be in nail polish and enamel).

Nelumbo nucifera-derived ingredients – September 2025 – Thushara Diyabalanage	
Comment Submitter: Alexandra Kowcz, MS, MBA **Date of Submission: March 4, 2025**	
Comment	**Response/Action**
Cosmetic Use – Although the description of MoCRA in the Cosmetic Use section is better, it is still not very clear. The report currently states: "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." We suggest the following changes (shown in red): "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated discontinued in 2023, and as of 2024, manufacturers and processors have been mandated are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. 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, and the facilities that manufacture these products are not included in this exemption."	Addressed
Cosmetic Use – Please correct: "200 fuses reported to the VCRP" ("fuses" should be "uses")	Addressed
Non-Cosmetic Use – Rather than saying that the various plant parts of Nelumbo nucifera are edible, perhaps it would be clearer to state that the various plant parts are used as food. This website on Thai cooking describes how some parts of the lotus are prepared https://shesimmers.com/2013/01/lotus-in-thai-cooking-culture.html . The following reference may also be useful Yang H, He S, Feng Q, et al. 2024. Lotus (Nelumbo nucifera): a multidisciplinary review of its cultural, ecological, and nutraceutical significance. Bioresources and Bioprocessing 11:18 https://doi.org/10.1186/s40643-024-00734-y .	Addressed
Anti-Carcinogenicity – What concentrations/doses were associated with the effects in breast cancer cells and colon cancer cells?	Addressed
Effects on Pigmentation – Units of µg/ml should be called concentrations rather than doses.	Addressed
Photoprotective Effects, Nelumbo Nucifera Leaf Extract – In the description of reference 71, it is not clear what is meant by "maintained for 2 h up till the tenth day". It would be clearer if "maintained" was replaced by "irradiated".	Addressed

Nelumbo nucifera-derived ingredients – September 2025 – Thushara Diyabalanage	
Comment Submitter: Alexandra Kowcz, MS, MBA **Date of Submission: March 4, 2025**	
Comment	**Response/Action**
Photoprotective Effects – Reference 23 states that the hairless mice were treated with a seed extract for 6-months before they were irradiated. Although they do not explicitly state that treatment continued during the additional 15-weeks during which they were irradiated, it appears that treatment continued. Rather than stating: "After the 6-mo treatment period", it would be better to state it as it was stated in the paper: "After 6 months of treatment,".	Addressed
Dermal Irritation and Sensitization, Summary – Please correct: "was not an irritating to rabbit skin" (delete "an").	Addressed
More details of reference 9 (number of subjects and concentrations tested) should be included in the text.	Addressed
Summary – Please correct "si it is included in this report" ("si" should be "so")	Addressed
Please revise: "(administered in drinking fluid for 6 mo)" to "(administered in drinking fluid for 6 mo before irradiation)"	Addressed
Table 9, Nelumbo Nucifera Flower Extract – The high use concentration is listed as 0.13% and in the summary part of the table 0.13% is associated with "Nail", but in the section by product category, no nail products are included (it should be in nail polish and enamel)	Addressed

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: April 24, 2025

SUBJECT: Tentative Report: Safety Assessment of *Nelumbo nucifera*-Derived Ingredients as Used in Cosmetics (release date April 10, 2025)

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

Key Issues

Although Nelumbo Nucifera Flower Oil is not an INCI name, it is being included in this report because there are uses of this ingredient reported to the FDA. Internet searching indicates that lotus flower essential oil is an item of commerce. Therefore, Nelumbo Nucifera Flower Oil is likely an essential oil. If the Expert Panel agrees, it would be helpful if information on lotus flower essential oil was included in this report. For example, the following references (also attached) are helpful (especially for method of manufacture and composition information).

> Jeon S, Kim N-H, Koo B-S, et al. 2009. Lotus (*Nelumbo nuficera* [sic]) flower essential oil increased melanogenesis in normal human melanocytes. Experimental and Molecular Medicine 41(7): 517-524.
>
> Zhang C-Y and Guo M. 2020. Comparing Three Different Extraction Techniques on Essential Oil Profiles of Cultivated and Wild Lotus (*Nelumbo nucifera*) Flower. Life doi:10.3390/life10090209.

Method of Manufacture – Although details were not provided, a supplier indicated that Isostearyl Isostearate and a mixture of Propanediol (70-90%) and Glycerin (10-30%) were used as the extraction solvents to make their Nelumbo Nucifera Flower Extracts. This information should be added to the Method of Manufacture section.

Discussion – In CIR reports, usually use of a plant (or specific parts of a plant) as food is sufficient to address concerns about potential systemic toxicity. In the Discussion of this report,

it would be helpful if the Expert Panel provided an explanation as to why food use with the systemic toxicity data included in the report is not sufficient to address systemic toxicity concerns regarding flower-, germ-, leaf- and root-derived ingredients.

Additional Considerations

Abbreviations – Sodium should be added to the definition of Na-CMC. If this abbreviation is defined in the abbreviation list, it should be used in the text of the report in addition to being used in Table 10.

Composition and Impurities, Nelumbo Nucifera Flower Extract – Please check reference 9. Rather than containing the listed concentrations of heavy metals, arsenic and cfu/ml microbes, it is likely that the extract contained less than the stated values of contaminants.

Cosmetic Use – 211 uses were reported in leave-on face and neck products (not face and neck cleansing products as stated in the Cosmetic Use section). There were 43 uses reported in cleansing products which is a separate FDA cosmetic product category.

Please correct: “and in 2023, 200 uses reported in the VCRP in 2023” (delete one 2023)

Photosensitization/Phototoxicity – When available, please include the details of the light exposure (found in Table 13) in the text.

Ocular Irritation – Please correct: “Details on the ocular irritation and sensitization studies” (delete “and sensitization studies” as it does not belong in the Ocular section)

Summary – Please correct: “was not an irritating to rabbit skin” (either delete “an” or change “irritating” to “irritant”)

Discussion – In the UV data request, please correct “data are needed data” (delete the second “data”)

Table 11 – The information about the acute study in mice in the Protocol column (reference 60) should be moved to Table 10. “Swiss mice” should be deleted from Table 10 as mice were used in the acute study, not the 4-week study.

Table 12 – For reference 20 in the Animals/Group column, please note that the male rats were sexually mature, while the female rats were sexually immature at the start of the study.

Table 12 – In the Procedure column for reference 63, please describe the fertility testing (completed before the experiment and at days 55-60 controls and treated animals were mated 1:2 females).

Nelumbo nucifera-derived ingredients – September 2025 – Thushara Diyabalanage	
Comment Submitter: Alexandra Kowcz, MS, MBA. Personal Care Product Council **Date of Submission: April 24, 2025**	
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Although Nelumbo Nucifera Flower Oil is not an INCI name, it is being included in this report because there are uses of this ingredient reported to the FDA. Internet searching indicates that lotus flower essential oil is an item of commerce. Therefore, Nelumbo Nucifera Flower Oil is likely an essential oil. If the Expert Panel agrees, it would be helpful if information on lotus flower essential oil was included in this report. For example, the following references (also attached) are helpful (especially for method of manufacture and composition information). Jeon S, Kim N-H, Koo B-S, et al. 2009. Lotus (Nelumbo nuficera [sic]) flower essential oil increased melanogenesis in normal human melanocytes. Experimental and Molecular Medicine 41(7): 517-524. Zhang C-Y and Guo M. 2020. Comparing Three Different Extraction Techniques on Essential Oil Profiles of Cultivated and Wild Lotus (Nelumbo nucifera) Flower. Life doi:10.3390/life10090209.	Addressed. This information was added to the report.
Method of Manufacture – Although details were not provided, a supplier indicated that Isostearyl Isostearate and a mixture of Propanediol (70-90%) and Glycerin (10-30%) were used as the extraction solvents to make their Nelumbo Nucifera Flower Extracts. This information should be added to the Method of Manufacture section.	Addressed
Discussion – In CIR reports, usually use of a plant (or specific parts of a plant) as food is sufficient to address concerns about potential systemic toxicity. In the Discussion of this report, 2 it would be helpful if the Expert Panel provided an explanation as to why food use with the systemic toxicity data included in the report is not sufficient to address systemic toxicity concerns regarding flower-, germ-, leaf- and root-derived ingredients.	Panel should review this suggestion and make recommendations.
Abbreviations – Sodium should be added to the definition of Na-CMC. If this abbreviation is defined in the abbreviation list, it should be used in the text of the report in addition to being used in Table 10.	Addressed
Composition and Impurities, Nelumbo Nucifera Flower Extract – Please check reference 9. Rather than containing the listed concentrations of heavy metals, arsenic and cfu/ml microbes, it is likely that the extract contained less than the stated values of contaminants	That's correct. Industrial submission (reference 10) states that the presence of heavy metals in this product is unavoidable, but it does not indicate that it is beyond 10 ppm. The reference 9, a publication from a cosmetic manufacturer confirms it further.
Cosmetic Use – 211 uses were reported in leave-on face and neck products (not face and neck cleansing products as stated in the Cosmetic Use section). There were 43 uses reported in cleansing products which is a separate FDA cosmetic product category	Addressed
Please correct: "and in 2023, 200 uses reported in the VCRP in 2023" (delete one 2023)	Addressed
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Ocular Irritation – Please correct: "Details on the ocular irritation and sensitization studies" (delete "and sensitization studies" as it does not belong in the Ocular section)	Addressed

***Nelumbo nucifera*-derived ingredients – September 2025 – Thushara Diyabalanage**	
Comment Submitter: Alexandra Kowcz, MS, MBA. Personal Care Product Council **Date of Submission: April 24, 2025**	
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PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – December 2, 2024

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.

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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.

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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.

All righty. Coming to the next ingredient, Paeonia, Dr. Cohen.

MARCH 2025 MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – March 13, 2025

DR. SNYDER: Okay. The next one is *Nelumbo nucifera-derived* ingredients.

DR. BELSITO: Hey.

DR. SNYDER: Our favorites, huh? This is a Draft Tentative Report. Now let me get it open here first before I go into that. All right. Here we are. Okay. This is a Draft Tentative Report. In December 2024, we issued an Insufficient Data Announcement. And on Page 13 are all of the needs. Or Page 3, I'm sorry. Hold on, bear with me.

And on Page 3 are all of the data needs. And it's quite an extensive list. We received lots of new data. There were PCPC comments and they were all addressed already. So, where are we at with this report? Did we get everything we needed as far as the insufficient data announcement?

DR. BELSITO: I guess the first question that I have looking at this is I'm always -- I guess I'm still confused about when we get these reported food uses or traditional medicine. So, I'm on PDF Page 45 under non-cosmetic. So, where it says flowers, leaves, rhizomes, stems, and seeds are all edible and widely used in traditional medicine. Flowers are ornamental. Seeds are used in food. That's not GRAS, but do we accept it as data?

Do we accept that use to exonerate us from looking at systemic toxicity endpoints for those particular parts of the plant? Because, remember, we did this GRAS thing, and then Europe had another designation. Priya probably remembers what that was, like PLR or something. I forget what it was. But here it's just saying that it's used traditionally. Do we accept it?

DR. SNYDER: I guess typically we have. Right?

DR. BELSITO: I think we have. I'm just bringing it up for a discussion again because, if we do, then those systemic endpoints for those parts of the plant sort of go away. Right?

DR. SNYDER: Yeah.

DR. BELSITO: And we're not concerned about impurities and all that other stuff.

DR. RETTIE: I lean towards accepting it for those particular pieces of the plant that are widely consumed. Doesn't mention Europe, but traditional medicine in Southeast Asia for the most part. There's a lot of information over thousands of years probably embedded in there.

DR. BELSITO: So, you are happy accepting those as being food edible?

DR. RETTIE: Yeah. I'd lean that way. I'd like to hear what the other team thinks and our team.

DR. KLAASSEN: Well, I guess it gives some confidence. One of the problems is that we don't know how much of this they're eating. Is this a main ingredient, like potatoes, or is it a minor thing that they at most sprinkle on their food?

DR. SNYDER: Yep.

DR. KLAASSEN: So, again it's always the potential problem with the dose.

DR. ZANG: May I just add another question to that because, yeah. We also don't have the proper information. Sometimes the chemical composition of light versus raw foods are different.

DR. KLAASSEN: Right.

DR. ZANG: And then, if we don't have the manufacturing information, we might not be certain.

DR. SNYDER: Did you hear that, Don?

DR. BELSITO: Yeah. The compositions could be completely different, essentially is what she said.

DR. SNYDER: Based on the method of manufacturer. Yeah. Without method of manufacturer data. Yeah. Well, I guess do we want to go out for method of manufacture and composition?

MS. FIUME: So, that's been asked for all the ingredients already.

DR. SNYDER: I know.

MS. FIUME: So, are they all insufficient for that? Oh, are you asking are they all insufficient for that?

DR. SNYDER: Yeah. Right. Yeah.

DR. RETTIE: They were last time, and we got nothing.

DR. SNYDER: Yeah. So, we're still going IDA, Don?

DR. BELSITO: I mean, if we're not willing to accept these reported food uses from Asia, then yeah. I think we need that data. Right?

DR. SNYDER: Yeah.

DR. BELSITO: Also concerned there's ultraviolet absorption. I didn't understand what was being said. This is PDF Page 44, for the germ abstract. It says that the absorption was determined according to industry submissions. Three trade name mixtures that consisted of the germ extract in water and butylene glycol of maximum absorption at 272 and 273. That's nice. Well, 273 gets close to 290.

How far does that tail go out into the UVB, possibly UVA range? So, that's not an acceptable UV spectra. We need the whole spectra here, not just the absorption peak. Right?

DR. SNYDER: Yep.

DR. RETTIE: Yeah. That was my note too.

DR. BELSITO: So, it's also insufficient for UV absorption.

DR. SNYDER: Okay.

DR. BELSITO: And then, I had a question on PDF Page 40, under method of manufacture for plant part extracts, the second paragraph. It says something about preparation of crude food extracts, the fruit of the lotus. What is the fruit of the lotus? I didn't know lotuses had fruits. It's also not listed as an ingredient.

MS. FIUME: We can double check that citation, Don.

DR. BELSITO: Okay. And then, on PDF Page 42, under composition, the first line, it says that main chemical classes of compounds are proteins, amino acids, and steroids. What classes of steroids? There are multiple different classes. Are they like anabolic steroids? What kind of steroids are these?

DR. SNYDER: So, we'll get clarification of that also.

DR. BELSITO: Yeah.

MS. FIUME: So, I'm sorry, which page?

DR. SNYDER: Page 42, under composition and impurities. The first line lists proteins, amino acids, and steroids, mostly in the seeds.

MS. FIUME: Okay. Okay.

DR. SNYDER: But steroids is just kind of a general. So, we'd like to have a little bit more specific of what classes of steroid.

DR. BELSITO: Yeah. Do they say what kind of steroids are they?

DR. SNYDER: Yeah.

MS. FIUME: Okay. Don, I was looking. I do want to clarify. The title of the reference does say lotus fruits, extracts of lotus fruit. So, I don't know. I can look at the paper later and see if it actually defines what the fruit is. But that is in the name of the title of this, of the reference.

DR. BELSITO: Okay. Maybe there is a fruit to the lotus that I've never seen.

MS. FIUME: Oh, Priya just said there is a fruit that grows on the plant, but it's not listed.

DR. BELSITO: Okay.

DR. SNYDER: But it's not listed as an ingredient, right, in the ingredients list?

DR. BELSITO: No.

MS. FIUME: But in the ingredient, *Nelumbo nucifera* extract, if that is the extract of the whole plant, it could include the fruit.

DR. SNYDER: We're just going to make sure that we have that, that the fruit is included in the list of ingredients that are used.

MS. FIUME: So, *Nelumbo nucifera* extract is the extract of the whole plant. So, usually that includes --

DR. BELSITO: Okay. And we need the fruit.

DR. SNYDER: Okay.

DR. BELSITO: And, on PDF Page 48, the inhibitory effects on atopic dermatitis formation and inflammation, this is not atopic dermatitis at all. It's delay-type hypersensitivity to DNCB. So, where's the atopic dermatitis come in?

DR. SNYDER: I think that's a typo. But yeah. Where did that atopic come from because that's not atopic?

DR. BELSITO: No, it's not. It has nothing to do with atopic dermatitis. It's inhibition of the induction of sensitization to DNCB.

DR. SNYDER: Yeah.

MS. FIUME: We will fix that.

DR. BELSITO: So, we have some issues with botanical boilerplates, heavy metals, skin lightening effect. And then, I had a question on PDF Page 49 about anti aging in fibroblasts. I didn't think that needed to be mentioned in a discussion. But I just wanted to bring it out for others. Thoughts?

DR. KLAASSEN: I agree with you, Don.

DR. RETTIE: Yeah. It's out of place.

DR. SNYDER: So, just remove that whole section?

DR. BELSITO: No. I think we can leave the section in. I just don't think it's a discussion item.

DR. SNYDER: Oh, okay.

DR. BELSITO: And then, on PDF Page 50, there's a phototoxicity study that's under dermal irritation and sensitization. Shouldn't that be a separate heading? The last study for the germ extract did not indicate phototoxic potential in vitro. It was not phototoxic or photosensitizing in guinea pigs.

MS. FIUME: So, when we do the tables and we summarize under the section, we don't include the subheadings. And photosensitization and irritation is a subsection of the irritation and sensitization main heading. Which is why it would not have its own subheading right now because they're all in the same table, typically.

DR. BELSITO: But this isn't a table. This is the written report.

DR. SNYDER: Right.

DR. BELSITO: This is PDF Page 50.

DR. SNYDER: Yeah.

DR. BELSITO: The paragraph right above ocular irritation study. I thought we typically had a separate heading for photo.

MS. FIUME: We would if all of the studies were described in full in text. But, because the phototox is part of the table, it's only given as a paragraph. We don't normally include irritation.

DR. SNYDER: Split it out.

DR. RETTIE: We don't normally split it out. But we can add it if you would prefer the clarification and just say that these are also described in that table. So, we could add a subheading.

DR. KLAASSEN: I would prefer that, myself.

DR. BELSITO: Go ahead and put it under subheading because otherwise you can use it.

MS. FIUME: So, Don, going back because I'm reading through the draft Discussion briefly. So, you said that the anti-aging should not be mentioned. It's not mentioned there now. Right?

DR. SNYDER: Yeah. Right.

MS. FIUME: It just does not need to be brought in?

DR. SNYDER: Correct.

DR. BELSITO: Yeah. I don't think it needs to be brought in.

DR. SNYDER: Yeah.

MS. FIUME: So, is there anything that needs to be brought into the discussion as we go forward? I mean, besides the insufficiencies will, but the other. Right? You had mentioned the heavy metal.

DR. BELSITO: Skin lightning, metal, and botanical boilerplates were what I had in Discussion.

MS. FIUME: Okay. So I think we're missing the skin lightning now.

DR. BELSITO: Right. If we're discounting the food use for the flower, leaf, stem, root, and seed, we do have a four-week oral on the whole extract and a 90-day on the stamen extract. So, are those data okay for systemic effects? Because, if they are, then we can clear those maybe.

DR. SNYDER: I think that goes back to the method of manufacturer in a composition, right, or insufficiency because they're all different compositions?

DR. BELSITO: Well, we're never going to know what the composition. I mean, even if we got the composition, right, are we going to know that the four-week oral on the whole extract was exactly the same composition that we're told on something else?

DR. SNYDER: Oh, that's true. Okay.

DR. BELSITO: Or a 90-day on the stamen extract? I'm just pointing this out. We have four week's systemic data on the whole extract and 90-day on the stamen extract. And, with that, clear systemic effects because they were funneled.

DR. SNYDER: I think so.

DR. BELSITO: But we don't have sensitization and irritation on the stamen extract. But if we clear the whole extract --

DR. SNYDER: Yeah. yeah.

DR. BELSITO: We clear the whole extract on the four week, why are we concerned about parts? Philosophical question. I don't know where to go with this. I spent a hell of a lot of time on this ingredient.

DR. SNYDER: Yeah. These are difficult.

MS. FIUME: So, can I ask, when you clear typically, because you have tox data and so you're clearing impurities, you generally know the purity of the test ingredient, right, in order to be able to clear it for method of manufacturing impurities. So, being that this is a botanical, does that still follow?

DR. SNYDER: Yeah. I don't think so.

DR. RETTIE: I don't think so.

DR. SNYDER: No, I don't believe so. Do you, Don?

DR. BELSITO: I mean, that's always the problem. Right? I mean, we can get composition for the whole extract from one company. And then, we get data on a four-week oral on the whole extract. Do we know it's the same, the same whole extract that we got the composition on? Typically, we don't. Right? I mean, that's always the conundrum with these botanicals.

DR. KLAASSEN: Yeah. This is not a new problem. It's a problem that we've had with all the botanicals. And one of the things with botanicals, they can also, as was mentioned earlier, can have different compounds within them at different times of growth, if it's a wet season or a dry season.

DR. SNYDER: Yeah. What stage of the growth, which phase it's in? Yeah.

DR. KLAASSEN: Yeah. And it's just so complicated that I think we kind of bend over backwards to try to help them. We really don't know the chemicals, and we don't know the dose. Other than that, we're pretty good.

DR. SNYDER: So, I guess my synopsis of all of this discussion is we're still insufficient data for the UV absorption, right, because all we have is UV absorption.

DR. BELSITO: That's right.

DR. SNYDER: That's it. The rest of it, we're saying that the food use is edible. Traditional medicine use clears a lot of our concerns about systemic toxicity endpoints and impurities. And then, the rest of it's pretty much all editorial. Right?

DR. BELSITO: Yeah, except that we still need data for the callus culture, the phytoplacenta culture, and not sure about germ extract. I mean, I think the germ extract is covered by the whole extract. Right? Well, we definitely need 28-day dermal on callous culture and phytoplacenta culture. And then, we need sensitization and irritation of callus culture extract, phytoplacenta culture, seed and stamen extract, because we don't really know how we can read-across from these plant parts. Right?

I mean, I don't think we have really good composition data for one part against the other. At least that was my take. I mean, we have all this data, like flavonoids and terpenoids. And they don't really seem to be all that similar. But we don't have really very detailed data telling us what the composition is. All those tables are like, okay, these are the flavonoids. These are the blah, blah, blah. I mean, that was my take. I'm open to other people. Do we have enough? Are you happy with all those tables like alkaloids and flavonoids?

DR. RETTIE: It's difficult to be happy with them. I understand why that's what we've got because maybe that's all we can get. But it's not enough detailed data to do the read-across thing that we typically do and we'll probably never be able to do for the botanicals.

DR. SNYDER: Right.

DR. BELSITO: Right.

MS. FIUME: We do stipulate when we do the priority list that the discrete chemicals are grouped for read-across. The botanicals are grouped because they're from the same genus and species. But it doesn't necessarily mean there's read across.

DR. RETTIE: I mean, parts of a given plant can be totally poisonous, and other parts can be very tasty. I mean, what would you do with that?

DR. BELSITO: So, I don't think we can read across with sensitization and irritation. So, we need that for the callus culture extract, the nucifera extract, the phytoplacenta culture, seed and stamen extracts. We don't have sensitization and irritation on those.

DR. SNYDER: Yeah. It's the original list there on Page 3, yeah, the callus, phytoplacenta, and stamen. Yeah.

DR. BELSITO: Yeah. So, we need a 28-day dermal on callous culture, phytoplacenta culture. Sensitization and irritation we just mentioned. And we need more data on the photo. Right?

DR. SNYDER: Yep.

MS. FIUME: So, I have the list correct. So, the photo absorption is for all. The 28-day dermal tox is for the callus culture and phytoplacenta culture. And sensitization and irritation is for the whole plant extract, the seed, and the stamen ingredients. Is that correct?

DR. BELSITO: And the phytoplacenta culture and callous culture.

DR. SNYDER: Yeah.

DR. RETTIE: Nobody's mentioned genotox data? That was an insufficiency the last time. We kind of danced around whether we could clear systemic toxicities. But I thought we'd come down on the side of not being able to do that. So, is genotoxicity still an insufficiency for all of the things it was an insufficiency for last time?

MS. FIUME: Which is all the ingredients for the in vivo.

DR. RETTIE: All, except the flower and germ for in vitro.

DR. BELSITO: And the photo data that we got, this is PDF Page 77. It was just all summary data from the company saying, okay, it wasn't phototoxic or photosensitizing. We don't have their protocols at all. It's just a statement by them. Is it possible to ask them for their actual protocols for phototoxicity and photosensitization so that we could determine whether they were valid?

MS. FIUME: We can.

DR. SNYDER: We might as well ask for it. We're going out insufficient.

MS. FIUME: But it's a tentative report insufficient.

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

MS. FIUME: I mean, we can put that in our -- we can note it when we send it out.

DR. SNYDER: Okay.

MS. FIUME: I think, as you know, we've done it before. We can do it again. Sometimes when we get the summary info, that's all we get. Once in a while, they'll send us additional details, but we can always state that it's needed.

DR. BELSITO: Yeah. I think, particularly given the fact that we're very concerned that this could, you know, go into a region where phototoxicity and photosensitization could be an issue, I would like to see those protocols and not just have a summary telling me they weren't phototoxic or photosensitizing.

DR. RETTIE: So, the minimal data that we have in that Table 13 for humans is only for flower water and root water. We're missing a whole lot of the plant.

DR. BELSITO: Oh, yeah. I agree. But even then, Allan, when you go to the -- I don't know where the PDF page is here. The data that is based on is -- yeah. So it's, I think, PDF Page 90, phototoxicity and Photosensitization. It's just a summary. 26 subjects, non phototoxic, not photosensitizing, period. Amen.

They don't tell us how they did this study. The induction phase, they used 290 to 399 nanometers. I mean, was this a real -- phototoxicity I'm less concerned about, but photosensitization, what was that protocol?

DR. RETTIE: Fair enough.

MS. FIUME: So is it for all because, on Page 89, it does list the induction phase, what the UVB and UVA ranges were. I guess it's easier to ask for details on all than try and pull it out here and there.

DR. BELSITO: Well, in a photosensitization study, how were they doing it? How was the material applied every other day? When was it irradiated? You know, after the induction phase, when was the elicitation phase done? None of that information is there. They gave a good amount of UVA light. Five joules per centimeter squared is pretty standard. Some people use ten. They used three quarters of an M.E.D of UVB. But I don't know how often the material was applied and irradiated.

In a phototox study you put it on once, you irradiate it, you see if there's erythema, and you're done with it. But, photosensitization, you know, it's an HRIPT with photo. Right? And that data is not there.

MS. FIUME: So, since it's a list of the insufficiencies, that couldn't be listed as insufficiency as detail --

DR. SNYDER: Yeah.

DR. RETTIE: Sure.

DR. SNYDER: Yeah. Yep.

DR. BELSITO: Yeah. I would just like to see what their protocol was for photosensitization.

DR. SNYDER: So, we're still insufficient data. We cannot read across for sensitization. So, we still have those needs for sensitization we just discussed. We also need 28-day dermal on the phytoplacenta, the callus culture, and the stamen-derived ingredients. We need more information on the UV data, on the protocols and how they were conducted with regard to induction period, how often it was applied, irradiation, et cetera. Is that it?

DR. BELSITO: Yeah.

DR. SNYDER: Oh, I'm sorry. Is that it?

MS. FIUME: Yeah. So, you said the sensitization, irritation, the 28-day dermal, UV absorption spectra, and the details.

DR. SNYDER: Yep.

MS. FIUME: Okay.

DR. SNYDER: Okay.

DR. RETTIE: Do we have a rule that we only have one botanical per meeting?

DR. SNYDER: Exactly.

DR. RETTIE: Could we have a rule?

DR. SNYDER: We should.

MS. FIUME: I wish. I wish.

DR. SNYDER: Well, I think we'll take a break there. It's ten minutes to 12, and the next one is another botanical. So, I don't think we can get it done in ten minutes. So, I think we'll take a break. Reform at 1:00. Is that okay? You all right, Don?

DR. BELSITO: Sounds good. Thanks, Paul.

DR. SNYDER: Okay. buddy. Thank you. Don't get used to this now, you're not staying home.

DR. BELSITO: Paul, believe me, I wish I were there.

DR. SNYDER: Oh, tonight you will be sadly missed. Tonight you'll be sadly missed at dinner. It's always one of my favorite times, interacting with the Panel. All right. We'll see you at 1:00.

DR. BELSITO: Okay. Take care.

Cohen Team - March 13, 2025

DR. DAVID COHEN: All right. So *Nelumbo nucifera*-derived products, of which there are many.

In December, we issued an Insufficient Data Conclusion on the 14 *Nelumbo nucifera*-derived products. Among them, one common is the flower oil is not included in the dictionary. We have reported uses in 2023 from the VCRP database and in the RLD. And that's in the manuscript.

We issued a highly-comprehensive IDA with the following requirements: For all ingredients, composition and impurities, method of manufacturing, 28-day dermal tox, and, if positive, further DART and genotox. We wanted dermal irritation and sensitization at max use for the phytoplacenta and stamen-derived ingredients. And for all except the flower and germ, we wanted genotox for the flower and whole plant developmental and repro tox and flower in vitro ocular irritation. We received just a little bit of information.

I must say, I had a difficult time going through this. But I just want to open up that when you search online, virtually every part of this plant is edible. In fact, I couldn't find anything to suggest that there was a part of the plant that wasn't edible. Like, the entire plant is eaten. And so, when I looked at this, I said is this like the yeasts or other things we've done where we have edible products and then we just ask for irritation and sensitization data of some sort?

So we have in vitro sensitization data on germ extract. We had HRIPT on flower extract, flower water, germ extract, leaf extract, root water. Maybe some of the details on these we can get a little bit more on because it said details weren't available. But do we need all this information? Or can we go to clearing these things on its food use and irritation and sensitization understanding that there's some other toxicity, toxicology things we would have to talk about?

David, you looked the most puzzled just now, so we'll start with you. I'm kidding.

DR. ROSS: That's my natural state. But yeah. With botanicals, I'm guaranteed to be puzzled with botanicals. But, yeah.

I'll be brief because I think we might have fairly lengthy discussion about some of these things. But if I stick to the high points here, I think we're still missing many of the maximum concentrations of use. The ones I've listed that I didn't see were callus culture extract, nelumbo nucifera extract, flower oil, germ extract, phytoplacenta culture, root water, seed extract, seed powder, and stamen extract. So that's quite a long list. We don't have concentrations of use there.

I think we need irritation and sensitization on all extracts that are either unreported or where we don't have maximal concentrations of use. We need max concentrations of use, and we need irritation and sensitization where it's not reported.

DR. DAVID COHEN: Just one comment.

DR. ROSS: Go ahead.

DR. DAVID COHEN: If we don't have concentration of use, but we have concentration of the sensitization data --

DR. ROSS: So you got data but no concentration of use. Yeah.

DR. DAVID COHEN: Yeah. Do you not just anchor to the HRIPT concentration data that we have and say that's the concentration we'll clear? We can still ask for the concentration, but at the next meeting, if we don't get it, are we not clearing it with all this data? It's food. We have HRIPT at specific concentrations. Why wouldn't we clear that?

DR. ROSS: Yeah. I think that's a reasonable approach if you can't get your concentration. We asked for the concentrations last time, right, and we didn't get them. Is that correct?

DR. DAVID COHEN: We asked for just about everything last time.

DR. ROSS: Yes. Yes.

DR. DAVID COHEN: We asked for like the full report almost.

DR. ROSS: Well, those were my comments. A couple of major issues that the missing concentrations of use to irritation and sensitization.

And then a little bit lower priority down the list, I had a couple of comments. It was difficult to judge the DART effects with the seed extract because that was a pretty low dosage, 7.5 mgs per kg, since again we got no maximum concentrations of use with seed. And I think a comment I made last time, flower contains some of the alkaloids flavonoids as the seed but no DARTS. But do we really need it since we have many, many years of food use, which gets to your point.

DR. DAVID COHEN: Yeah, and people eat the seeds.

DR. ROSS: Yeah. It's to your point, David. So maybe we don't need that. So maybe we just focus down on the irritation and sensitization. And then there was some skin whitening concerns, and I wanted your comments on that, David.

DR. DAVID COHEN: Yeah, okay.

DR. ROSS: With three extracts, leaf, flower and callus.

DR. DAVID COHEN: I think we put it in the Discussion.

DR. ROSS: Yeah. But anyway, those were mine, so I'll leave it there. And I do have a table of what we're missing: sensitization and irritation if we get that far down the line here.

DR. BERGFELD: So you're suggesting that, in the Discussion, we put that on the insufficient list, but we also say this is a food? We can't say it's GRAS. It's not GRAS. And so it then delineates that we don't need all the tox data?

DR. ROSS: I'm not sure we don't need all the tox data. I mean, I ask the question in here that we don't have some of the tox data because it's many years as a food, include a need for that? I'm not sure the answer to that if we'll know until after this discussion.

DR. BERGFELD: Well, it's certainly a discussion point.

DR. ROSS: Yeah. Yeah.

DR. DAVID COHEN: And if we do anchor to the HRIPTs, they're very low concentration challenges, aren't they?

DR. ROSS: Yes.

DR. DAVID COHEN: Irritation of these are 1.21 and a half percent and the sensitizations are 1 percent, 1.5 percent.

DR. ROSS: And 2.15, 3. And we have data with no maximum concentration of germ root water and seed, and the sensitization for those extracts was 2.5 and 1.5 percent. So yeah. We can probably, as you pointed out, really, anchor back to that. So yeah. That's okay because we have the data.

DR. DAVID COHEN: Right. We have that data, and that's right. So it's almost if the concentration of use was below that, it would be immaterial. If the maximum concentration was below that, we wouldn't stop, right?

DR. ROSS: Correct.

DR. DAVID COHEN: And if it was above it, we wouldn't clear it, perhaps, without -- we would go back and say we want irritation and sensitization at max use. If we don't get that, well, this is what everyone's stuck with. But it doesn't hold up because on this pathway, it's not going to ever clear from what I can gather.

We asked for a lot. We got back very little, right? The new report doesn't have much yellow in it, right? And it just dawned on me that this is going to get stuck for not good reasons.

DR. ROSS: It would be really nice to have in there a table which says what the extract is in its maximum use, another column with what's being tested for sensitization, and another column of the percentages that have been tested for irritation.

DR. DAVID COHEN: Yes, we had that for yeast and we had that for coral, right?

DR. ROSS: That would be great.

DR. DAVID COHEN: Because it gets too difficult to put it in your head what we need. So you get what I'm saying. If you looked at some of the -- coral, I think -- do I have it right, Bart -- the coral and yeast had that, like, the report?

DR. HELDRETH: Yeah, the yeast, specifically, and algae had these.

DR. DAVID COHEN: Yeah, the algae, the algae, yeah.

DR. HELDRETH: Had these tables that helped mitigate systemic tox. It felt like food use was going to expose the consumer way more than they could possibly get from the cosmetic product than we deemed that the systemic toxins was mitigated. If a product wasn't in food use in those reports, then we wanted a 28-day dermal.

DR. DAVID COHEN: That's exactly how we had it. So it was a column that was food use, yes or no. If it was yes, we cleared tox. If it was no, then we wanted a tox. And then on the other side, it was, did we have HRIPT or some sensitization data, yes or no? If it was yes and yes on the other column, it was cleared, right?

In this case, I think in the table, we would want a concentration of the HRIPT because it may be we're setting max use using that if we don't get that. Is that right? Yeah, that sounds correct.

DR. HELDRETH: Yeah, I mean, absolutely. I mean, historically in a situation like this where it seems like sensitization is kind of the point of departure there, and they're not concerned about the other ones, historically, the Panelists just either went down one of two pathways. They said, all right, safe as used up to 2 percent. And in the Discussion they explain it's based on the HRIPT we have and so forth.

Alternatively, in situations where the highest concentration of use is below that, but we're concerned about other products where we don't have a concentration of use, the conclusion will just be safe as used but have this caveat, this little asterisk, saying we expect other products or other ingredients in this report to be used in similar products and concentrations of use as the ones in this report. So you have a couple of options there, historically.

DR. DAVID COHEN: So why don't we -- if we could get, Susan?

DR. TILTON: So with regard to historically, my short time on the committee so far, we have utilized food use to mitigate concern about systemic effects. And so I would support doing that in this case. We can focus primarily on sensitization and irritation.

If we are to do that, it certainly would help to have this organized in a way where we could see that information by ingredient. But then can we move to a discussion to talk about going ahead and moving forward with some of the ingredients that have that data currently?

DR. DAVID COHEN: You mean give the issue safe as used now? Is that what you mean?

DR. TILTON: Yes. We're at a tentative report, right? Where are we?

DR. DAVID COHEN: Yeah.

DR. HELDRETH: It's a Draft Tentative Report.

DR. DAVID COHEN: This is a draft tentative.

DR. HELDRETH: So you could issue a tentative report. If you had new data needs, you could issue a new IDA.

DR. DAVID COHEN: Well, fortunately our original IDA was pretty comprehensive, right?

DR. TILTON: Although I don't think we asked for concentration.

DR. BERGFELD: I did see that risk, but I don't see it now.

DR. DAVID COHEN: We did.

DR. ROSS: Yeah, we did.

DR. DAVID COHEN: Did we?

DR. TILTON: Yeah, we did switch it.

DR. DAVID COHEN: I don't see it.

DR. SAMUEL COHEN: No, just composition and manufacture and concentration.

DR. DAVID COHEN: There it is.

DR. BERGFELD: It's a composition and impurities but not concentration.

DR. ROSS: I think you should ask for concentration.

DR. DAVID COHEN: So we're issuing a new insufficient data, right?

DR. BERGFELD: Yeah. In December we said composition and impurities, but we didn't include concentration. Do you want to see it?

DR. DAVID COHEN: No, I see it. No, I see exactly. Yeah, I think -- was this the one where, right, Don couldn't pull it up on his computer. We were going back and forth on it. Was that this one? I'm not sure because we had so many on the list.

DR. HELDRETH: I mean, so you're left with a few options. You could do a new IDA if you think there's a reasonable chance we'll actually get that concentration of use data.

If we really don't think that's going to come in for those other ingredients, since it hasn't come in so far, we may be spinning our wheels and waiting on it when we could come out with a safe with qualifications, safe up to 2 percent, base it on the HRIPT, or have a conclusion that safe as used with the caveat of similar uses and concentrations of other products. But it's the Panel's prerogative.

DR. DAVID COHEN: I think Susan's point is really good. We could start clearing things now. And in the Discussion, say we don't have concentration of use. This is what we're clearing, this concentration.

DR. BERGFELD: Two percent.

DR. DAVID COHEN: Well, no. I think it would be at the percentages of the HRIPTs. That's our only anchor, right?

DR. HELDRETH: Right. Yeah, you have to have a solid rationale for it. We get dinged on having an arbitrary number. Here we have the HRIPT results that are very telling.

DR. DAVID COHEN: No, I think quite the opposite. It's very specific.

DR. HELDRETH: Right.

DR. DAVID COHEN: All right, so Susan, can I come back to you on this, and then we'll conclude our tentative conclusions? Sam, what did you have?

DR. SAMUEL COHEN: Some minor points in addition to what you've already done. It listed as kind of a cure-all for all and everything. It was immunomodulatory, anti-inflammatory, it was going to cure everything, but I think that could be ignored.

But there was some animal studies with reproductive toxicity, and I didn't know how to interpret that. And I couldn't put the concentrations in perspective of what would be absorbed from cosmetic use. It seemed like we still had a decent margin, but I didn't know how to address that.

The only other comment I had was that it states in composition that it contains steroids. That always raises concerns when you say steroids, so I think it would either qualify by saying to plant steroids or even sterols to avoid the word steroids completely. Just the connotation that it could raise alarms. So, I think just using sterols instead.

But I would be interested in what the comments are of others about the reproductive tox. I don't think it's a concern, but I really couldn't interpret that myself.

DR. ROSS: Yeah. I meant to comment on the seed extracts. Was that the one you were referring to?

DR. DAVID COHEN: Yeah. You talking about the DART on the seed?

DR. ROSS: Yeah. And again, I just found it difficult to interpret since we didn't have a maximum concentration of use.

DR. DAVID COHEN: Well, what concentration of use would concern you?

DR. ROSS: Well, you need relate somehow the 7.5 mgs per kg where you're seeing effects.

DR. DAVID COHEN: This is the seed oil, right?

DR. ROSS: Seed extract.

DR. DAVID COHEN: Seed.

DR. ROSS: I think your original IDA, if I amalgamate Susan's comments with David's here, of listing, anchoring back to the irritation and sensitization, listing the percentages you have in that table and clearing and all based on that percentage. And I mean, you can do that with the caveat of Sam's point of how do you interpret some of this DART data because I think we're close on this one in terms of getting the data we need but not quite there.

So what would we do? You can ask for maximum concentrations of use in an IDA, or you can list what you have, clear everything you have based on irritation and sensitization.

DR. DAVID COHEN: That's what we would clear anyway.

DR. ROSS: Yeah. I don't think we'll get much more data on this. We asked for an awful lot in the first time through, but we didn't ask for concentrations of use.

DR. DAVID COHEN: We did not. We asked for a lot of stuff and got very little back, which may suggest we might not get a lot back. But again, even if the concentration that was used was 3x the sensitization and irritation, we would go back and say, we want sensitization and irritation at max use. We may or may not get it, but we already have some now.

DR. ROSS: So your argument is you clear up to those concentrations?

DR. DAVID COHEN: Yeah.

DR. ROSS: And I think that's okay.

DR. DAVID COHEN: Let's move it along because I suspect we could. Additional IDAs will slow the process down unnecessarily. And these are very labor-intensive reports. And so, if they come back in six months, we have to read it all again.

And this has nothing to do with conservation of time, effort, or wellness. It's got nothing to do with that. It just won't add anything. It doesn't protect the consumer anymore, which is what our real goal is.

DR. ROSS: But there are some, David, where you don't have sensitization at all.

DR. DAVID COHEN: Right. The seed oil, right?

DR. ROSS: And the root.

DR. DAVID COHEN: We're not clearing those.

DR. ROSS: We've got irritation on the root at 1 percent, but at least my table that I have here says that I don't have sensitization on the root.

DR. BERGFELD: You have on your Table 3, though, root water.

DR. ROSS: Yeah.

DR. DAVID COHEN: If we have root water, we just have to -- what did you say you wanted root what?

DR. ROSS: Root.

DR. DAVID COHEN: Just root?

DR. ROSS: Just root. Root extract.

DR. DAVID COHEN: We should look at method of manufacturing.

DR. ROSS: Yeah. Powders weren't derived from root water from the roots. This is particularly the reason we don't want to see this again.

DR. TILTON: And the question is, can some of these be grouped?

DR. ROSS: Yeah. Good point.

DR. DAVID COHEN: We don't have a root water --

DR. TILTON: We can't group this.

DR. DAVID COHEN: -- method of -- we don't have anything on the root in method of manufacturing?

DR. ROSS: No, we don't.

DR. HELDRETH: Just root extract.

DR. ROSS: Well, it was a good idea. Yeah.

DR. DAVID COHEN: Oh, we have root extract.

DR. BERGFELD: Yeah. Yeah, the second paragraph talks about water, distilled water, as well as some alcohol based.

DR. ROSS: It doesn't define root water because, presumably, it's just some sort of aqueous extracted of that. But I don't know that.

DR. DAVID COHEN: Well, could you have a root water that's separate -- that is more inclusive than a root extract?

DR. BERGFELD: Don't you think you have to pulverize the root and suspended it in something? Because the beginning of the root extract talks about freeze drying and grinding the root.

DR. DAVID COHEN: And then adding that to distilled water and hydrocephanol and methanol.

DR. BERGFELD: That sort of addresses that.

DR. ROSS: So, Susan made the comment just to me, why not group in some of these and maybe they, too, could be in the group? You got any of these that could be in the group?

DR. DAVID COHEN: Well, should we just make a list of ones we can clear now?

DR. ROSS: Yeah. We could do that. We could still have (inaudible) with the DART.

DR. DAVID COHEN: Huh?

DR. ROSS: There's still the DART issue; how do we interpret the DART? Is that something that we should be concerned about?

DR. DAVID COHEN: The DART in the seed?

DR. ROSS: Seed extract.

DR. DAVID COHEN: And we can't clear the seed anyway because we don't have HRIPT anyway, and we still have outstanding IDAs on that, don't we?

DR. ROSS: We've got irritation in the seed up to 1 percent.

DR. DAVID COHEN: Yeah, that's not sensitization though.

DR. ROSS: No, no sensitization.

DR. DAVID COHEN: Hold on, I'm just going back to the tables.

DR. ROSS: For sensitization, I'm missing roots, stems, root water --

DR. DAVID COHEN: Wait, wait. Let me start capturing some of this. We don't have --

DR. ROSS: -- sensitization. At least my tabulation says we're missing roots, stem, root water, and seed. If I have that wrong, please correct me because --

DR. DAVID COHEN: Susan, what did you have -- what? You want to go? You want to start? Let's do what we have safe for, and then we'll backtrack from there.

DR. ROSS: Okay.

DR. TILTON: That would be easy.

DR. DAVID COHEN: All right.

DR. ROSS: At least for sensitization, irritation/sensitization, flower -- do you want me to list them?

DR. DAVID COHEN: Yeah. Yeah, I'll take notes if you list them.

DR. ROSS: Okay. Just for irritation and sensitization, irrespective of any other concerns. But for irritation and sensitization, if you want to go with clearing these based on that, then you could clear flower, because that has a max of 0.13 percent.

DR. DAVID COHEN: What is it? Max of what?

DR. ROSS: The flower has a max of 0.13 percent, so I think you could clear the flower. You could clear the flower water based on irritation and sensitization. You could clear the leaf, and you could clear --

DR. DAVID COHEN: What about the germ?

DR. ROSS: The germ, you've got no max concentration. At least I couldn't see it. But you've got data from half to one and a half percent.

DR. BERGFELD: You had, in Table 13, the germ extract.

DR. DAVID COHEN: Yeah.

DR. SAMUEL COHEN: Yeah.

DR. DAVID COHEN: At 0.0001 percent?

DR. ROSS: Is that a max?

DR. DAVID COHEN: Huh?

DR. BERGFELD: No, it's higher than that. It's 0.25 to 0.75, the actual effective test concentration.

DR. DAVID COHEN: For the germ?

DR. BERGFELD: Yeah.

DR. DAVID COHEN: Oh, 1.5. It says mixture containing.

DR. BERGFELD: No, but the active was in the next column, test concentration dose.

DR. DAVID COHEN: I see 0.3 for germ.

DR. BERGFELD: Yeah, germ extract at 0.5 to 1.5. And then it says test concentration dose, 50 percent effective test concentration, which I take as the active, 0.25-0.75 percent was negative.

DR. DAVID COHEN: This is in humans, you're looking?

DR. BERGFELD: 46 subjects, yes.

DR. DAVID COHEN: Are you looking at irritation or are you looking at --

DR. BERGFELD: It's on under Table 13.

DR. DAVID COHEN: Are you looking at irritation? I was looking at sensitization.

DR. BERGFELD: Oh, sensitization? Okay.

DR. DAVID COHEN: At sensitization, we have 0.3 percent on the germ extract, right? What do we have for the flower water?

DR. ROSS: I have up to 0.2 percent.

DR. DAVID COHEN: For the flower water?

DR. ROSS: What was the value?

DR. DAVID COHEN: 0.2.

DR. ROSS: So germ was 0.5 to 1.5 on irritation. Is it also 0.5 to 1.5 on sensitization?

DR. DAVID COHEN: No, but they were using -- they used the product and then diluted the product because if you look -- are you talking about for germ?

DR. ROSS: Yeah. Where is that?

DR. DAVID COHEN: Germ extract, it's 0.5 to 1.5 percent is the test article.

DR. ROSS: Yeah.

DR. DAVID COHEN: And then test concentration is 20 percent. So the effective test concentration was 0.1 to 0.3.

DR. ROSS: But was that irritation, or was it sensitization?

DR. DAVID COHEN: Sensitization.

DR. ROSS: Sensitization.

DR. DAVID COHEN: It's in Table 13.

DR. ROSS: That's what Wilma was saying here.

DR. DAVID COHEN: For the flower extract, it looks like we could go to 0.15, right? I don't know why I put 0.13.

DR. ROSS: Yeah.

DR. DAVID COHEN: And then the leaf --

DR. SAMUEL COHEN: 0.125 to 0.3.

DR. DAVID COHEN: It's for leaf?

DR. SAMUEL COHEN: Leaf extract, yeah.

DR. BERGFELD: Could go to 0.3 on this one.

DR. DAVID COHEN: Trying to find it – germ.

DR. BERGFELD: It's in the table. It's best seen in the table, I think.

DR. DAVID COHEN: Yeah, and leaf extract 0.3, right?

DR. BERGFELD: Mm-hmm.

DR. DAVID COHEN: 0.3. Is that what you got?

DR. SAMUEL COHEN: Yeah.

DR. DAVID COHEN: The germ we had 0.3. I just want to make sure we've got it. The flower water, we have --

DR. ROSS: 0.2.

DR. DAVID COHEN: Right. Oh, so we have flower. We should have flower water, germ extract, root extract, root, water. And we covered those.

DR. SAMUEL COHEN: I'd recommend the bark and stem confirm all the numbers are (inaudible).

DR. DAVID COHEN: Yeah, yeah, yeah. I got the stem.

DR. BERGFELD: Did you say the flower water was 0.2?

DR. DAVID COHEN: 0.2.

DR. BERGFELD: Yeah.

DR. ROSS: So you're clearing germ also on the basis of Table 13?

DR. DAVID COHEN: I was.

DR. TILTON: Looks like it was immersed.

DR. DAVID COHEN: So I have four cleared, but we should have more than that.

DR. ROSS: Yeah. I'm still not seeing the germ clearance. Maybe I'm just missing it. Table 13.

DR. DAVID COHEN: On germ extract? It's in the middle of Table 13 on sensitization.

DR. ROSS: All right.

DR. DAVID COHEN: It's between the two -- it's the two in between the yellow.

DR. BERGFELD: It's one of your best saying just less than 1 percent.

DR. DAVID COHEN: What's that?

DR. BERGFELD: Concentrations of less than 1 percent because they're all pretty low.

DR. SAMUEL COHEN: Yeah.

DR. DAVID COHEN: They're all low.

DR. ROSS: They are low.

DR. DAVID COHEN: Why do I count four when I've listed five flowers?

MS. EISENMANN: Is that leaf extract?

DR. DAVID COHEN: What's that?

MS. EISENMANN: Leaf extract?

DR. DAVID COHEN: I have leaf extract. Oh, I have leaf. Yeah, I guess leaf extract I have.

DR. SAMUEL COHEN: Flower extract and flower water.

DR. DAVID COHEN: Flower extract and flower water. So we have flower, flower water.

DR. SAMUEL COHEN: Germ extract, leaf extract, and root water.

DR. DAVID COHEN: Oh, I don't have root water. That's the one I'm missing. Root water.

DR. SAMUEL COHEN: Doesn't give a time. It's says 40 microliters at 0.2 percent.

DR. DAVID COHEN: Where are we?

DR. SAMUEL COHEN: It's the last one under sensitization.

DR. DAVID COHEN: 0.2.

DR. SAMUEL COHEN: At 0.3 percent.

DR. DAVID COHEN: I'm assuming it's neat.

DR. ROSS: It would be really useful to see a table of all these concentrations. They're trying to do this on the fly of clearing things as we go here. It would be really useful to see a table of concentrations that have sensitization and irritation data that are fine. And you could clear those at that point.

DR. DAVID COHEN: Think it's true, but --

DR. ROSS: We don't want to come back to this in nine months. I know what you're saying, yes.

DR. DAVID COHEN: But right now, we have five, and we only have to look at one table. And then I guess the hard part now is what are the remaining insufficiencies?

DR. ROSS: So we haven't cleared root, root water, seeds.

DR. DAVID COHEN: We cleared root water.

DR. ROSS: We cleared root water.

DR. DAVID COHEN: Yeah.

DR. SAMUEL COHEN: Root water was cleared but not root extract.

DR. ROSS: So root extract is still to be cleared. What about stems?

DR. SAMUEL COHEN: Nothing on stem.

DR. ROSS: We got 1 percent irritation on stem. That's okay.

DR. SAMUEL COHEN: No sensitization.

DR. ROSS: No sensitization.

DR. DAVID COHEN: Okay. So not clear: root extract, stem. What else?

DR. BERGFELD: Did you do seeds?

DR. TILTON: Seeds.

DR. DAVID COHEN: Seed.

DR. ROSS: Yes.

DR. DAVID COHEN: Well, how many seeds are there though?

DR. TILTON: It says seed extract and the seed powder.

DR. DAVID COHEN: Wait, let me get to that for that one.

DR. BERGFELD: So you're saying the seed?

DR. DAVID COHEN: No. And that's where we have issues with the DART.

DR. SAMUEL COHEN: Right.

DR. ROSS: Yeah. So I think that's still got to be dealt with.

DR. DAVID COHEN: Yeah. I'm looking for that table with all the things in them.

DR. TILTON: I mean, if we could get clarity on the relationship between the root extract and the root water extract, it might group it together.

DR. DAVID COHEN: So we don't have seed extract, seed powder, right?

DR. TILTON: That's right.

DR. DAVID COHEN: Callus culture?

DR. SAMUEL COHEN: How's the callus culture made?

DR. DAVID COHEN: Can we clear it through another way?

DR. ROSS: I think that's the one you had some skin whitening concerns as well.

DR. DAVID COHEN: The total plant extract we don't have, right?

DR. ROSS: Yeah. We are not clearing that. It's a shame we didn't have that. Then we could clear --

DR. DAVID COHEN: Well, then we would have to have so -- that's always the Holy Grail of those is that.

DR. ROSS: Yes.

DR. DAVID COHEN: So the root, the stem, flower, leaf, stem juice, right, we don't have?

DR. BERGFELD: We don't have much on the stem at all.

DR. TILTON: Well, it says we do in the table.

DR. SAMUEL COHEN: Not on sensitization.

DR. DAVID COHEN: Can we clear stamen for flower? Isn't the stamen part of the flower? It is, right?

DR. BERGFELD: Center of it, isn't it?

DR. DAVID COHEN: Yeah, so --

DR. BERGFELD: Center of the flower.

DR. DAVID COHEN: It's a date.

DR. ROSS: It is, yeah.

DR. DAVID COHEN: Dry powder stamens. Someone's pulling stamens out of the flower and drying them out. Seems like a lot of work.

DR. HELDRETH: It's expensive spices that is produced that way.

DR. BERGFELD: Can't hear you.

DR. HELDRETH: Well, one of the most expensive spices is produced that way, the crocus stamen.

DR. BERGFELD: What weight do you give to this Keratino-sensitization?

DR. DAVID COHEN: KaratinoSens? None. You talking to me?

DR. BERGFELD: Yeah.

DR. DAVID COHEN: I knew you would laugh back there.

DR. ROSS: And there, too, we're guessing. Yeah.

DR. DAVID COHEN: But the Keratino- -- by the way, I would pay attention to it. Okay, aside, but that was -- the KeratinoSens was for the germ extract, and we already have human data on the germ extract. But I intended to use that data positively to clear.

DR. BERGFELD: Okay. Well, not only the germ, but it has the flower extract in it.

DR. DAVID COHEN: Which we already cleared as well.

DR. BERGFELD: Leaf extract, and what supports it, germ?

DR. DAVID COHEN: Germ.

DR. BERGFELD: Germ, yeah.

DR. DAVID COHEN: And (inaudible) is germ. So it wasn't one of those contentious situations at all.

DR. BERGFELD: So supportive.

DR. DAVID COHEN: So I have safe for flower, flower water, leaf extract, germ extract, root water at the concentrations we mentioned.

I have not clear: root extract, stem, seed extract, seed powder, callus culture extract, flower with stem juice, and placenta.

DR. ROSS: Yeah.

DR. DAVID COHEN: But can we --

DR. BERGFELD: How about callus?

DR. DAVID COHEN: Callus. I don't remember how they made the callus.

DR. TILTON: It's part of the germ.

DR. DAVID COHEN: Is it a method of manufacturing?

DR. BERGFELD: No, it's defined in the --

DR. DAVID COHEN: Germ.

DR. BERGFELD: It says literally a cultured product, so it's not just a simple piece of the germ. It's something they've produced in a Petri dish.

DR. DAVID COHEN: So what part is it then? Is the germ -- that's early part of the plant?

DR. BERGFELD: I've got to find it again.

DR. DAVID COHEN: I got it.

DR. TILTON: Table 1 has additional information.

MR. ZHU: I think the callus of the process is there. We could actually use like a small piece of tissue and then use a culture media and then make it grow.

DR. DAVID COHEN: Okay. They just define the germ as the extract of the germ.

DR. BERGFELD: It says, undifferentiated massive cells, thickened area of the organ of a plant, or scar tissue that covers a wound in a plant. Callus culture undifferentiated mass of cells produced through tissue culture. So there are two definitions. I don't know what to make of that.

DR. DAVID COHEN: Can we clear stamens from the flower? Anyone else?

DR. BERGFELD: Male reproductive organ. It's a male reproductive organ. It just says, male reproductive organ in flowers usually formed by a filament and anther. Part of the stamen that produces and contains pollen. Typically originates at the stalk/stem. So it's part of the stem.

DR. SAMUEL COHEN: It's the stem.

DR. DAVID COHEN: But it's in the flower, isn't it?

DR. BERGFELD: I guess it comes into it.

DR. DAVID COHEN: Extract of the flower. Anyone up for -- wait. So we do have -- we don't have stamen data anyway, right? But do we clear it for the flower because we have a lot of flower material. We have flower, flower water.

DR. ROSS: But it depends how it's extracted, doesn't it?

DR. DAVID COHEN: Yeah.

DR. ROSS: You might get flavonoids and other things in an extract if you concentrate the extract, which are different.

DR. DAVID COHEN: Right, there may be a part of that that's so concentrated that in the flower you dilute it so much.

DR. ROSS: Correct.

DR. DAVID COHEN: Okay. So did I miss anything? How many do we have? Fourteen in total. One, two, three, four, five, six, seven.

DR. TILTON: So in Table 1 -- I can't turn mine.

DR. DAVID COHEN: I only have 13.

DR. TILTON: So in Table 1, I'm just looking at the root water extract versus root extract. So the root extract is defined as extraction with water. The root water abstract is the aqueous solution of the steam distillate obtained from the roots.

DR. DAVID COHEN: You're saying it's the same thing?

DR. TILTON: So I'm just wondering if -- yeah. They seem very similar.

DR. ROSS: It's the roots. So are you comparing root extract to water extract?

DR. TILTON: Yes.

DR. DAVID COHEN: Which table are you looking at?

DR. TILTON: Table 1.

DR. DAVID COHEN: Table 1?

DR. ROSS: But that root water's going to be mainly volatile.

DR. SAMUEL COHEN: Yeah.

DR. ROSS: So it is different.

DR. TILTON: Okay.

DR. DAVID COHEN: Because it's steam?

DR. TILTON: It's the steam.

DR. ROSS: Steam distillation.

DR. DAVID COHEN: And the root extract.

DR. DIYABALANAGE: The root extract, the solvent used is not mentioned, right? So it could be anything.

DR. ROSS: Exactly. So some of these extracts are still good and characterized. So I think we're clearing on the basis of deriving one from the other when you don't actually know how they're extracted. It's a little on the difficult side.

DR. DAVID COHEN: Okay. That's fine. So I think there are -- are there 14 total?

DR. ROSS: Fourteen.

DR. DAVID COHEN: I have 13 items. I'm missing one.

DR. SAMUEL COHEN: That's the zero -- Table 1, there's 13.

MS. EISENMANN: Do you got the whole plant, Nucifera extract, the whole thing?

DR. DAVID COHEN: I have the whole plant as extract.

MS. EISENMANN: Right.

DR. DAVID COHEN: But didn't it say there were 14 derived ingredients?

DR. ROSS: I've got 14 on my original list.

DR. DAVID COHEN: Fourteen. So I'll read off what I have.

DR. SAMUEL COHEN: Well, there's 13 in Table 1.

DR. HELDRETH: I think it's the phytoplacenta culture extract.

DR. DAVID COHEN: I don't have phytoplacenta. And that's not cleared, right? That's a good pickup. I have placenta. Is that separate than phytoplacenta?

DR. HELDRETH: No, it's phytoplacenta culture extract.

DR. DAVID COHEN: No, I have placenta. I have phytoplacenta.

MS. EISENMANN: What about flower oil --

DR. DAVID COHEN: Flower --

MS. EISENMANN: -- which is not an (inaudible), so it wouldn't be in Table 1.

DR. DAVID COHEN: I don't have flower oil.

DR. ROSS: That's probably your 14th.

DR. DAVID COHEN: Yeah, it is. And I don't have it cleared.

DR. ROSS: No.

DR. TILTON: It's right here.

DR. DAVID COHEN: Okay.

DR. SAMUEL COHEN: And it's not listed in Table 1 either.

DR. DAVID COHEN: Okay. So now for the hard part. We're clearing five. We're not clearing nine. What do we want from the nine, hopefully, from the original IDA.

DR. ROSS: Well, plus concentrations of use. Same thing we asked on the original IDA plus sensitizations.

DR. DAVID COHEN: That's a new IDA.

DR. SAMUEL COHEN: Well, we're basing the five that we're clearing, they're based on sensitization data. So if we had sensitization data on the other nine --

DR. DAVID COHEN: So sensitization or -- well, we need sensitization and not – or --

DR. SAMUEL COHEN: Yeah.

DR. ROSS: And irritation.

DR. SAMUEL COHEN: And irritation. But also, on the seed, I think we need some clarification of the DART.

DR. DAVID COHEN: So we need concentration of use on seed.

DR. ROSS: Yeah. This is something you discussed last time. It's in the transcript, but I think we need that. Sam, I think you're right.

DR. DAVID COHEN: So for seed extract and seed powder, we want concentration of use, right? Is that accurate?

DR. SAMUEL COHEN: Yes.

DR. DAVID COHEN: Because I'm presenting this tomorrow, I want to have this really locked down.

So for those two, we want concentration of use. Do we need concentration of use on the others if we have sensitization data?

DR. SAMUEL COHEN: No, because we've already cleared these five based just on the --

DR. DAVID COHEN: Sensitization?

DR. SAMUEL COHEN: No, concentration of use.

DR. ROSS: The only other reason -- the only reason where the seed is cropping up is because we've got these other concerns.

DR. DAVID COHEN: Because we have the DART issues.

DR. SAMUEL COHEN: Yeah.

DR. TILTON: We may get some clarity, too, if we continue to ask for composition and impurities on the relationship between the different ingredients.

DR. DAVID COHEN: Well, you know what we could do? We could leave the IDA standing. I mean, there's a lot in there.

DR. HELDRETH: Yeah, I mean, you can either issue a new IDA if you have new data needs. Or if it's just a continuation, then it's time to move on with Insufficient Data Conclusion.

DR. DAVID COHEN: It's not an IDC because we added concentration of use.

DR. BERGFELD: So it's new.

DR. DAVID COHEN: It's new.

DR. HELDRETH: Yeah. Then that would go out as a second IDA if you have a new need.

DR. DAVID COHEN: So this is coming back. But it's for good reason. The DART is a real thing, and we need to know. And the irony is the seeds are commonly eaten. It doesn't mean it's necessarily safe. People eat a lot of things that aren't so good.

DR. BERGFELD: Well, don't say that because you're clearing everything on food. You'll get a lot of comments.

DR. DAVID COHEN: No, no, but we have specific data on DART on the seed. That's why I'm holding it up.

DR. BERGFELD: I'm confused where you are.

DR. DAVID COHEN: That makes all of us. All right. We're going to go as safe as used for flower, flower water, leaf extract, germ extract, root water. We're not cleared for the remaining where we need sensitization data, and we need concentration of use for seed extract and seed powder.

DR. ROSS: Can we get a list of clearing again?

DR. DAVID COHEN: Flower, flower water, leaf extract, germ extract, root water.

DR. HELDRETH: If it's going out as another IDA, you don't have to mention anything about what you've cleared because you're not coming up with the draft conclusion if that is your pathway to do another IDA.

DR. DAVID COHEN: So an IDA --

DR. HELDRETH: You just have to list your data needs.

DR. DAVID COHEN: So I think -- yeah. Well, we could talk about it. We're just not going to make it official, right?

DR. BERGFELD: So how are you presenting this?

DR. DAVID COHEN: No, we're still putting it together.

MR. ZHU: Well, I have a question. Like, so in your cleared list, do you have germ?

DR. DAVID COHEN: We cleared germ.

MR. ZHU: You cleared germ. Okay.

DR. DAVID COHEN: So guys, what are our data needs? We want sensitization --

DR. SAMUEL COHEN: On all.

DR. DAVID COHEN: -- on all of them that we don't have?

DR. SAMUEL COHEN: Right.

DR. DAVID COHEN: We want concentration of use --

DR. SAMUEL COHEN: On seed.

DR. DAVID COHEN: -- on seed extract and seed powder? And what of the original IDA do you want to continue?

DR. ROSS: Well, there was an awful lot in the original IDA.

DR. DAVID COHEN: Yes.

DR. TILTON: Well, if we could continue to request composition and impurities.

DR. DAVID COHEN: Now, in composition and impurities, we have verbiage in there.

DR. TILTON: Right, but we were talking about details related to understanding the extraction, the relationship between root extract, root water extract. So I mean, if there's ways to group these for clearing based on composition and impurities, some of that data we don't have. I'm not sure you could in that case.

DR. DAVID COHEN: You would clear just on that? I mean, we have in the past.

DR. TILTON: We have.

DR. DAVID COHEN: But I'm not sure these things would clear. Like when we had things that were just calcium carbonate, we cleared them.

DR. TILTON: No, not just on composition impurities alone, but on understanding if we could clear one ingredient based on information from the other by how similar they are.

DR. DAVID COHEN: Okay. I think I get that. All right. So can you articulate what our IDA is? This is going to be a showdown tomorrow.

DR. HELDRETH: Yeah.

DR. SAMUEL COHEN: It really would come down to is this either/or if you had the composition. If you had the sensitization of all fourteen --

DR. TILTON: Yeah, you wouldn't need it.

DR. SAMUEL COHEN: -- then you wouldn't need the composition. But if you're going to just have the sensitization data on selected ones, the composition one, information on the others could be used for read across.

DR. DAVID COHEN: Well, I don't know how comfortable I'll be just on composition without sensitization data, right, on the plant.

DR. SAMUEL COHEN: Well, then we probably just need the sensitization data, and we don't need the composition.

DR. DAVID COHEN: So are we going out with an IDA that just sensitization on the ones we didn't clear, concentration of use on the seed extract and seed powder? What else must we have? We have DARTs.

DR. SAMUEL COHEN: Clarification of DART.

DR. DAVID COHEN: What does that mean?

DR. SAMUEL COHEN: Well, I just don't know how to interpret that data. You know, it looks like the minimum concentration given effect was 7.5 milligrams per kilogram.

DR. DAVID COHEN: It's a lot.

DR. SAMUEL COHEN: Yeah, it's quite a bit. And so if the concentration of use give us a large enough margin, then that's all we need.

DR. DAVID COHEN: So we're back to we want concentration of -- well, we have concentration of use as one of our IDAs. So we're back to -- what am I missing here? That's what I want to try to get the train to leave the station now.

DR. SAMUEL COHEN: I think you got it all.

DR. TILTON: I think that's it.

DR. ROSS: Yeah, I think that's probably pretty close. And I think in the discussion you got to deal with the skin whitening concerns. I think I heard that from Wilma in our introduction to this. But if we get irritation and sensitization on all that we're missing, we get some clarity around the DART effects of the seed.

DR. DAVID COHEN: And the clarity on the DART effects of the seed is concentration of use.

DR. ROSS: Basically, it's concentration of use, so we can --

DR. DAVID COHEN: Right, because we need to be specific. I mean, clarification of DART is not going to return anything to us.

DR. ROSS: You're not going to get any new DARTS, at least for the -- I mean, we can try and interpret what's there if we have concentration of use.

DR. DAVID COHEN: Okay.

DR. BERGFELD: I got it.

DR. DAVID COHEN: You got it?

DR. BERGFELD: But the clarification, maybe Carol can help us, clarification of the DART.

MS. EISENMANN: I'm not sure where the DART came from, so I don't think it came from anything I provided. So if you're looking for concentration of use, I've asked. I can only ask again, but --

DR. ROSS: That would be the clarification, Carol, would be the concentration of use and --

MS. EISENMANN: I can ask again, but if they didn't provide it the first time --

DR. DAVID COHEN: Right. But if we get sensitization data, we'll have a concentration to deal with. And you guys can take that and work with it and back engineer from the DART that you have.

DR. ROSS: You're right.

DR. DAVID COHEN: See yeah. No, we have faith. But we may get numbers that are like 0.2 percent or something, right, in which case you'll have some information there. So let's not make this more complicated than it is.

DR. ROSS: Hallelujah.

DR. DAVID COHEN: Okay? So are you satisfied with this?

DR. BERGFELD: We're done.

DR. DAVID COHEN: Are you okay with this, Bart?

DR. ROSS: Yeah.

DR. HELDRETH: I'm fine, yeah, we're fine with it. I think maybe you could proceed with the second IDA and do this. I also think it would be absolutely reasonable since we've already asked for concentration of use before. Didn't get it --

DR. ROSS: We haven't.

DR. DAVID COHEN: We didn't. We didn't ask for it.

DR. HELDRETH: Well, no. When we start the report --

DR. DAVID COHEN: Oh, yeah, yeah.

DR. HELDRETH: -- with concentration of use, it didn't come up. And as Carol mentioned, that's always a good indicator that you're not going to get it when we ask again. Do we instead want to go with what we cleared and maintain all of our insufficient data for everything else in there?

DR. DAVID COHEN: Well, we can maintain the -- you mean keep the IDA as is?

DR. HELDRETH: I mean, again, it's Panel's prerogative, not mine, but I'm suggesting a tentative report with the five that you say safe as used, and everything else is insufficient data. Because, like we did on the previous report, if we're pinning it on, well, we need concentration of use, we know we're not going to get it.

DR. DAVID COHEN: But we might get sensitization, right? Maybe?

DR. HELDRETH: But we've already asked for that, haven't we?

DR. TILTON: Yeah.

DR. DAVID COHEN: Well, we can ask again with a more strongly-worded letter.

DR. HELDRETH: Well, I mean, but I think it becomes stronger when we threaten, okay, now we have a conclusion of insufficient data.

DR. DAVID COHEN: That's the point. That's the point.

DR. HELDRETH: I think putting out a tentative conclusion with insufficient data is a bigger stick than another IDA.

DR. DAVID COHEN: It is. I see this is not a change in what we've asked for. It's a change in verbiage because in the beginning you were saying not to even talk about our final findings. And now you're saying use that as --

DR. HELDRETH: If it's going to go IDA, you don't have a conclusion.

DR. DAVID COHEN: Right.

DR. HELDRETH: But if you're going to go conclusion --

DR. DAVID COHEN: So we're not going IDA. We're going Insufficient Data Conclusion.

DR. BERGFELD: For part of it.

DR. DAVID COHEN: Yeah, for part of it.

DR. BERGFELD: For nine of them.

DR. ROSS: Yeah.

DR. DAVID COHEN: I like that.

DR. ROSS: It's a split decision. You're clearing five and the rest you need more stuff.

DR. HELDRETH: Yeah, I mean, and ultimately, when we don't get a response on concentration of use or something, means there's not a lot of interested stakeholders out there. I mean, so, ultimately, putting it in that insufficient bucket means it --

DR. DAVID COHEN: Just remind me what the use on seeds. Are we talking about a lot of products?

DR. ROSS: Yeah. We weren't clearing, I think, root, stem, seed, seed powder, full extract, placenta, flower oil, and --

DR. DAVID COHEN: Callus, right?

DR. ROSS: No.

DR. DAVID COHEN: Ther's a fair number of seed juice.

DR. BERGFELD: Yeah, and also it has a preservative effect as well as the antioxidant effect.

DR. DAVID COHEN: All right. So are we okay with that, team? We're going to go insufficient on those, so they have one more crack at it. That's it.

DR. BERGFELD: Okay.

DR. DAVID COHEN: I think I could live with that. All right?

DR. BERGFELD: Can I make a comment? It was made earlier. It would be very helpful to see what we've just done in a table form for future botanicals, especially if there's a food --

DR. DAVID COHEN: Particularly if it's food. Yeah.

DR. BERGFELD: This is difficult.

DR. HELDRETH: She did such a good job of it before. We'll have Priya help us out with the table.

DR. DAVID COHEN: It was a great table. It made it so --

DR. BERGFELD: Easy.

DR. DAVID COHEN: -- easy to do and extremely complicated. I mean, those were very, very difficult.

Any other comments or questions, thoughts? Hearing none, we'll go to the gum.

Full Panel – March 14, 2025

DR. DAVID COHEN: This is a lotus. So this is a Draft Tentative Report on 14 Nelumbo nucifera-derived ingredients. And at the December meeting we issued insufficient data with a very large needs list that was well outlined in the memo, and it's available to all.

We received only some data. Our group deliberated on this for some time. And there's sufficient evidence the entire plant is edible and is widely consumed. And we believe such food use would mitigate some toxicological needs, yet we have some DART signals with seed-derived ingredients.

We have HRIPT on certain products despite not having concentration of use on all of them. So, we would go out with safe as used for flower extract, flower water, leaf extract, germ extract, and root water in this discussion anchoring to the HRIPT concentrations that we have.

We have insufficient data conclusion with the following needs: sensitization on root extract, stem, callus culture extract, flower, leaf, stem, juice, phytoplacenta, flower oil, in addition to sensitization we'd like concentration of use for seed extract and seed powder because of the DART issues.

DR. BERGFELD: So your conclusion is safe for five and insufficient for nine, is that what I understand?

DR. DAVID COHEN: Safe for five, insufficient for nine.

DR. ROSS: David, can you just repeat the five you wanted to clear, just so I have it straight here?

DR. DAVID COHEN: Flower extract, flower water, leaf extract, germ extract, root water. We're open for discussions.

DR. BERGFELD: Or a motion, second.

DR. ROSS: Root water.

DR. DAVID COHEN: Root water.

DR. BELSITO: The DART data for the seed, you really think it's applicable given the doses that were used? We had this discussion, Paul, did you want to comment?

DR. DAVID COHEN: What dose? Do we have concentration of use on the seed or seed extracts? I don't know the dose.

DR. BELSITO: I mean, don't we usually assume that the maximum concentration of use across the product category is what's given for a particular ingredient? We don't always have concentration of use for ingredients in these groups.

DR. DAVID COHEN: So, Don, are you suggesting that we just need sensitization on the seed extract and seed powder?

DR. BELSITO: Yes, I thought we need sensitization and irritation. I didn't understand why you wanted root. I had callus culture extract, phytoplacenta culture, seed and stamen extract for sensitization and irritation.

DR. DAVID COHEN: I think our issue was with root extract. We know what the root water is.

DR. BELSITO: You think that's going to be sufficiently different from root extract?

DR. DAVID COHEN: Stand by, Don. Let me just check one thing.

DR. ROSS: David, I think root cleared irritation at one percent.

DR. DAVID COHEN: Root extract?

DR. ROSS: Root extract, yes.

DR. DAVID COHEN: Okay, yes, I think we went back and forth. So root extract cleared. Hold on one second.

DR. ROSS: These groups are difficult.

DR. BELSITO: And particularly because I don't think you can read across for sensitization and irritation, we don't have enough composition data.

DR. DAVID COHEN: Which one are we talking about?

DR. BELSITO: I mean, I think we need sensitization and irritation on each of the individual ingredients. Because I don't think we understand the composition sufficiently to say that they would necessarily read across.

DR. SNYDER: That was our conclusion. We said we cannot read across for sensitization, so we need for all.

DR. BELSITO: Right.

DR. SNYDER: We also thought we needed a 28-day dermal on the phytoplacenta, the callus culture, and the stamen-derived. And then we need more information on the UV spectra because we were only given summary data with the peaks given. And so, the Belsito Team wanted to see the range of the spectra to see whether the tails went into any absorption areas. And we wanted to make sure that that was reviewed to make sure there were no issues there.

DR. BELSITO: Because the peak comes very close to the UVV region. And we don't know -- I mean, so we know a peak, but we don't know the tail on how far out it goes.

DR. RETTIE: Only have that for the germ extract, right? UV absorption for all.

DR. SNYDER: We need it for all of them, yes.

DR. RETTIE: Yes, but we've only got it done for the germ extract.

DR. BERGFELD: Do I understand that we have needs for every single ingredient that's in here, these 14?

DR. SNYDER: Yes, that's correct, because we said we can't read across for sensitization.

DR. BERGFELD: So, it's basically an insufficient.

DR. BELSITO: Right.

DR. SNYDER: Yes, insufficient data, as we would prefer that.

DR. DAVID COHEN: Okay, so, you have insufficient across the board because of the phototox needs?

DR. SNYDER: Well, for the sensitization we cannot read across, so we need it for all. Oh, no, for those three, phytoplacenta, callus culture and stamen-derived, 28-day dermal on those three, and then information on the UV spectra for all of them.

DR. ROSS: I was going to say, Paul, because on a number of these we've got sensitization above their max concentrations. So I think a number of them is okay.

DR. DAVID COHEN: Right, I think we could clear six. But, we can't clear six if your team has the IDA on phototox.

DR. ROSS: Correct.

DR. DAVID COHEN: We can't clear anything.

DR. SNYDER: I mean, Don was concern just that with summary data, and we can't interpret it because we don't have the data to know in fact if they interpreted it correctly. No protocols, okay, and we don't know what the induction period was. We

don't know how often it was applied. We don't know how it was irradiated. And Don wanted to see that everything was done according to the current --

DR. DAVID COHEN: I'm fine with -- I think that's a reasonable -- I'm going to amend my motion. My motion is an Insufficient Data Announcement with the following needs: phototox on all items and sensitization data on stem, callus culture extract, flower, leaf, stem, juice, phytoplacenta, flower oil. And we'd still like concentration of use on the seed extract and powder.

DR. SNYDER: Don, did you still want to have the 28-day dermal on those three, the phytoplacenta, the callus culture and the stamen-derived? We asked for that in our list.

DR. BELSITO: Yes, because they're not listed as foods, so we need to clear them systemically. Right? We don't have adequate --

DR. DAVID COHEN: Well, it seems like the whole plant is eaten. I couldn't find any part of the plant that wasn't eaten. But, I suppose some of these others like the cultures maybe they wouldn't be available for general consumption. So, we can add that on.

DR. SNYDER: Well, we have an IDA. We can go with it. And then we can deal with it if we get information related, okay.

DR. DAVID COHEN: Okay.

DR. SNYDER: I second the motion.

DR. BELSITO: And, I mean, I just think as one alternative is if they could just give us a UV spectrum on the whole plant, that might help us just clear instead of having to do each individual, you know.

DR. DAVID COHEN: Well, there is a whole plant as one of the 14.

DR. BELSITO: Right, I understand. But, the UV absorption we have is on germ extract. And it basically says that the absorption maxima is at 2783 essentially, which is, you know, getting close to UVV range. So the question is where does that tail go, and we don't know.

DR. DAVID COHEN: Okay, I think we have concurrence and we have a second on the motion, so.

DR. BERGFELD: Bart?

DR. ROSS: Can someone just repeat the motion? Sorry.

DR. HELDRETH: I just want to interject that it sounds like all of these data needs are just more specific versions of what was in the original IDA. So the Panel has the option instead of creating a second IDA to go to a Tentative Report with an insufficient conclusion, but it's your option.

DR. DAVID COHEN: You know, that's a really good point. If we look at the original IDA, it has all those. It has UV absorption spectra in there. So, instead of creating a new IDA, I guess this is an Insufficient Data Conclusion.

DR. HELDRETH: Yes. And we can get to the more specifics that were discussed today in the Discussion of that report.

DR. DAVID COHEN: We have four -- all ingredients UV absorption spectra. We have that. So, is there anything different in the original IDA that we need to add here, or we just --

DR. ZHU: Actually, yesterday you discussed you needed to have concentration of use for all ingredients.

DR. DAVID COHEN: Well, the question is, if we were going to use the HRIPT data as an anchor that would be the concentration of use we would accept in the Discussion, right? But, yes, we wanted concentration of use, particularly for the seed components. But for all of them it would be -- well we have for some of them, right, for ones that we don't have.

DR. HELDRETH: Right, but I mean, concentration of use is always something we're asking for and Council is always striving to provide. So I don't think that that's like a new need.

DR. DAVID COHEN: I don't think we have to change an Insufficient Data Conclusion to an Insufficient Data Announcement now just for that. So, if we got an HRIPT on seed that would be our max concentration we would consider. That would be okay with you?

DR. ROSS: Yes, then you work back from that and look at the other endpoints where there's a problem.

DR. DAVID COHEN: Yes, okay. So, we have an Insufficient Data Conclusion on the existing IDA.

DR. BERGFELD: So, it's going to go out as an insufficient report?

DR. DAVID COHEN: Yes.

DR. BELSITO: I mean, there are things that we asked for previously that we don't need now. But, I mean, on the other hand we don't need them now because we've used other methods to sort of get around those needs. So, I guess I'm okay with just continuing with that IDA.

DR. BERGFELD: All right. If there's no more discussion, I think we've discussed this particular ingredient a lot.

DR. DAVID COHEN: Paul, did you second that, if we do an Insufficient Data Conclusion.

DR. BERGFELD: He did.

DR. SNYDER: Belsito Team seconds, yes.

DR. DAVID COHEN: Okay, I just wanted to check it.

DR. BERGFELD: Okay. So I'm going to call the question, all those in favor of an insufficient conclusion please indicate by raising your hand. Unanimous. Our next ingredients is Acacia, Dr. Snyder presenting.

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
GC-MS	gas chromatography-mass spectroscopy
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
IgE	immunoglobulin E
INCI	International Nomenclature Cosmetic Ingredient
LD_{50}	median lethal dose
l.o.	leave-on
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	sodium 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
r.o.	rinse-off
RLD	Registration and Listing Data
ROS	reactive oxygen species

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

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 14 *Nelumbo nucifera*-derived ingredients, most of which are reported to function in cosmetics as skin-conditioning agents and/or antioxidants. The Panel reviewed the available data to determine the safety of these ingredients. Industry should minimize impurities that could be present in cosmetic formulations, such as heavy metals and pesticide residues, according to limits set by the US Food and Drug Administration (FDA) and US Environmental Protection Agency (EPA). The Panel concluded that the available data are insufficient to make a determination of safety for all 14 *Nelumbo nucifera*-derived ingredients under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This assessment reviews the safety of the following14 *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

Nelumbo Nucifera Flower Oil is not included in the *Dictionary*; however, it had reported uses in 2023 in the US FDA Voluntary Cosmetic Registration Program (VCRP) database and in RLD for 2024, and thus is included in this review.

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] 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 August 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.

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.[13] 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.[14] 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.

According to a submission from a manufacturer, Nelumbo Nucifera Flower Extract is produced by the extraction of *Nelumbo nucifera* flowers in the solvent isostearyl isostearate.[10] The resultant solvent extract is a pale-yellow transparent liquid that contains 1-5% *Nelumbo nucifera flower* extract.

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 Oil

The essential oil components in the flower of *Nelumbo nucifera* are separated using enfleurage, cold pressing, solvent extraction (using organic solvents such as hexane) and steam distillation.[15] In industrial applications, the steam distillation method is reported to be widely used.

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 phytosterols (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) 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.

The presence of heavy metals, arsenic, and microbes was measured in a *Nelumbo nucifera* flower extract.[9] The extract met the specification levels of 10 ppm heavy metals, 2 ppm arsenic, and 100 cfu/ml microbes.

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 Flower Oil

The composition of the essential oil present in wild *Nelumbo nucifera* flower was analyzed using the flower oil obtained via three different extraction methods (head space extraction, steam distillation, solvent extraction) and analyzed by gas chromatography-mass spectroscopy (GC-MS).[15] Altogether 42 secondary metabolites belonged to chemical classes, alkanes, alkenes, alcohols, aldehydes, acids, and esters have been identified. The composition of essential oil obtained in these three different methods seems to vary significantly. In the head space extraction method, acetic acid was the major constituent (38.1%), while two olefine aldehydes Z,Z-10,12-hexadecadienal (16.3 %) and E-14-hexadecenal (16.7), were the major components in the product obtained by steam distillation. However, the essential oil produced by solvent extraction method indicated two fatty acids, n-hexadecanoic acid (25.5%, palmitic acid) and Z, Z-9,12-octadecadienoic acid (26.8%, linoleic acid), as main constituents. In another study, using solvent extraction followed by GC-MS analysis, reported nine chemicals with more than 1% composition (Table 6).[40] Among them, methyl hexadecanoate (palmitic acid methyl ester) and methyl *cis, cis,* 9, 12-ocatdecadienoate (linoleic acid methyl ester) were the main constituents at 22.66 and 11.16%, respectively.

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.[41] Quantification of phenolic, flavonoid, and anthocyanin content in a *Nelumbo nucifera* seed embryo is presented in Table 7.[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.[42] 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 7 .[39]

Nelumbo Nucifera Root Extract

A phytochemical screening of an ethanolic extract of *Nelumbo nucifera* roots was performed.[43] 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.[44] 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.[45] 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 8. 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 9.[46]

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.[47] 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.[48] 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 7.[39]

UV Absorption

Nelumbo Nucifera Germ Extract

According to an industry submission, the ultraviolet (UV) absorption of Nelumbo Nucifera Germ Extract was determined in three trade name mixtures.[49] These trade name mixtures that consisted of Nelumbo Nucifera Germ Extract in water and butylene glycol (concentrations not stated; two of the three were identified as lotus germ extract), displayed UV 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 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 discontinued in 2023 and, as of 2024, manufacturers and processors are required to register and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h and the facilities that manufacture these products are not included in this exemption.[50] 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 reported in the RLD in 2024 (211 of which are for face and neck products)[51] and, 200 uses reported in the VCRP in 2023[52] (Table 10). The results of the concentration of use survey conducted by the Council in 2022 and updated in 2025 indicate that Nelumbo Nucifera Root Water has the highest maximum reported concentration of use; it is reported to be used at up to 0.2% in foundations.[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 (e.g., 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.

None of the *Nelumbo nucifera*-derived ingredients named in the report are 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 used as food and widely used in traditional medicine.[55,56] *Nelumbo nucifera* flowers are ornamental and the species is of religious significance in South East Asia.[57] *Nelumbo nucifera* seeds are used in East Asian cuisine and are sometimes sold as a snack food.[58] *Nelumbo nucifera* seed powder is used in baked goods, and *Nelumbo nucifera* seeds are used to produce milk and other food products.[59,60] *Nelumbo nucifera* seeds have also been used in the production of biofuels.[58]

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 11 .

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.[61] The acute oral toxicity of several ethanolic extracts of *Nelumbo nucifera* plant parts were evaluated using rats.[43] 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.[44] 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.[25,62]

Short-Term, Subchronic, and Chronic Toxicity Studies

Details on the repeated dose oral toxicity studies summarized below can be found in Table 12 .

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.[61] 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.[63] 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.[63] 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 13 .

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.[64] 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.[65] 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.[66] 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.[67-69] (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.[69,70] An aqueous *Nelumbo nucifera* rhizome extract exhibited antiproliferative effects in both epidermoid and breast cancer cells[71] and an ethanolic *Nelumbo nucifera* stamen extract exhibited 86.3% inhibition at 400 µg/ ml and induced apoptosis in HCT 116 human colon cancer cells.[72]

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 concentrations of 10, 50, 100, or 200 µg/ml, in both a tyrosinase inhibition assay and a 4-dihydroxyphenyl-alanine (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.[13] 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 Flower Oil

In a study to determine the effect of the essential oil from the flower of *Nelumbo nucifera* towards melanogenesis in human melanocytes, it was shown to stimulate melanin synthesis and tyrosinase activity.[40] Nelumbo Nucifera Flower Oil induced the expression of tyrosinase and increased microphthalmia-associated transcription factor M (MITF-M) which controls pigmentation by regulating the expression of tyrosinase. It also induced the expression of tyrosinase-related protein-2 but not tyrosinase mRNA. Further studies have revealed that palmitic acid methyl ester as the principal component in Nelumbo Nucifera Flower Oil that seems to increase melanogenesis as a consequence of increased tyrosinase expression.

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.[73] 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.[73] 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 irradiated 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 6 mo of treatment, 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 Induction of Delayed-Type Hypersensitivity

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.[74] 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 given 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 (IgE) 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.[75] 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 dermal irritation and sensitization studies summarized below can be found in Table 14.

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 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[76] or 0.2% Nelumbo Nucifera Root Water[77] reported very good tolerance and no comedogenicity. Irritation was not observed in 24-h patch tests that examined the irritation potential of extracts of several plant parts (1% leaf, root, flower, or stem extracts or 4% combined extract; 20 subjects).[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 Nelumbo Nucifera Callus Culture Extract (97% in pentylene glycol),[78] 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);[79] with a serum containing 0.001% Nelumbo Nucifera Germ Extract,[80] or with foundations (as supplied) containing 0.00001% Nelumbo Nucifera Flower Extract,[81] 0.2% Nelumbo Nucifera Flower Water,[76] or 0.2% Nelumbo Nucifera Root Water.[77]

Photosensitization/Phototoxicity studies

Details on the photosensitization/phototoxicity studies summarized below can also be found in Table 14.

A trade name mixture containing 0.5 – 1.5 w/v% Nelumbo Nucifera Germ Extract did not indicate phototoxic potential in an in vitro reactive oxygen species (ROS) assay and in a 3T3 NRU phototoxicity assay conducted in accord with OECD TG 432.[16] It was also not phototoxic or a photosensitizer in guinea pigs (tested at up to 30%). Foundations containing 0.2% Nelumbo Nucifera Flower Water[76] or Nelumbo Nucifera Root Water[77] were not phototoxic or photosensitizing; testing was performed with 28 and 26 subjects, respectively. The phototoxicity studies used UVB and UVA (290 - 390 nm), with a dose equal to 0.75 MED, or with UVA only (315 - 390 nm) and a dose equal to 20 J/cm^2. The photosensitization studies used UVB and UVA (290 - 390 nm); at dose levels equal to 1.5 times the MED for induction, and UVA only (315 - 390 nm) with a dose equal to 5 J/cm^2 UVA for challenge.

OCULAR IRRITATION STUDIES

Details on the ocular irritation studies summarized below can be found in Table 15.

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.[76] Results were primarily negative in all studies. A short time exposure test (STE) was conducted with a raw material containing 1% Nelumbo Nucifera Germ Extract.[82] The test substance was non-irritating to the eyes at a concentration of 100%.

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 as in use in the VCRP and RLD, and accordingly, 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 in cosmetics 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 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 IgE levels was statistically significant in animals treated with 25 and 50 mg/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 in drinking fluid for 6 mo before irradiation) 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 irritant 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 24-h patch tests (20 subjects) that examined the irritation potential of extracts of several plant parts (1% leaf, root, flower, or stem extracts or 4% combined extract).

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 Nelumbo Nucifera Callus Culture Extract, 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); a serum containing 0.001% Nelumbo Nucifera Germ Extract or with foundations 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.

An STE was conducted with a raw material containing 1% Nelumbo Nucifera Germ Extract was non-irritating to the eyes at a concentration of 100%. 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.

DISCUSSION

This assessment reviews the safety of 14 *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 data in this report and concluded that the available data are insufficient for determining the safety of these ingredients under the intended conditions of use in cosmetics. The Panel noted a lack of relevant safety data and determined that the data needs from the Insufficient Data Announcement issued following the December 2024 Panel meeting have not been fulfilled. In order to come to a conclusion of safety for these 14 ingredients, the following additional data are needed:

- For all ingredients
    - Composition and impurities
    - Methods of manufacturing
    - 28-d dermal toxicity data
        - if positive; additional data (e.g. development and reproductive toxicity data) may be needed.
    - UV absorption data (as well as more detailed information about the previously submitted UV spectra)
        - if absorbed, phototoxicity/photosensitization data are needed (additional protocol details are needed for the previously-submitted studies)
- For the callus-, phytoplacenta-, stamen-, and seed-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
- For flower- and whole plant-derived ingredients
    - Development and reproductive toxicity data
- For all except flower- and leaf-derived ingredients
    - In vitro ocular irritation data

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.

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

The Panel also 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. Inhalation toxicity data were not available. However, the Panel noted that the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which 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

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination of safety for the following 14 *Nelumbo nucifera*-derived ingredients under the intended conditions of use 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

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 (extracted in water)		
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[27-31,42,44,48,70,83-87]

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[27-31,42,44,48,70,83-87]

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		♦			

Table 4. Main constituents in *Nelumbo nucifera*, organized by chemical class and presence in plant parts[27-31,42,44,48,70,83-87]

Constituent	Embryo	Flower	Leaf	Seed	Stamen
Luteolin glucoside		♦			♦
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. Fatty acid composition of a *Nelumbo nucifera* flower oil[40]

Component	Amount (%)
heptadecadiene	1.23
8-heptadecene	1.13
heptadecane	2.04
methyl 9-hexadecenoate (palmitioleic acid methyl ester)	7.55
methylhexadecanoate (palmitic acid methyl ester)	22.66
methyl cis, cis-9-octadecadienoate (linoleic acid methyl ester)	11.16
methyl 9, 12, 15-octadecatrienoate (linolenic acid methyl ester)	5.16
heneicosane	5.55
methyloctadecanoate	1.04

Table 7. 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 8. Amino acid profile of a *Nelumbo nucifera* lotus seed protein and its protein fractions (g/kg crude protein on a DW basis)[45]

	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 9. Fatty acid composition of a whole *Nelumbo nucifera* seed oil[46]

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 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
	Nelumbo Nucifera Callus Culture Extract			Nelumbo Nucifera Extract			Nelumbo Nucifera Flower Extract		
Totals*	**40**	**8**	**NR**	**64**	**7**	**0.02**	**544**	**200**	**0.00025 – 0.13**
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*8*	*NR*	***	*5*	*0.01*	***	*151*	*0.00025 – 0.13*
Rinse-Off	***	*NR*	*NR*	***	*2*	*0. 02*	***	*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	0.01	***	1; 35[b]; 5[c]	0.1; 0.001 – 0.05[c]
Dermal Contact	***	8	NR	***	5	0.02	***	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***		
Perfumes							NR	1	NR
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 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
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
Manicuring Preparations (Nail)							***2***		
Nail Polishes and Enamels							NR	NR	0.13
Other Manicuring Preparations							2	NR	NR
Personal Cleanliness				***6***			***17***		
Bath Soaps and Body Washes				5	NR	NR	13	10	0.00025
Deodorants (underarm)									
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 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
	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)									

Table 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
Hair Rinses (coloring)							7 (r.o.)	NR	NR
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
Manicuring Preparations (Nail)									
Other Manicuring Preparations									
Personal Cleanliness Products				***2***			*1*		
Bath Soaps and Body Washes				1	2	NR			
Deodorants (underarm)									
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 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
	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 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
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									
Manicuring Preparations (Nail)									
Other Manicuring Preparations									
Personal Cleanliness	***1***			***5***					
Bath Soaps and Body Washes	1	NR	NR	3	1	0.00025			
Deodorants (underarm)				1 (spray)	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 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
	Nelumbo Nucifera Root Extract			Nelumbo Nucifera Root Water			Nelumbo Nucifera Seed Extract		
Totals*	**190**	**15**	**NR**	**21**	**1**	**0.2**	**72**	**25**	**NR**
summarized by likely duration and exposure**									
Duration of Use									
Leave-On	***	*8*	*NR*	***	*NR*	*0.2*	***	*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	NR	***	1	0.2	***	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 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
Hair Rinses (coloring)									
Other Hair Coloring Preparation									
Other Hair Coloring Preparation							NR	2	NR
Makeup Preparations (not eye; not children's)	***13***			***15***					
Blushers and Rouges (all types)									
Face Powders				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									
Manicuring Preparations (Nail)									
Other Manicuring Preparations									
Personal Cleanliness Products	***4***			***2***			***1***		
Bath Soaps and Body Washes	4	NR	NR	1	NR	NR	1	1	NR
Deodorants (underarm)									
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 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
	Nelumbo Nucifera Seed Powder			Nelumbo Nucifera Stamen Extract					
Totals*	**13**	**1**	**NR**	**6**	**1**	**NR**			
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)									

Table 10. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category[51,52]

	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use	# of Uses		Max Conc of Use
	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]	RLD (2024)[51]	VCRP (2023)[52]	% (2025)[53]
Hair Rinses (coloring)									
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									
Manicuring Preparations (Nail)									
Other Manicuring Preparations									
Personal Cleanliness	***1***								
Bath Soaps and Body Washes									
Deodorants (underarm)									
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 11.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.	61
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.	43
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.	43
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.	43
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	62
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.	44
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_{50}> 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 12. 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)	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.	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.	61
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.	63
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.	63

Table 12. 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 13. 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 (sexually mature) (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

Table 13. Reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
Nelumbo nucifera seed extract (petroleum ether)	peanut oil	Female Wistar albino rats (sexually immature) (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 (sexually immature) (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
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. Fertility testing was completed before the experiment and at days 55-60 in controls and treated animals. The male rats cohabitated with proestrous females in ratio of 1:2.	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.	64

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 14. 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
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	30 subjects	28-d use test (details not provided)	very good tolerance, no comedogenicity	76
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 solution (1%); *Nelumbo nucifera* leaf, root, seed, and stem extracts		1% of individual extract	20 subjects	Several patch tests were performed to evaluate the irritation potential of each extract. Patches were 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

Table 14. Dermal irritation and sensitization studies

Test Article	Vehicle	Test Concentration/Dose	Test Population/System	Protocol	Results	Reference
Water cream containing 1% each of *Nelumbo nucifera* flower, leaf, root, and 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	11
HUMAN						
97% Nelumbo Nucifera Callus Culture Extract in pentylene glycol	none	tested neat (40 µl)	43 subjects	HRIPT; Finn chambers were applied (to the "flat oxter area") for 48 h and then removed. After 24 h, the Finn chamber was reapplied for 48 h; a total of 5 applications were made. After a 2-wk non-treatment period, a 48-h challenge patch was applied. Tested sites were then evaluated after 1, 48, and 96 h.	mean irritation index = 0.097; not an irritant or a sensitizer	78
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	81
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	76
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	79
serum containing 0.001% Nelumbo Nucifera Germ Extract	not specified	no other details provided	53 subjects	HRIPT (details not provided)	Not an irritant or sensitizer	80

Table 14. 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	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
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
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	76
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	76
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

Table 14. Dermal irritation and sensitization studies

Test Article	Vehicle	Test Concentration/Dose	Test Population/System	Protocol	Results	Reference
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 15. 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	76
foundation containing ~0.2% Nelumbo Nucifera Flower Water	not specified	not specified	not specified	HET-CAM	practically non-irritant	76
raw material containing 1% Nelumbo Nucifera Germ Extract	physiological saline	0.05 and 5%	SIRC cells	Short-time exposure (STE) test (OECD TG 491) To evaluate the test substance at a concentration of 100%, it was prepared to 5% and further diluted to 0.05% through a 2-step dilution with a dilution factor of 10. Solutions of the test substance at 0.05 and 5% were used for the tests.	0.05% cell viability: 96.5 ± 5.2% 5% cell viability 92.9 % ± 12.4% Test substance determined to be non-irritating to the eyes at 100%	82
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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Concentration of Use by FDA Product Category – *Nelumbo nucifera*-Derived Ingredients*

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

Ingredient	**Product Category**	**Maximum Concentration of Use**
Nelumbo Nucifera Flower Extract	Baby shampoo	0.00055%
Nelumbo Nucifera Flower Extract	Eye shadows	0.00025%
Nelumbo Nucifera Flower Extract	Eye lotions	0.0015%
Nelumbo Nucifera Flower Extract	Face powders	0.1%
Nelumbo Nucifera Flower Extract	Lipstick	0.1%
Nelumbo Nucifera Flower Extract	Nail polish and enamel	0.13%
Nelumbo Nucifera Flower Extract	Bath soaps and detergents	0.00025%
Nelumbo Nucifera Flower Extract	Face and neck products Not spray	 0.001%
Nelumbo Nucifera Flower Extract	Body and hand products Not spray	 0.01-0.05%
Nelumbo Nucifera Flower Extract	Moisturizing products Not spray	 0.0015%
Nelumbo Nucifera Leaf Extract	Bath soaps and detergents	0.00025%
Nelumbo Nucifera Extract	Face and neck products (not spray) Leave-on Rinse-off	 0.01% 0.02%
	Body and hand products Leave-on (not spray)	 0.001%
Nelumbo Nucifera Root Water	Foundations	0.2%
Nelumbo Nucifera Flower Water	Face and neck products Not spray	 0.001%
Nelumbo Nucifera Flower/Leaf/Stem Juice	Hair conditioners	0.000023%
Nelumbo Nucifera Flower/Leaf/Stem Juice	Face and neck products Not spray	 0.0034%

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

Information collected in 2022
Table prepared: July 6, 2022
Updated November 4, 2024: added uses for Nelumbo Nucifera Extract
Correction: April 23, 2025 Root Extract corrected to Root Water

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: April 23, 2025

SUBJECT: Nelumbo Nucifera Callus Culture Extract

P&K Skin Research Center Co., Ltd. 2011. Clinical Safety Evaluation Study of Three Kinds of Callus Culture Extracts by Skin Repeated Insult Patch Test (third item tested was Nelumbo Nucifera Callus Culture Extract).

Authentication

P&K Skin Research Center Co., Ltd. reports test result of the "Safety Evaluation Clinical study of Three Kinds of Callus Culture Extracts by Skin Repeated Insult Patch Test" requested by BIO-FD&C Co., Ltd. this clinical test was conducted in accordance with Korea Food and Drug Administration (KFDA) regulations for approval regarding the functional cosmetics and with Frosch & Kligman CTFA guideline as the standard.

March 30, 2011

Research Facility :	P&K Skin Research Center Co., Ltd.	President	Jin O Park
Researcher in Charge :	P&K Skin Research Center Co., Ltd. Chung-Ang University Hospital Dermatology Department	Director Professor	Beom Joon Kim
Researcher :	Chung-Ang University Hospital Dermatology Department	Dermatologist	Woo Sun Jang
		Dermatologist	Ju Hee Park
	P&K Skin Research Center Co., Ltd.	Researcher	Jong Ho Park
		Researcher	Deok Su Son
		Researcher	Jang Mi Seok
		Researcher	Mi Rim Jang
		Researcher	Yoon Sun Cho
		Researcher	Taek Jin Shin

Final Report

Test Title	Clinical Safety Evaluation Study of Three Kinds of Callus Culture Extracts by Skin Repeated Insult Patch Test	
Researcher in Charge	Name	Doctor of Medicine. Beom Joon Kim
	Position	Chung-Ang University Hospital Dermatology Department P&K Skin Research Center Co., Ltd
	Address	Green-villa 202, 45-3 Nonhyeon-dong, Gangnam-gu, Seoul, Korea
Test Period	February 16, 2011 ~ March 22, 2011	
Date of Report Completion	March 30, 2011	
Requester	Requested Date	February 09, 2011
	Company Name	BIO-FD&C Co., Ltd.
	Location	451-7 Nonhyeon-dong, Namdong-gu, Incheon, Korea
	Person in Charge	Jung Hoon Lee
	Address	451-7 Nonhyeon-dong, Namdong-gu, Incheon, Korea Tel: +82-32-811-2027 Fax: +82-32-822-2027
Research Facility	Name	P&K Skin Research Center Co., Ltd
	Research President	Jin O Park
	Location	Citi B/D 2F, 118-2 Heukseok-dong, Dongjak-Gu, Seoul, Korea
	Person in Charge	Jang Mi Seok (Senior Researcher)
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Contents

Summary Report of The Test Result

<table>
<tr><td>Test Title</td><td colspan="3">Clinical Safety Evaluation Study of Three Kinds of Callus Culture Extracts by Skin Repeated Insult Patch Test</td></tr>
<tr><td>Research Facility</td><td>P&K Skin Research Center Co., Ltd</td><td>Test Number</td><td>PNK-11216-R1</td></tr>
<tr><td>Test Period</td><td colspan="3">February 16, 2011 ~ March 22, 2011</td></tr>
<tr><td>Test Products</td><td colspan="3">[redacted]
3. Nelumbo Nucifera Callus Culture Extract</td></tr>
<tr><td>Test Objective</td><td colspan="3">This clinical test, requested by BIO-FD&C., LTD.. has been conducted for the evaluation of potential skin irritation induction by the three kinds of callus culture extract.</td></tr>
<tr><td>Test Method</td><td colspan="3">1. Selection of Subjects : Selection of the minimum 40 healthy subjects who is satisfied with condition for selection without any reasons for disqualification.
2. Occlusive patch application Area : Subject's flat outer area except for coloring and skin damaged area.
3. Evaluation
- Preliminary research of the subjects : Skin Type, Skin condition
- Evaluation Item : Visual evaluation (by researcher), Subjective Evaluation (by Subjects)
- Evaluation Method : Evaluation according to Frosch & Kligman, CTFA Guideline</td></tr>
<tr><td>Test Result</td><td colspan="3">1. Subjects
- 44 healthy volunteer
- Dropout: One person (S21)
- Tested people : 43 people
2. Result
<table><tr><th>Products name</th><th>Scoring of Mean Irritation Index</th><th>Skin Irritation Grade</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>[redacted]</td><td>0.045</td><td>Non-irritant</td></tr><tr><td>Nelumbo Nucifera Callus Culture Extract</td><td>0.097</td><td>Non-irritant</td></tr></table></td></tr>
<tr><td>Conclusion</td><td colspan="3">Under the condition of the repeated insult patch test(RIPT), there was no evidence of any induced skin irritation by three tested products, so this study results provide evidence for the lack of skin sensitization potential for the three test products.</td></tr>
</table>

Research on The Actual Condition of Test Facilities

Research Center	Name : P&K Skin Research Center Co., Ltd
	address : Citi B/D 2F, 118-2 Heukseok-dong, Dongjak-Gu, Seoul, Korea
	President Jin O park
	Tel :☎ +82-2-6925-1501~3, (Fax) +82-2-6925-1504
The Object of Establishment	This research center was founded for accomplishing efficacy test and clinical test on human skin such as safety tests, skin moisturizing improvement test, acne skin improvement test and skin dead cell elimination effect test as well as evaluating functional effects like whitening, wrinkle improvement and sun Protection. Through these scientific evaluation, P&K Skin Research Center provides its clinical test reports and all its related technical information to the requester.
Test Lists	Efficacy Evaluation & Study of Cosmetics. Safety Test & Study of Cosmetics. Efficacy Evaluation & Study of Functional Cosmetics. Evaluation & Study of Functional Cosmetics.
Chief Researcher	P&K Skin Research Center Co., Ltd Chung-Ang University Hospital Dermatology Department Beom Joon Kim
Researcher	Jong Ho Park, Deok Su Son, Jang Mi Seok, Mi Rim Jang, Yoon Sun Cho, Taek Jin Shin, Woo Sun Jang, Ju Hee Park
Main facilities and equipments	Multi Probe-Adaptor MPA5, MPA5Data recorder, Sebumeter SM815, corneometer probe CM825, Skin-pH meter probe PH905, Skin-Thermometer probe ST500, Mexameter MX18, Sensor for Room Condition RHT100, Delfin VapoMeter, Skin Visiometer SV600, Skin Visiometer VC98, Skin Visiometer VD300, Skin Visiometer data recorder, Visoface Quick, Digital clinical thermometer, Digital Moisture Measurement Instruments, Chromameter CR400, Multiport Solar Simulator 601-300W, Xenon Lamp Power Supply, Adjustable Multiport Column, Electric Lift, Special chair , Radio meter PMA2100, UVA Detector PMA2113, SUVDetector PMA2103, Micropipette, Chemical Balance, Timer, Whirl pool System, Folliscope 4.0, Digital Camera, Tripod, Face Fixing Frame Set(Wood), Face Fixing Frame Set(Steel), Scopeman, Thermo-hygrostat, STHC-MB, Photographing System, Whitening Evaluation Lab, Anti-Wrinkle Evaluation Lab, SPF Evaluation Lab, PFA Evaluation Lab, In-Vitro Lab, Moisture Evaluation Lab, Hair Evaluation Lab, Cleansing Room, Waterproof System room, Shower Room, Studio.

1. Test Title : Clinical Safety Evaluation Study of Three Kinds of Callus Culture Extracts by Skin Repeated Insult Patch Test

2. Test Object : This clinical test has been conducted for skin safety evaluation about potential skin irritation induction and potential contact dermatitis by the Three Kinds of Callus Culture Extracts.

3. Test Period : February 16, 2011 ~ March 22, 2011

4. Test Products

<Table1. Effective component & Sample Type of the Test products>

No.	Test Sample Name	Control Number of Test Product	Effective component	Content	Sample Type
[redacted]					quid
[redacted]					
C	Nelumbo Nucifera Callus Culture Extract	11216-R1-S3	Nelumbo Nucifera Callus Culture Extract	97%	Liquid
			Pentylene Glycol	3%	

* A, B, C : Application Number of Test Product

5. Test Materials

Finn chamber(Smart Practice, Denmark), 3M Micropore Tape, Marking Pen, Micro pipette

6. Standard of Test : This clinical test was conducted in accordance with the guideline in below.

Test guidelines for assessment of skin compatibility of cosmetic finished products in man., Task Force of COLIPA, the European Federation of National Cosmetic, Toiletry and Perfumery Associations, Walker AP, Basketter DA, Baverel M, Diembeck W, Matties W, Mougin D, Paye M, Rothlisverger R, Dupuis, J. Food Chem Toxicol., 1996 34(7): 651-60.

7. Selection of Subjects

Healthy Adults who is satisfied with condition for selection without any reasons for disqualification.

7.1. Condition for selection

- Healthy volunteer, aged 20 to 50 years
- Subjects who free from acute and chronic diseases containing a skin ailment
- Subjects who have signed a consent form voluntarily after being informed orally, as well as in writing, of its test object and all related contents.
- Subjects who can be observed and traced for all the experiment period.

7.2. Exclusion of Selection Conditions.

- Woman who are in a period of pregnancy and lactation.
- Individuals with tatoo or scar or external wounds such as erythema, crust ,scratch on the test area.
- Individuals with a medical history related with skin response or medical treatment.
- Individuals who have systemic allergies or serious irritation for cosmetics and medical supplies and/or hypersensitivity to sunlight (general photosensibility)
- Individuals who are using steroid and a medicine for external application.
- From the study starting time, individuals who ever participated in other similar study within 3 months
- Individuals who are brought judgment being in trouble with the clinical test by chief researcher or the researcher in charge, besides all of the above.

7.3. Exclusion Criteria During The Study Period

- Non-complience to the study orders/study restrictions
- The unexpected occurrence of an exclusion is happened or diseases which may affect study result for the observation period.
- Subject who doesn't want to participate to the study.

8. Number of Subjects & Calculation Basis

Number of subjects selected over 30 people and it was conducted in accordance with Korea Food and Drug Administration (KFDA) regulations for approval regarding the functional cosmetics and others(2009-166).

9. Test Method

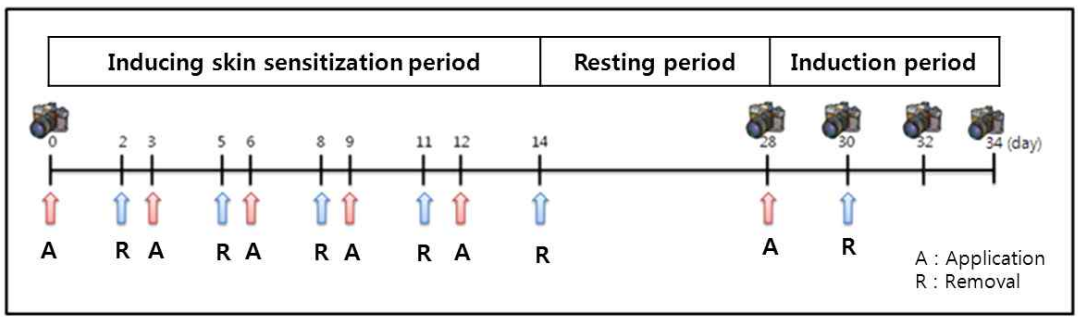
9.1. Application Area of Test sample : Subject's flat oxter area except for coloring and skin damaged area.

9.2. Before application of the test sample, we did take a picture of test area and drew up a questionnaire about the subject's skin type.

9.3. Application of the test sample

- After equipped with filter paper to Finn chamber, 40ul of test sample is loading on the middle part of filter and then, attached to the skin and fixed it with 3M Micropore Tape.
- Finn chamber applied with test sample is attached on the test area for 48 hours.
- After 48hours, removed Finn chamber.
- After 24 hours from removing Finn chamber, attached it for 48 hours over and over again about 5 times.
- Took a rest period for 2 weeks without any treatment.
- After 2 weeks of rest period, attached finn chamber with test sample on the test area for 48 hours.
- After 48hours, removed Finn chamber. and then took a picture of patch's application area and, at the same time, dermal reactions level were evaluated at each 1hr, 48hr and 96hr. Also conducted inspecting of questionnaire evaluation about stinging, glow and itching for the test area. (Fig 1.)

<Fig 1. Test Schedule>



10. Evaluation Method

Skin Type, Skin condition

- Evaluation Item : Visual evaluation (by researcher),
  Subjective Evaluation (by Subjects)
- Evaluation Method :
  Evaluation according to Frosch & Kligman, CTFA Guideline

10.1. Preliminary research of the subjects : This study was inspected through a subject's questionnaire.

- Skin Type : Check skin type which the subject has (dry skin, normal-dry skin, normal skin, normal-oily, oily skin trouble skin)

- Skin Condition : Skin ailment, iching, stinging, erythema, side effect of the cosmetic, side effect of the drug, photosensitization, Baby eczema & Atopy experiments

10.2. Evaluation Item

- Visual evaluation by researcher : The level of comming out in erythema, horny substance and edema on the test area.
- Subjective Evaluation by Subjects : The level of stinging, glowing and itching which the subjects felt by themselves.

10.3. Evaluation Method of skin irritation grade

Evaluation according to Frosch & Kligman, CTFA Guideline

- Visual evaluation by researcher was estimated by following standards (Table2, Fig1) which are conducted in accordance with Frosch & Kligman and The Cosmetic, Toiletry, and Fragrance Association(CTFA) guideline.

<Table2 . Recording of patch test reactions>

Mark	Grade	Evaluation criteria
+	1	Slight erythema, either spotty or diffuse
++	2	Moderate uniform erythema
+++	3	Intense erythema with edema
++++	4	Intense erythema with edema & vesicles

- Skin Reaction Grade is calculated by following formula.

$$\text{Skin Reaction Grade} = \left(\frac{\sum_{i=1}^{43} Score}{43}\right)_{1h} + \left(\frac{\sum_{i=1}^{43} Score}{43}\right)_{48h} + \left(\frac{\sum_{i=1}^{43} Score}{43}\right)_{96h}$$

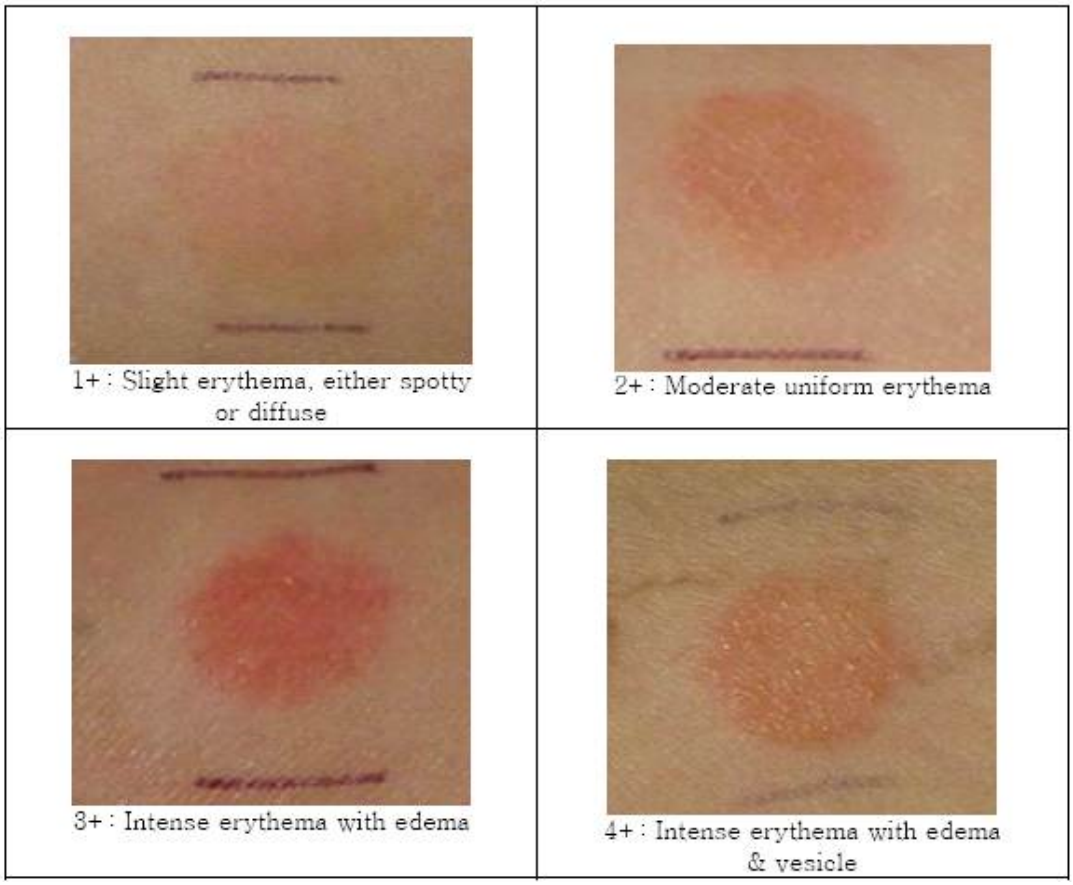
(i: The number of subjests, 43 : The number of total subjects)

- Skin Irritation Index of test sample is calculated by following formula.

$$\text{Skin Irritation Index} = \frac{Skin\ reaction\ grade}{n}$$ (n: The number of evaluation)

- Skin Irritation Grade of test sample is evaluated by referring to Skin Irritation Index (Table 3.)

<Fig 2. Clinical standard photographs of visual assessment for human patch test>



<Table3 . Skin Irritation Index>

Skin Irritation Index	Classification	Remark
0.00 - 0.25	Non-Irritant	6.25%
0.26 - 1.00	Slightly irritant	25.00%
1.01 - 2.50	Very irritant	62.50%
2.51 - 4.00	Strong irritant	100.00%

10.4. The subjective reaction evaluation was marked personally by subjects according to each evaluation list.

At this time, made the subjects be well-known for whether reaction by the test products or reaction by application area of the 3M Micropore Tape.

This results of subjective reaction evaluation could be used as a reference for skin irritation grade.

10.5. Strange reaction & Using of combined medicines.

After selection inspection of subjects for this study, every time when the subjects visited, inspected whether there was strange reaction or not, and

ever used combined medicines for the period when was from previous visiting to relevant data.

11. Test Results

11.1. Subjects Informations

Age average of 44 subjects who participated in this study is 37.0±6.7 years. Subjects are consist of 10 subjects of 21~30 years, 21 subjects of 31~40 years and 13 subjects of 41~50 years. and there are 13 male subjects and 31 female women. (Table 4.)

<Table 4. Age classification of Subjects>

Age	Number of Subjects
21-30	10
31-40	21
41-50	13

11.2. Subject who drop out during the study period.

One subject of 44 participated subjects was left out of this study because of failing to follow the visiting-schedule. so that all 43 subjects has finished this study.

This subject, who drop out, information was shown to Table 5.

< Table 5. Dropout's Infromation (n=1)>

Dropout	S21
Dropout reason	Do not follow the visit-schedule.
Date of drop out	D
Sex	Female
Age	27

11.3. Skin type and Feature of subjects

There were are 6 people of dry-skin type, 28 people of normal-dry skin type, 9 people of normal skin type as skin type of participated subjects in this study. there is no subject of oily-skin type. (Table 6.)

<Table 6. Skin type of subjects>

Skin type	Number of subjects
Dry Skin	6
Normal-Dry Skin	28
Normal Skin	9
Normal-Oily Skin	1
Oily Skin	0

For each subject, there was no skin ailment, itching, stinging, erythma, side effect of cosmetics, side effect of medicine and photosensitization as well as there was any experience of baby eczema and atopy disease.
In addition, there was also no subject who had experience of any other lists.

11.4. Evaluation results of skin irritation for three kinds of callus culture extracts by the reseacher .

After inducing skin sensitization (48hr) for three kinds of callus culture extracts, the research conducted visual evaluation for the skin irritation index and skin irritation grade. Dermal reactions were scored at 1hr, 48hr and 96hr after the application and removal of patch.

According to this evaluation result, skin irritation index of the [redacted] and skin irritation index of the *Nelumbo Nucifera Callus Culture Extract* is 0.097. All these three products are identified as a non-irritant. (Table 7.)

<Table 7 Skin Irritation Index & Skin irritation Grade of Test Products>

Products Name	Skin Irritation Index	Skin irritation Grade
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Non-irritant
Nelumbo Nucifera Callus Culture Extract	0.097	Non-irritant

11.5. The subjective skin irritation evaluation result of three kinds of callus culture extracts by the subjects

By the subjects, it has been conducted subjective evaluation about stinging,

glowing and itching for three kinds of callus culture extracts.
This test result are shown to following (Table 8.)

<Table 8. Subjective skin irritation grade evaluation of the test products by the subject >

Test products Name	Evaluated List	Checking Time	Scoring	Number of Subdects
[redacted]	Stinging	1hr	0	0
		48hr	0	
		96hr	0	
	Glowing	1hr	2	1
		48hr	0	
		96hr	0	
	Itching	1hr	0	6
		48hr	2	
		96hr	0	
[redacted]	Stinging	1hr	0	0
		48hr	0	
		96hr	0	
	Glowing	1hr	3	2
		48hr	0	
		96hr	0	
	Itching	1hr	10	6
		48hr	4	
		96hr	0	
Nelumbo Nucifera Callus Culture Extract (C)	Stinging	1hr	0	0
		48hr	0	
		96hr	0	
	Glowing	1hr	3	2
		48hr	1	
		96hr	0	
	Itching	1hr	9	4
		48hr	3	
		96hr	1	

11.6. Evaluation results of skin irritation grade for three kinds of callus culture extracts.

After inducing skin sensitization (48hr) for three kinds of callus culture extracts, the results was evaluated visual skin reaction by the research, dermal reactions were scored at 1hr, 48hr and 96hr after the application and removal of patch, as well as another test results was shown subjective evaluation by the subjects.
Through the all these results, three samples mav have been identified as non-irritant.

11.7. Strange reaction and combined medicines.

There is not strange reaction and using of combined medicines.

12. Conclusion

This clinical test has been conducted for the evaluation of potential skin irritation induction by the three kinds of callus culture extract for the subjects, whose mean age is 20 to 50 years, who is free from acute and chronic diseases.

After inducing skin sensitization for test sample, took a 2 weeks of rest period and applied 40ul of test sample on the test area. and then it is patched on inside of upper arm for 48hr.

After removing patch, a researcher in charge evaluated skin reaction visually at each 1hr, 48hr and 96hr as well as, at the same time, subjects conducted subjective evaluation about stinging, glowing and itching.

Separately, the test is inspected for strange reaction and using of combined medicines.

The number of subjects participated in this test were 44 people and one subject was left out of this test because of failing to follow the visiting-schedule. so that all 43 subjects has finished this study.

There were are 6 people of dry-skin type, 28 people of normal-dry skin type, 9 people of normal skin type as skin type of participated subjects in this study. there is no subject of oily-skin type and sensitive skin type as well as there are not any kinds of unexpected feature.

After inducing skin sensitization (48hr) for three kinds of callus culture extract, each of skin irritation index is shown as 0.016, 0.045 and 0.09, according to the results of evaluated visual skin reaction by the research (1hr, 48hr and 96hr) and subjective evaluation by the subjects. so that these three callus culture extracts did not show any skin irritation and did not have any potential about allergic contact dermatitis induction. All these three test samples are judged as safety materials of non-irritant.

References

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Appendix 1. Subject's Information

Identification Code of Subjects	Initials	Date of birth	Age	Sex
11216-R1-01	[redacted]		39	F
11216-R1-02			43	F
11216-R1-03			39	F
11216-R1-04			42	F
11216-R1-05			37	F
11216-R1-06			29	M
11216-R1-07			28	M
11216-R1-08			25	M
11216-R1-09			26	M
11216-R1-10			48	F
11216-R1-11			43	F
11216-R1-12			28	M
11216-R1-13			38	F
11216-R1-14			46	F
11216-R1-15			33	M
11216-R1-16			31	M
11216-R1-17			31	M
11216-R1-18			39	F
11216-R1-19			40	F
11216-R1-20			39	M
11216-R1-21			27	F
11216-R1-22			24	M
11216-R1-23			36	F
11216-R1-24			40	F
11216-R1-25			37	F
11216-R1-26			25	M
11216-R1-27			41	F
11216-R1-28			38	F
11216-R1-29			39	F
11216-R1-30			44	F
11216-R1-31			45	F
11216-R1-32			37	F
11216-R1-33			38	F
11216-R1-34			44	F
11216-R1-35			28	M
11216-R1-36			43	F
11216-R1-37			30	M
11216-R1-38			50	F
11216-R1-39			42	F
11216-R1-40			39	F
11216-R1-41			37	F
11216-R1-42			37	F
11216-R1-43			37	F
11216-R1-44			44	F

Appendix 2. Skin Type and Feature of Subjects

Identification Code of Subjects	Initials	Skin Type	Skin Feature
11216-R1-01	[redacted]	Dry	None
11216-R1-02		Normal-Dry	None
11216-R1-03		Normal-Dry	None
11216-R1-04		Dry	None
11216-R1-05		Normal	None
11216-R1-06		Noemal-Oily	None
11216-R1-07		Normal-Dry	None
11216-R1-08		Normal	None
11216-R1-09		Normal-Dry	None
11216-R1-10		Normal-Dry	None
11216-R1-11		Normal-Dry	None
11216-R1-12		Normal-Dry	None
11216-R1-13		Normal-Dry	None
11216-R1-14		Normal-Dry	None
11216-R1-15		Normal	None
11216-R1-16		Normal	None
11216-R1-17		Normal	None
11216-R1-18		Dry	None
11216-R1-19		Normal-Dry	None
11216-R1-20		Normal-Dry	None
11216-R1-21		Normal	None
11216-R1-22		Normal	None
11216-R1-23		Dry	None
11216-R1-24		Normal-Dry	None
11216-R1-25		Normal	None
11216-R1-26		Normal-Dry	None
11216-R1-27		Normal-Dry	None
11216-R1-28		Normal-Dry	None
11216-R1-29		Normal	None
11216-R1-30		Normal-Dry	None
11216-R1-31		Dry	None
11216-R1-32		Normal-Dry	None
11216-R1-33		Normal-Dry	None
11216-R1-34		Dry	None
11216-R1-35		Normal-Dry	None
11216-R1-36		Normal-Dry	None
11216-R1-37		Normal-Dry	None
11216-R1-38		Normal-Dry	None
11216-R1-39		Normal-Dry	None
11216-R1-40		Normal-Dry	None
11216-R1-41		Normal-Dry	None
11216-R1-42		Normal-Dry	None
11216-R1-43		Normal-Dry	None
11216-R1-44		Normal-Dry	None

Appendix 3. Visual Evaluation result by the researcher

Identification code of subjects	[redacted]			[redacted]t (B)			Nelumbo Nucifera Callus Culture Extract (C)		
	1hr	48hr	96hr	1hr	48hr	96hr	1hr	24hr	96hr
11216-R1-01	0	0	0	0	0	0	0	0	0
11216-R1-02	0	0	0	0	0	0	0	0	0
11216-R1-03	0	0	0	1	0	0	0	0	0
11216-R1-04	0	0	0	0	0	0	3	1	1
11216-R1-05	0	0	0	0	0	0	0	0	0
11216-R1-06	0	0	0	0	0	0	0	0	0
11216-R1-07	0	0	0	0	0	0	0	0	0
11216-R1-08	0	0	0	0	0	0	0	0	0
11216-R1-09	0	0	0	1	0	0	0	0	0
11216-R1-10	0	0	0	0	0	0	1	0	0
11216-R1-11	0	0	0	0	1	0	0	1	0
11216-R1-12	0	0	0	0	0	0	0	0	0
11216-R1-13	0	0	0	0	0	0	0	0	0
11216-R1-14	0	0	0	0	0	0	0	0	0
11216-R1-15	0	0	0	0	0	0	0	0	0
11216-R1-16	0	0	0	0	0	0	0	0	0
11216-R1-17	0	0	0	0	0	0	0	0	0
11216-R1-18	2	0	0	0	0	0	0	0	0
11216-R1-19	0	0	0	0	0	0	0	0	0
11216-R1-20	0	0	0	0	0	0	0	0	0
11216-R1-22	0	0	0	0	0	0	0	0	0
11216-R1-23	0	0	0	0	0	0	0	0	0
11216-R1-24	0	0	0	0	0	0	0	0	0
11216-R1-25	0	0	0	0	0	0	0	0	0
11216-R1-26	0	0	0	0	0	0	0	0	0
11216-R1-27	0	0	0	0	0	0	0	0	0
11216-R1-28	0	0	0	0	0	0	0	0	0
11216-R1-29	0	0	0	0	0	0	0	0	0
11216-R1-30	0	0	0	0	0	0	0	0	0
11216-R1-31	0	0	0	0	0	0	0	0	0
11216-R1-32	0	0	0	0	0	0	0	0	0
11216-R1-33	0	0	0	0	0	0	0	0	0
11216-R1-34	0	0	0	0	0	0	0	0	0
11216-R1-35	0	0	0	1	0	0	1	0	0
11216-R1-36	0	0	0	0	0	0	0	0	0
11216-R1-37	0	0	0	0	0	0	0	0	0
11216-R1-38	0	0	0	0	1	0	0	1	0
11216-R1-39	0	0	0	0	0	0	0	0	0
11216-R1-40	0	0	0	0	0	0	0	0	0
11216-R1-41	0	0	0	0	0	0	1	0	0
11216-R1-42	0	0	0	0	0	0	0	0	0
11216-R1-43	0	0	0	0	0	0	0	0	0
11216-R1-44	0	0	0	0	0	0	1	0	0

Appendix 4. Subjective evaluation result by the subjects.

Identification code of subjects	[redacted]									[redacted]									Nelumbo Nucifera Callus Culture Extract (C)								
	Stinging			Glowing			Itching			Stinging			Glowing			Itching			Stinging			Glowing			Itching		
	1 h	48 h	96 h	1 h	48 h	96 h	1 h	48 h	96 h	1 h	48 h	96 h	1 h	48 h	96 h	1 h	48 h	96 h	1 h	48 h	96 h	1 h	48 h	96 h	1 h	48 h	96 h
11216-R1-01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-04	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-05	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-08	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-09	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-10	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	4	0	0	0	0	0	0	0	0	4	0	0
11216-R1-11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-12	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
11216-R1-13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-15	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0
11216-R1-16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
11216-R1-19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-26	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-37	0	0	0	2	0	0	2	0	0	0	0	0	2	0	0	2	0	0	0	0	0	2	0	0	2	0	0
11216-R1-38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-41	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11216-R1-43	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	1	1	0
11216-R1-44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	2	2	1

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: April 23, 2025

SUBJECT: Nelumbo Nucifera Germ Extract

Anonymous. 2023. Summary Information HRIPT data for the serum containing 0.001% Nelumbo Nucifera Germ Extract.

Summary Information

HRIPT data for the serum containing 0.001% Nelumbo Nucifera Germ Extract

Test procedure: Human repeated insult patch test

Date of final report: May 30, 2023

Test article: Serum containing 0.001% Nelumbo Nucifera Germ Extract

Test subject： 53 subjects (7 males and 46 females)

Results:

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.

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)

Conclusion: Test article was not associated with skin irritation or allergic contact dermatitis.

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: May 22, 2025

SUBJECT: Nelumbo Nucifera Germ Extract

Anonymous. 2025. Safety Data of Nelumbo Nucifera Germ Extract Short Time Exposure (STE) test (OECD TG 491) (Raw material containing 1% Nelumbo Nucifera Germ Extract).

Safety data of Nelumbo Nucifera Germ Extract

Here we summarized the Ocular irritation data (*in vitro*) of raw material containing 1% Nelumbo Nucifera Germ Extract.

Ocular irritation

Test guideline: Short Time Exposure (STE) test (OECD TG 491)

Test substance: Raw material containing 1% Nelumbo Nucifera Germ Extract

Year: 2025

The aim of this study was to classify the ocular mucosal irritancy of the test substance using the *in vitro* ocular mucosal irritation test method (TG 491) of the OECD test guidelines, which is an alternative to animal testing. In this study, the positive control, negative control, and test substance were each exposed to SIRC cells for 5 minutes, and the cell viability was measured using the MTT assay. The ocular mucosal irritancy was classified based on the cell viability. To evaluate the test substance at a concentration of 100%, it was prepared to 5% with physiological saline and further diluted to 0.05% through a two-step dilution with a dilution factor of 10. Solutions of the test substance at 5% and 0.05% were used for the tests.

Results:

5% cell viability: 92.9% ± 12.4% (Mean ± standard deviation)

0.05% cell viability: 96.5% ± 5.2% (Mean ± standard deviation)

Conclusion:

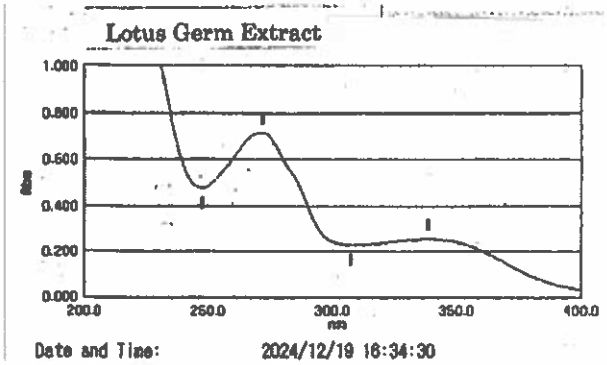
Category: No category

The test substance at a concentration of 100% is non-irritating to the eyes.

Memo 9 Jan 2, 2025

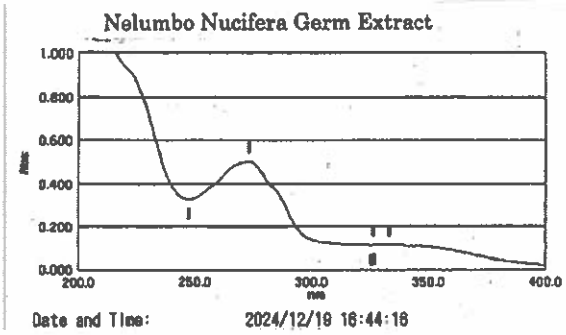
Addition

5. UV absorption spectra



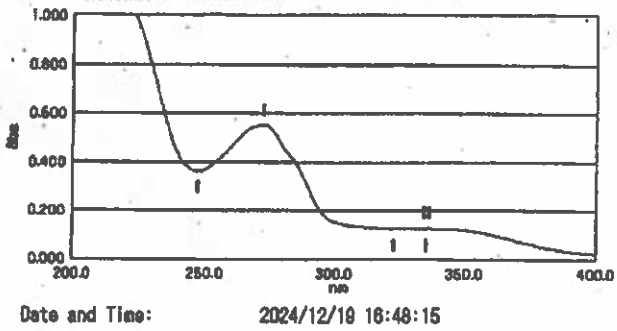
Peak
WL/nm Abs
338.90 0.250
272.10 0.716

Valley
WL/nm Abs
307.30 0.224
247.70 0.476



Peak
WL/nm Abs
333.50 0.111
326.40 0.111
273.00 0.502

Valley
WL/nm Abs
327.00 0.111
325.70 0.110
247.40 0.325



Peak
WL/nm Abs
337.10 0.124
335.30 0.123
273.00 0.552

Valley
WL/nm Abs
336.00 0.123
323.10 0.122
247.40 0.358

All extracts in water and Butylene Glycol

Trade name	Absorption maximum
Lotus Germ Extract	272.1nm
Nelumbo Nucifera Germ Extract	273.0nm
Lotus Germ Extract	273.0nm