Safety Assessment of *Zingiber officinale* (Ginger) – Derived Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	November 10, 2022
Panel Meeting Date:	December 5 – 6, 2022

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

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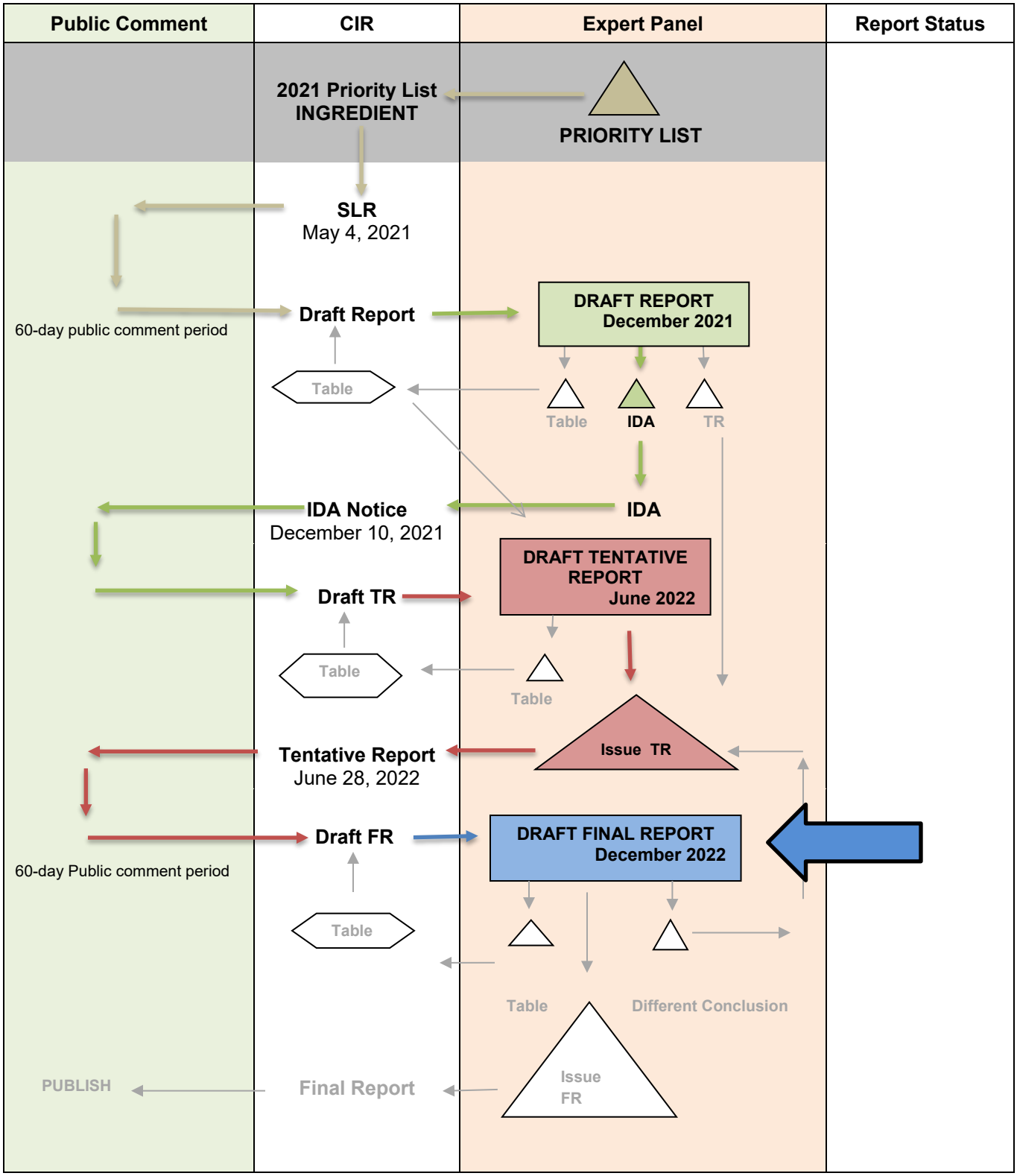
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Zingiber officinale* (ginger)-derived ingredients

MEETING December 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Senior Scientific Analyst/Writer, CIR
Date: November 10, 2022
Subject: Safety Assessment of *Zingiber officinale* (Ginger)-Derived Ingredients

Enclosed is the Draft Final Report of the Safety Assessment of *Zingiber officinale* (Ginger)-Derived Ingredients as Used in Cosmetics (*report_Ginger_122022*). The following 9 ginger-derived ingredients are reviewed in this report:

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Leaf Cell Extract
Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

At the June 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that the 7 *Zingiber officinale* (ginger) root- and rhizome-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing. In addition, the Panel concluded that the available data are insufficient data to make a determination that Zingiber Officinale (Ginger) Extract and Zingiber Officinale (Ginger) Leaf Cell Extract are safe under the intended conditions of use in cosmetic formulations.

In order to determine safety for Zingiber Officinale (Ginger) Leaf Cell Extract, the Panel requires method of manufacturing, composition, and impurities data. If the composition of Zingiber Officinale (Ginger) Leaf Cell Extract notably differs from the root-derived ginger ingredients, systemic toxicity data (e.g., 28-d dermal toxicity, genotoxicity, developmental/ reproductive toxicity, and carcinogenicity data) would also be required. Insufficiencies for Zingiber Officinale (Ginger) Extract are irritation and sensitization data at the maximum use concentration.

No additional data were submitted. Comments on the Tentative Report that were received from the Council (*PCPCcomments_Ginger_122022*) have been addressed. A comments response checklist is included (*response-PCPCcomments_Ginger_122022*).

Also included in this packet are the report history (*history_Ginger_122022*), data profile (*dataprofile_Ginger_122022*), search strategy (*search_ Ginger_122022*), transcripts of the previous meetings (*transcripts_ Ginger_122022*), 2022 FDA VCRP data (*VCRP_Ginger_122022*), and flow chart (*flow_ Ginger_122022*).

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

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: July 11, 2022

SUBJECT: Tentative Report: Safety Assessment of *Zingiber officinale* (Ginger) – Derived Ingredients as Used in Cosmetics (release date June 28, 2022)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of *Zingiber officinale* (Ginger)–Derived Ingredients as Used in Cosmetics.

Method of Manufacture, Zingiber Officinalis (Ginger) Extract – Please revise "rotary vapor" to "rotary evaporator" to be consistent with what this apparatus is called in the rest of this section.

Non-Cosmetic Use – Using the words "has been used", "may be consumed" and "may also be incorporated" suggests there might be some doubt that ginger is currently used in many types of food. Please change these to "is used", "are consumed" and "is incorporated".

Acute – Please indicate the endpoints examined in the acute toxicity studies (references 38 and 40).

Short-Term – The last sentence of the summary of the 60-day study states: "Test effects were reversed after study termination." Which implies a recovery group. A recovery group is not mentioned in the description of the methods. What dose was used for the recovery group? How long was the recovery period?

Subchronic; Summary – Since both the fixed and volatile oils are mentioned in this report, it would be helpful to clarify the oil used in the 13-week oral study in Wistar rats (reference 44). The abstract states that the oil tested contained 31.08% zingiberene (which would be helpful to state in the CIR report), consistent with the essential oil.

Immunomodulatory Effects, ginger extract; Summary – In the study from reference 57 was there an HDM control group? It does not make sense that ginger decreased effects compared to control mice treated with vehicle only. The control mice were likely treated with HDM and the vehicle used for the ginger extract.

Ginger-derived ingredients - December 2022 – Priya Cherian	
Comment Submitter: Personal Care Products Council **Date of Submission: July 11, 2022**	
Comment	**Response/Action**
Method of Manufacture, Zingiber Officinalis (Ginger) Extract – Please revise "rotary vapor" to "rotary evaporator" to be consistent with what this apparatus is called in the rest of this section.	addressed
Non-Cosmetic Use – Using the words "has been used", "may be consumed" and "may also be incorporated" suggests there might be some doubt that ginger is currently used in many types of food. Please change these to "is used", "are consumed" and "is incorporated".	addressed
Acute – Please indicate the endpoints examined in the acute toxicity studies (references 38 and 40).	details were not provided for reference 38
Short-Term – The last sentence of the summary of the 60-day study states: "Test effects were reversed after study termination." Which implies a recovery group. A recovery group is not mentioned in the description of the methods. What dose was used for the recovery group? How long was the recovery period?	addressed
Subchronic; Summary – Since both the fixed and volatile oils are mentioned in this report, it would be helpful to clarify the oil used in the 13-week oral study in Wistar rats (reference 44). The abstract states that the oil tested contained 31.08% zingiberene (which would be helpful to state in the CIR report), consistent with the essential oil.	addressed
Immunomodulatory Effects, ginger extract; Summary – In the study from reference 57 was there an HDM control group? It does not make sense that ginger decreased effects compared to control mice treated with vehicle only. The control mice were likely treated with HDM and the vehicle used for the ginger extract.	addressed

Zingiber officinale (Ginger)-Derived Ingredients – History

February 2021

- Concentration of use received for ingredient group

May 2021

- SLR posted
- Data received:
    - Repeat insult patch test; 104 subjects; serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract
    - 48-h dermal irritation assay; 10 subjects; product containing 0.0995% Zingiber Officinale (Ginger) Root Extract
    - Repeat insult patch test; 53 subjects; product containing 0.2% Zingiber Officinale (Ginger) Root Extract
    - Manufacturing information on Zingiber Officinale (Ginger) Water
    - Ingredient breakdown of Zingiber Officinale (Ginger) Water
    - Manufacturing information on Zingiber Officinale (Ginger) Root Extract
    - Composition information on Zingiber Officinale (Ginger) Root Extract
    - Specifications on a Zingiber Officinale (Ginger) Root Extract
    - In vitro dermal and ocular irritation assays on a Zingiber Officinale (Ginger) Root Extract
    - In chemico skin sensitization assay on a Zingiber Officinale (Ginger) Root Extract
    - In vitro skin sensitization assay on a Zingiber Officinale (Ginger) Root Extract

June 2021

- Comments on SLR received from PCPC

December 2021

- Comments on Draft Report received from PCPC
- Panel reviews Draft Report and issues an IDA. The Panel requested method of manufacturing, composition, and impurities data on Zingiber Officinale (Ginger) Leaf Cell Extract. If the composition of Zingiber Officinale (Ginger) Leaf Cell Extract notably differed from the composition of the remaining ginger ingredients, systemic toxicity data (28-d dermal toxicity, genotoxicity, developmental/reproductive toxicity, and carcinogenicity data) and dermal irritation/sensitization data was also requested. In addition, if available, the Panel requested information regarding the specific plant parts (e.g., leaves, rhizome) used in the preparation of the whole plant extract (Zingiber Officinale (Ginger) Extract).

January 2022

- Unpublished data received: Product specifications for a trade name mixture consisting of Ginger Officinale (Ginger) Root Extract (1-5%) and helianthus annus (sunflower) hybrid oil
- Unpublished data received: Chemical/physical properties and specifications on a trade name mixture consisting of Zingiber Officinale (Ginger) Water (98.5%) and phenoxyethanol (1.5%)
- Unpublished data received Manufacturing, specifications, and composition/impurities data on a trade name mixture consisting of Zingiber Officinale (Ginger) Root Extract (≤ 1.5%), propylene glycol (68.5%), and water (30%)

February 2022

- Unpublished data received: HRIPT performed using a moisturizer containing 0.1% Zingiber Officinale (Ginger) Rhizome Extract (n = 54); negative results

June 2022

- Panel reviews Draft Tentative Report
- Tentative Report posted

July 2022

- Comments on Tentative Report received from PCPC

December 2022

- Panel reviews Draft Final Report

***Zingiber officinale* (ginger)-derived ingredients Profile – December 2022 – Writer, Priya Cherian**																														
				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**	**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**
Zingiber Officinale (Ginger) Extract	**x**	**x**		x				x			x				x				x			x				x			x
Zingiber Officinale (Ginger) Leaf Cell Extract																														
Zingiber Officinale (Ginger) Rhizome Extract	**x**	**x**						x			x			x										x					
Zingiber Officinale (Ginger) Root																														
Zingiber Officinale (Ginger) Root Extract	**x**	**x**	x		x	x					x								x	x	x	x		x		x			
Zingiber Officinale (Ginger) Root Juice		**x**																												
Zingiber Officinale (Ginger) Root Oil	**x**	**x**									x				x															
Zingiber (Ginger) Root Powder	**x**	**x**	x					x			x			x																x
Zingiber Officinale (Ginger) Water		**x**	x																											

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

Zingiber Officinale (Ginger)-Derived Ingredients

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Zingiber Officinale (Ginger) Extract		yes	yes	no	no	no	no	yes	yes	yes	no	no	no	no	yes	no	yes
Zingiber Officinale (Ginger) Leaf Cell Extract		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Rhizome Extract		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Root		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Root Extract		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Root Juice		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Root Oil		yes	yes	no	no	no	no	yes	yes	no	no	no	no	no	no	no	yes
Zingiber (Ginger) Root Powder		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Water		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	AGRICOLA	IFRA	RIFM
Zingiber Officinale (Ginger) (general)		yes	yes	yes	no	no	no	no	no
Zingiber Officinale (Ginger) Extract		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Leaf Cell Extract		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Rhizome Extract		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Root		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Root Extract		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Root Juice		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Root Oil		no	no	no	yes	no	no	no	no
Zingiber (Ginger) Root Powder		no	no	no	yes	no	no	no	no

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	AGRICOLA	IFRA	RIFM
Zingiber Officinale (Ginger) Water		no	no	no	no	no	no	no	no

Search Strategy

- All search terms were used in PubMed and ToxNet
- INCI names and CAS numbers were searched in the "Pertinent Websites" listed below

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- Search terms:
  - Allergy
  - Sensitization
  - Irritation
  - Metabolism
  - Manufacturing
  - Production
  - Synthesis
  - Clinical
  - Reproduction
  - Inhalation
  - Maternal
  - Ocular
  - Eye
  - Dermal
  - Cosmetic
  - Respiratory
  - Dermal Penetration
  - Absorption
  - Toxicity
  - Carcinogenicity
  - Mutagenicity

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

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- 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/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- 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
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- 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) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- 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

DECEMBER 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – December 6. 2021

(Audio Skip - Beginning of Ginger Missing)

DR. BELSITO: -- because I said there are reports of it being used at a hundred percent.

MS. CHERIAN: That was actually --

DR. BELSITO: Yeah. That's the root oil and I was wondering if that was homeopathic or aromatherapy?

MS. CHERIAN: So that was actually one question that I had for Carol. When we got the concentration of use data, under ginger oil they had -- they're saying for a hundred percent but then there was an asterisk and it said, "essential oil 100 percent."

DR. BELSITO: Yeah.

MS. CHERIAN: I wasn't sure what the actual concentration of the ginger root oil was.

DR. EISENMANN: Well, they're selling a hundred percent ginger root essential oil. Like other essential oils come in these little, tiny bottles and you're just supposed to put a few drops in another carrier oil.

DR. BELSITO: So it's sold as a hundred percent pure ginger oil?

DR. EISENMANN: Right.

DR. BELSITO: But is it sold as a cosmetic or is it sold as a homeopathic or aromatherapy?

DR. EISENMANN: I don't know that it's specifically sold as a cosmetic, but you could add it to another oil and you then use the scented oil like a massage oil.

DR. BELSITO: Yeah, I mean, I had patients with that all the time, but I would not consider that a cosmetic use.

DR. EISENMANN: Yeah, I don't know whether I should be reporting that when somebody tells me that or not. But I just wanted to be sure you know the essential oil is being sold at a hundred percent.

DR. BELSITO: Yeah, but --

DR. EISENMANN: If you want to not put it in the cosmetic Use table and just put it in the report as another use, I wouldn't have a problem with that.

DR. BELSITO: Yeah, I mean because I get cosmetic ingredients at a hundred percent all the time when I'm interested in patch testing them and I order them from Sigma-Aldrich or some other supplier at a hundred percent. So they're sold at a hundred percent, many of them. I mean, it's just so far out of line because otherwise, the highest reported use is 0.004. I mean, I don't know what to do, but I mean, quite honestly, almost any cosmetic ingredient you can get in the ultimate pure form from the manufacturer or through a supply house.

DR. EISENMANN: You can, I mean, the average consumer could go out to a store and buy a hundred percent ginger oil.

DR. BELSITO: As well as a hundred percent of a lot of other things.

DR. EISENMANN: Right, right. So, I mean, I'm not sure the best place to put it, but I thought I needed to tell you that somebody told me this.

DR. BELSITO: Right.

MS. KOWCZ: Don, this is Alex, and I'm just going to jump in with Carol right now. Any essential oil, as you just pointed out very clearly, can be gotten at a hundred percent. I think we need to figure out what we want to do with this one, but I don't think this is how we are meant to look at this ingredient because the ingredient -- we have the concentration usage in the table.

DR. BELSITO: Right.

MS. KOWCZ: I think you should go with your best judgment, Don, and I think you're totally 100 percent right. Anybody can get anything at a hundred percent. You are correct.

DR. BELSITO: The experience of the North American group testing with essential oils is that when you start using them at fairly high concentrations, not even a hundred percent, but certainly a hundred percent you get significant irritation. So I doubt that anyone would formulate a cosmetic. I have no experience with ginger oil, but I have experience with a lot of other essential oils, and they are irritating. You really have to dilute them when you're testing.

MS. KOWCZ: Correct. Thanks, Don. Thank you for hearing us out.

DR. BELSITO: Yeah. I mean, I wouldn't even list it. I mean, I think this is a sale in some homeopathic or aromatherapy shop. It's not a cosmetic sale.

DR. HELDRETH: We could move it to non-cosmetic use if that's amenable?

DR. BELSITO: Yeah. Put it in non-cosmetic since we haven't been told that it's non-cosmetic. We could say that -- what did you get, Carol, one report?

DR. EISENMANN: Correct, one report.

MS. CHERIAN: Right.

DR. BELSITO: That there was one report to the council of a product containing a hundred percent ginger oil. Assumed by the Panel to be a non-cosmetic use or something like that. Let's hear what the other team has to say, but, I mean, that's just not believable to me. Okay.

DR. LIEBLER: I agree with that approach.

DR. BELSITO: In the irritation and sensitization study on page 22, for the HRIPT, do we have the number of patients that were tested? They're not given.

DR. SNYDER: No, we received new data of 104 at 0.2 percent root extract, and 53 at 0.2 percent root extract. We got new data.

DR. BELSITO: Yeah, I guess I missed the ends there, okay. We just need to put the -- oh, no, I didn't -- we need to put the ends in -- sorry -- in the text. Okay, so I thought that the root, the rhizome, and the water are safe as used. And that we need to discuss the respiratory issues, whether we need anything in there, and that it was insufficient for the leaf, manufacturing, composition and impurities, and depending upon that other data endpoint. Is that where everyone else is?

DR. LIEBLER: Yeah, I think that's the only one that's insufficient, right?

DR. BELSITO: Leaf.

DR. LIEBLER: Yeah, the leaf cell culture extract.

DR. BELSITO: Right. Curt and Paul, you're okay with that?

DR. KLAASSEN: I'm okay with that. I have one other small point. The second page, with the abbreviations, the word abbreviation is misspelled.

MS. CHERIAN: I can fix that, thank you.

DR. BELSITO: Okay. So, for sufficiency for the leaf cell culture, we would need manufacturing composition, impurities, anything else? Do we need sensitization -- well, I guess in other data endpoints depending upon this, which would include sensitization?

DR. LIEBLER: Correct. So the usual downstream of defining it.

DR. BELSITO: Right.

DR. LIEBLER: Twenty-eight-day dermal, et cetera, et cetera.

DR. BELSITO: Okay. Discussion, obviously, here we need the botanical boilerplate because we have a bunch of potential sensitizers that we know are in ginger. Then the question is with respiratory. We have no -- the underarm, Carol, you said, is a non-spray?

DR. SNYDER: No, it's unknown. The A footnote says it's a spray. It does not indicate -- is not specified. It is possible these are sprays, so we don't know. Also, we don't know the concentration of use for that spray. Yeah.

DR. BELSITO: Okay. Where are we with -- we have no inhalation data at all on this.

DR. SNYDER: Again, I think we capture it by no tox signals. The concentrations of use are very, very low, so there wouldn't be significant exposure. Like the one report where we had that the -- even for the deodorant, we would expect it would be within the range of concentrations reported for other uses, right?

DR. BELSITO: Right. Okay. Go ahead.

DR. LIEBLER: Ginger deodorant? Oh my god.

DR. BELSITO: Well, I mean --

DR. LIEBLER: Just the thought of it made Priya cough.

DR. SNYDER: I do think we need to -- Carol, I would like to bring back up that we need to clarify this because, under the root oil, we have the deodorant underarm, and then we need to clarify what that means. I guess you'd clarify is that it could be a spray, and it's not specified otherwise.

DR. EISENMANN: Well, if it comes from the VCRP, I can't clarify it.

DR. SNYDER: Okay.

DR. EISENMANN: That's coming from the VCRP, so --

DR. SNYDER: All right.

DR. LIEBLER: But, Paul, I do like your idea of bringing in sort of the logic we articulated earlier for accessing the risk based on lack of toxicity signals for the ingredient and other endpoints, low concentration of use. So that dramatically decreases our concern about possible inhalation tox risk.

DR. SNYDER: Yeah, I mean, the tox on this is, I mean, off the charts. I mean, we got NOAELs of greater than 500 milligrams per kilogram, repro, NOAEL greater than 500 milligrams. So the toxicity signal is not there, the use is really low, and so, even with it being a deodorant, if it's in the range of this 0.0046 to 0.009, I mean, there's just no cause for concern.

DR. BELSITO: Okay.

DR. SNYDER: That's why I think we need to craft these all individually by ingredient.

DR. BELSITO: Right. Okay.

DR. SNYDER: That one that Wilbur did where he put in there that the concentrations of the two forms of the botanical and how -- that was really nice. I thought so.

DR. BELSITO: Okay. So, discussion so far, we have lack of respiratory data as indicated by the fact that there are no tox signals and low concentration of use. And botanical boilerplate for sensitizations, we can mention specifically citronellol or just say that there are other sensitizers there. Anything else to go into the discussion?

DR. LIEBLER: I think you've hit the main points.

DR. BELSITO: Okay, and then we're going insufficient for leaf and that would be composition, manufacturing, and impurities, and depending upon this, other data may be necessary.

DR. LIEBLER: Right.

DR. BELSITO: Okay. Anything else?

DR. SNYDER: It's significantly different from the root, yes. Yeah.

DR. BELSITO: Right, correct.

DR. SNYDER: Yeah. It's good.

DR. BELSITO: Anything else? Priya, you're all set with this?

MS. CHERIAN: I'm all set.

DR. BELSITO: Okay. So we're moving to acrylamide/acrylate copolymers.

Cohen Team – December 7, 2021

DR. COHEN: -- we have a frequency of use that's in a number of things and some issues about the rhizome versus the root and the leaf cell extracts sort of came up here. So, Lisa, can we -- what's your interpretation in profile in reading across?

DR. PETERSON: Yeah, so I mean based on -- I consider the root the same as a rhizome because when you look at the method of manufacturing for the rhizome or root it talks about the opposite, so I think that the industry probably use the rhizome and root as the same. And we have a method of manufacturing on everything but leaf cell extracts and the ginger root. But those aren't in use, but if they are, we don't have a method of manufacturing. We only have impurities for two out of the nine, but I think the main issue is basically a concern for pesticides and heavy metals so that -- and I believe we just need to include the boilerplate for that.

I mean, I thought the ginger root could be covered by the extracts for the root and rhizomes and oils, but of course it's going to have slightly more in it. But we don't really know -- when they say ginger root, we don't know what they mean. You know, it clearly isn't a chunk of ginger root. But it could be just ground up and dried or something, so it wasn't clear. And because it would've been the whole thing, I guess there might be some issues, some chemicals that get deleted in the extracts that might be present in the root that can cause problems. But, again, this is not one that's got any recorded use.

Those are the two that I thought needed more clarification where the leaf cell extract and the root.

DR. COHEN: For method of manufacturing or for impurities or --

DR. PETERSON: For both.

DR. COHEN: For both.

DR. PETERSON: For both. And then I felt that the impurities, we have it for the root extract, and we have it for the root powder. And the main concern about the impurities is the pesticides and heavy metals, that kind of thing, and I just think we put in the boilerplate -- could cover that. And, again, I'll defer to those who have been on this committee longer whether we need to actually get -- put that as insufficient and then use the boilerplate as a backup since this is the first (audio skip 00:45:24).

DR. SHANK: Ginger extract --

DR. SLAGA: Is sufficient.

DR. SHANK: The extract (audio skip 00:45:33) irritation and sensitization data on the extract and root extract at greater than maximum use concentrations in leave-on products and that was negative. So, I think the extract and the root extract, those are safe as used. We don't have any useful information on the leaf cell extract, and there are no uses listed. So that leaf cell extract would be insufficient.

DR. BERGFELD: Ron, do you think that the ginger extract does include the whole plant?

DR. SHANK: That's my understanding.

DR. BERGFELD: So, it would include the leaf?

DR. SHANK: Yeah.

DR. PETERSON: But we don't really know.

DR. SLAGA: That's right.

DR. PETERSON: Now, if you look at the method of manufacturing for the (audio skip 00:46:40).

DR. BERGFELD: You said it was dried and pulverized.

DR. COHEN: But isn't our sensitization just on root extract at 0.2 percent? We have two, 1.19 and 0.2 percent. They're both root extracts.

DR. SHANK: Right.

DR. SLAGA: Right.

DR. PETERSON: Could we get clarification (audio skip 00:47:04).

DR. SLAGA: I agree with Ron, I think the ginger root being GRAS can have sufficient data, sensitization/irritation. That part's fine.

DR. COHEN: So --

DR. SLAGA: The leaf is the only question.

DR. SHANK: I have this one question for Lisa. In the chemical properties -- physical and chemical properties, the roots extract, they give a log KOW. What does that mean? How do you get a partition coefficient for a mixture?

DR. SLAGA: You can't.

DR. PETERSON: Yeah, yeah. I had the same question.

DR. SHANK: Okay. It's there, but I don't know what it means.

DR. PETERSON: There's a reference. We could look it up and see what they actually did but --

DR. SHANK: We have the same thing in another report. I don't remember it right now what it is.

DR. PETERSON: Yeah, I remember that.

DR. SHANK: Okay. So, except for the leaf cell extract, I think this is safe as used.

DR. PETERSON: Yeah.

DR. COHEN: So, we're going with eight of the nine as safe as used?

DR. SHANK: Yes.

DR. BERGFELD: I guess you'd have to get clarification what they mean by ginger extract.

DR. SHANK: Right.

DR. COHEN: Leaf cell extract.

DR. BERGFELD: Yeah, it's the *zingiber officinale* ginger extract, the first one. If it includes the leaf, you don't need the leaf stuff --

DR. SLAGA: Right.

DR. BERGFELD: -- except what was noted in the impurities in the discussion, the boilerplates for the botanicals, the manufacturing practice, impurities, heavy metals, pesticides.

DR. SHANK: But we don't have any information on the use of the leaf extract. (audio skip 00:49:45).

DR. COHEN: Okay.

DR. BERGFELD: I'm sorry, which is the second that you're --

DR. COHEN: The extract and the leaf cell extract.

DR. BERGFELD: The two of them. Okay.

DR. SLAGA: Yeah.

MS. FIUME: That was useful, and I noted that in my document.

DR. ANSELL: We'll look into that, but I'm looking to the report. I'm not sure we're going to get much on leaf because it's not used.

MS. FIUME: Can I ask for (audio skip 00:51:10) being seen so this will be going out as an IDA?

DR. COHEN: IDA.

MS. FIUME: And then I just have a question. It's not the leaf. It's a cell extract, and I'm trying to think (audio skip 00:51:27) PCPC can help. I know sometimes when we get anything with the cell extract, it's actually different that the leaf itself because of the way its manufactured, and I can't remember if leaf cell extract is one of those issues as well because it's an extract of a culture.

DR. SHANK: Oh.

MS. FIUME: Not the leaf itself.

DR. SHANK: Oh.

MS. FIUME: And is that a concern?

DR. ANSELL: I don't think that I can --

DR. SHANK: And we don't know what it is.

DR. ANSELL: Yeah, and it's not used, and I'm not sure to what we've done historically on cell extracts as it relates to with the parent, so --

MS. FIUME: If I remember correctly, I think the cultures were treated differently than the leaves themselves. At tomorrow in full Panel there may -- because I do know it's come up. Others may have total recollection as to how it was treated, but usually, I think, because it's a culture, it's considered different.

DR. SHANK: That's a good point.

DR. COHEN: So, let me reiterate. So, we have safe as used for seven of the nine. We have an IDA for extract and leaf extract. We want to know if the extract is the whole plant. We don't have method of manufacturing on leaf cell extract, right?

MS. CHERIAN: No, we don't.

DR. COHEN: No. So, we want that. And what else do we specifically want in the IDA? I want to be as specific as possible in our ask.

DR. BERGFELD: Could I ask -- could I have you look at Table 1, and it says that the ginger extract is an extract of the whole plant. It says it there. And then the second item, the leaf cell extract, is an extract of a culture of the leaf cells.

DR. COHEN: What does that mean? I'm not sure I understand what that is.

DR. BERGFELD: Well, something must multiply -- some part of the leaf.

MS. FIUME: I know it was discussed a number of years ago. I don't know if I would be able to find it in the minutes. I can try and look later tonight because there was some clarification given. Bart may recall when we're in full panel tomorrow, or Don may recall as well because I know when we've talked about cultures it is different. They take them and grow them, so it could be different than the plant itself. But I'd have to look back and see if I can find that information.

MS. CHERIAN: With a Google search it says that leaf culture is the culture of excised young leaf primordia or immature young leaf of the shoot apex. And I'm kind of remembering that now -- the stem cells.

DR. COHEN: Okay. Well, that adds some clarity, and Wilma took out the question -- the extract is the whole plant. So, what are we left asking for? I'm still new at this, right? This is my one-year anniversary. So we're going to issue this IDA on two

of the seven, right?. And I'm getting the sense that we don't have comfort around what's in the leaf. We don't have irritation/sensitization around the leaf, right?

DR. SLAGA: But if it's part of the whole plant then extract was (inaudible) right? It's only the cell once we take the leaf and process it to try to grow it in culture is the only -- and I agree with Monice. We discussed this for half hour at one time in the past. And keep in mind when you put anything in culture and if it's growing on plastic, it's different -- it becomes different. And this has been a big issue in all type of research. Once you grow it on plastic, it changes. It has to adapt (audio skip 00:56:35). And we had the discussion of this a long time ago, and I don't remember the details.

DR. COHEN: But, Tom, the only reason I brought that up is -- and by the way, thank you for that -- is that our sensitization/irritation is only on the root extract.

DR. PETERSON: Right.

DR. SLAGA: Right.

DR. COHEN: We don't have sensitization and irritation on (audio skip 00:56:58) ask for that.

DR. PETERSON: Yeah, the insufficient would be for the leaf cell extract and (audio skip 00:57:13) data, right. You have (audio skip 00:57:23) dermal irritation. You have some data for dermal sensitization, and you have some --

DR. COHEN: Where's the dermal sensitization for -- oh, you mean the in vitro?

DR. PETERSON: Yeah, I'm looking at the table on page 8 -- the summary table of what's there, and we basically said that everything that's from the root --because the root is GRAS and we've got data on the extract -- that they're safe as used. The only two where there's some question would be the whole plant extract, which is the first line, and the leaf cell extract which you have no information on, and those have different components in it and then could potentially have different safety issues. So there's no data on the leaf extract, so we need almost everything for that.

And then for the ginger extracts, I mean according to this table there's dermal irritation. There's dermal sensitization, and there's ocular irritation. Some of it's in vitro.

DR. COHEN: It's all in vitro, isn't it?

DR. PETERSON: Right. So, if you want, then you need to ask for (audio skip 00:58:47) I guess you want the human.

DR. COHEN: Yeah, that's why I originally came back I wanted sensitization/irritation on the extract or the leaf extract. Now, I think if we got it for either one of those two, we'd probably be okay.

DR. SLAGA: Right.

DR. COHEN: Although, Tom, you're kind of leaning more towards worst case scenario is the leaf extract has morphed its character enough to be different than the plant, so if we had that, we'd probably role with the rest of them.

DR. SLAGA: Right, I would go with that.

DR. COHEN: And we want method of manufacturing and impurities for the leaf extract -- leaf cell extract.

DR. PETERSON: Yeah, we don't have any. We don't have it.

DR. COHEN: All right. I'm sorry I kept pulling us back around. I know when I have to present this -- oh no, this is Don's, but I wanted to be very specific because the group may come out with just a safe as used for the whole thing and just want to make sure we have our ducks in a row.

DR. SLAGA: Right.

DR. COHEN: Other comments, questions? Okay.

MS. CHERIAN: I have a question for Jay. So, for the concentration of use we got some data, and it said that the essential oil was used at 100 percent. I just wanted to clarify is it possible to know exactly the concentration of the ginger root oil being used? It was just part of the concentration of use data that we received.

DR. ANSELL: I don't have any information beyond what people sent back to us.

MS. CHERIAN: Okay.

DR. COHEN: Good point because is it shows up (audio skip 01:00:57) 0.001 --

MS. CHERIAN: Right.

DR. COHEN: -- or 100 percent.

MS. CHERIAN: Right.

DR. PETERSON: So, I think, my interpretation of the 100 percent is that -- and this would not be a cosmetic use -- or unless essential oils are classified as cosmetic use. But people do put essential oils on their skin as part of aroma therapy. And that's how I interpreted that 100 percent, that it would've been something like that. But I didn't know that if that fell under the -- it's that I wouldn't have considered that a cosmetic use.

DR. COHEN: So, I (audio skip 01:01:44).

MS. CHERIAN: -- that information but I think it might be helpful to note what (audio skip 01:02:03).

MS. FIUME: I don't know if it matters for that one, either, but according to the table, it says it's the oil of the whole plant. So, it looks like there's yet another ingredient where it says the whole plant, not the root. So, does that make any difference on how you do look at the maximum concentration of that?

DR. COHEN: I'm looking on Table 6. I see it under root oil.

MS. FIUME: No, but in Table 1, the definition says that the -- oh, I'm sorry. The water. I was looking at the water -- is an aqueous solution of the steam distillate obtained from ginger? I'm sorry, I was looking at the wrong ingredient.

DR. COHEN: And the water's the fragrance, I think, right? Yeah.

MS. FIUME: Yeah, that's what it says.

DR. COHEN: Okay. Why don't we add that to try to at least get some clarification because if for some reason there's a cosmetic use at 100 percent it would change the whole calculous on what we're going to ask for because we have HRIPT on 0.2.

MS. CHERIAN: Right.

DR. COHEN: Okay.

DR. SLAGA: Good.

MS. CHERIAN: Just a conclusion before we move on. So, it's an IDA, a sensitization/irritation for the extract and for the leaf extract?

DR. COHEN: Yes.

MS. CHERIAN: Method of manufacturing and impurities for the leaf cell extract and then the concentration of use for ginger root oil.

DR. COHEN: Yeah, that's what I was going to call out tomorrow.

DR. ANSELL: So, the 100 percent mentioned for the root oil, the double asterisks (audio skip 01:03:55) drops per teaspoon of an oil -- of a carrier oil.

DR. COHEN: So, a few drops per teaspoon is going to be more than maybe 0.2 percent, right?

MS. CHERIAN: That's what I was thinking, and that was the only clarification that we had. So I just wanted to make sure if we could get a real concentration instead of a vague definition.

DR. ANSELL: Okay.

DR. COHEN: That was a great pickup.

MS. FIUME: Can I also ask for method of manufacture, is it just the leaf cell extract or also the root as well?

DR. COHEN: I had method of manufacturing for leaf cell extract only. (audio skip 01:04:50).

DR. PETERSON: -- leaf extract, sorry.

DR. SLAGA: Yeah, yeah.

DR. PETERSON: So, as long as you're asking you might as well -- it's missing for the root. So, you could just add that method of manufacturing for the root.

DR. COHEN: Okay. We have impurities for the root, right?

DR. PETERSON: No, but we've talked about this already.

DR. COHEN: Yeah. Yeah, we did. Okay. Are we clear to move from ginger?

DR. SLAGA: Yes.

DR. COHEN: Okay.

DR. BELSITO: Yeah. Zingiber officinale, so this is again the first time that we're reviewing these nine ingredients. And ginger as we all know is a food substance. And looking at all of the material that we have here, I'm just trying to get here -- we thought it was sufficient for all except the leaf cell culture. And what we needed for that was manufacturing, composition, impurities and, depending upon that, other data endpoints.

DR. BERGFELD: So safe with the insufficient for the leaf cell extract?

DR. BELSITO: Cell culture. Correct.

DR. BERGFELD: And that's a motion?

DR. BELSITO: Yes.

DR. BERGFELD: Is there a second or discussion?

DR. COHEN: Yeah. Discussion. Don, we came to almost the exact same conclusion for -- we had the exception for the leaf cell extract and extract. Lisa, do you remember what our concerns were for the extract? I'm trying to find them in my notes.

DR. BELSITO: The leaf is going to be the spice ingredient which is definitely GRAS.

DR. LIEBLER: No, not the leaf.

DR. COHEN: No, no. The leaf cell extract.

DR. BELSITO: You're right. I'm sorry.

DR. COHEN: And the extract.

DR. LIEBLER: We said cell culture because we've seen so many cell culture ingredients in the past that actually the listed ingredient is the leaf cell extract. Is that what's causing you confusion, David?

DR. COHEN: I figured it was the same, leaf cell extract --

DR. LIEBLER: That's what we're talking about.

DR. COHEN: -- and I guess the extract. Tom or Ron, any concerns about the total extract -- the whole plant extract -- or Lisa?

DR. SLAGA: I have no concern.

DR. PETERSON: My only notes are missing impurities.

DR. SHANK: I had no concern.

DR. COHEN: That's what it was.

DR. BERGFELD: And, Tom, did you say something?

DR. SLAGA: Yes. I didn't have any problems with the extract.

DR. BERGFELD: Ron?

DR. SHANK: Same. No problem.

DR. COHEN: So, Lisa, the issue of the impurities on the extract --

DR. PETERSON: There were seven we didn't have impurities on. The impurities I'm worried about are heavy metals and pesticides, and they could be dealt with with the boilerplate. But that's the only thing I have highlighted on my document, and honestly, I can't remember this from yesterday.

DR. BERGFELD: So the only question is this is the leaf cell extract --

DR. COHEN: This is the whole plant extract.

DR. PETERSON: Oh, the whole plant extract. Now I remember, sorry. You were concerned that it was the whole plant -- you know, there was a question about when they talk about the plant was did they do just the rhizome or did they do the part that would be above the ground.

DR. COHEN: The aerial parts.

DR. PETERSON: That was where the question --

DR. COHEN: That's why we asked -- yes, we wanted to know what the impurities were for -- well, if there were other impurities in there that we needed to think about in the whole plant.

DR. PETERSON: And then the question was what constitutes the whole plant. I mean, it's basically the same issue that it's been with a number of botanicals. When they say plant extract, what do they actually mean by that?

DR. COHEN: So, Don, your team is comfortable with the whole plant extract and that you have a read on that enough to include it?

DR. BELSITO: I guess we do. I don't have that in my notes, David, but I'm looking at the definition. And it does say extract of the whole plant. It doesn't define it, and we don't have any information -- do we have any data on the -- we have a whole plant extract. I think we did discuss that. Paul, didn't you feel that there was data on the extract material? We have a genotox on the --

DR. SNYDER: Well, we said the water was from the root -- the distillation, so the root extract clears. And yeah.

DR. BELSITO: And we have quite a bit of data. We have the DART data on -- no, that's rhizome extract. We have human oral on the extract. It was 12 week fine. I think we went based upon the studies we had on the whole plant extract, but I'm not recalling. Paul, do you remember why we --

DR. SNYDER: Yeah. You were worried about the leaf cell culture extract because you just didn't know what was in there.

DR. BELSITO: Right. But they're asking why we went ahead with the whole ginger extract, which would include the aerial parts. And I think it was because we had a lot of tox data on that.

DR. SNYDER: That's correct, yeah. All the tox data is very, very high.

DR. COHEN: Would you be interested in irritation/sensitization on the extract because it's a completely different part of the plant?

DR. BERGFELD: And you would have to say in vitro testing.

DR. BELSITO: No, I mean, there may be data out there that's not in vitro. We don't have the in vitro.

DR. BERGFELD: I said and/or in vitro, basically.

DR. BELSITO: Right.

DR. COHEN: So, Don, would you add that on to the IDA for now since it's so early?

DR. BELSITO: We have sensitization at 100 percent --

DR. SNYDER: Extract.

DR. BELSITO: -- DPRA for the extract. We have root extract. We have animal non-irritating, concentration not reported. We have extract.

DR. COHEN: Don, doesn't the DPRA say sensitizing in table 7?

DR. BELSITO: Yes, you're right. Sorry. But this is a botanical that we would be going formulating to be non-sensitizing. So my comment in the discussion was botanical boilerplate including sensitizers, insufficient for the leaf, and the lack of respiratory data was okay because there were no tox signals in low concentration of use and that the whole extract was also supported by the tox data. So that's what I had.

DR. LIEBLER: The whole extract only has the in vitro DPRA. That's the only sensitization related data we have on the whole extract. Everything else is root extract, which looks okay. So that's where we are, so we can ask for the whole extract. There are four uses of the whole extract. Most of the other uses are the root derived ingredients.

DR. BELSITO: My point with that, Dan, is for the botanical boilerplate here since there are potential sensitizers -- citronella, et cetera. Remember, we discussed that yesterday that since we were going to include "when formulated to be non-sensitizing," we didn't need additional sensitization data.

DR. LIEBLER: Yeah. Bart has his hand up.

DR. HELDRETH: Yeah. Classically when we're looking at using the botanical boilerplate for sensitization, we're applying that boilerplate and the conclusion that has the caveat "when formulated to be non-sensitizing," purely for the concern of cumulative effects, per se having more than one ingredient in a formulation that all contain the same constituent of concern may raise above a threshold to cause sensitization. We don't, at least historically, use the non-sensitizing caveat on a botanicals boilerplate just for the sensitization of one ingredient.

DR. COHEN: Right. In other words, we're not putting that up just to just hide behind that. We want more data. Lisa brought this up a few times about the layering of ingredients that breach a sensitization threshold but each individual one is below. So, Don, maybe we can ask for irritation and sensitization on the extract.

DR. SNYDER: But don't we have the -- I have the maximum concentration used is the root extract at 0.2 percent. We have an HRIPT with 104 subjects at 0.19691, which is basically 0.2. Then we have another one at 0.095, which is 0.1, and another one at 0.2 on the root extract. So don't we have enough adequate sensitization data with concentration of use?

DR. BELSITO: Whole plant extract, Paul.

DR. PETERSON: Whole plant extract.

DR. SNYDER: Oh.

DR. COHEN: Yeah. The generic term "extract" for the whole plant.

DR. BELSITO: You know, David, at this point I think I'm fine with it. This is the first time we're seeing it. If you want some more information to be comfortable, that's okay.

DR. BERGFELD: All right. So we have now an insufficient data announcement going out, and you have agreed. Dr. Belsito, are you rescinding your original motion and restating the IDA?

DR. BELSITO: Yes, the IDA would be sensitization and irritation at concentration of use for the whole plant extract and manufacturing, composition, and impurities for the leaf cell extract and, depending upon this, other data endpoints may be needed.

DR. BERGFELD: Okay. That's agreeable to everyone?

DR. COHEN: Yes, seconded.

DR. BERGFELD: You're seconding it. I'm going to call the question. Opposing? Abstaining? Unanimously agree to move forward with the IDA on ginger with that which has been stated. Priya, do you -- I'm just going to ask Priya do you have any questions about what's been asked for?

MS. CHERIAN: No, but I did have a question about the essential oil use. In Dr. Belsito's team we talked about moving it to the non-cosmetic use section. I just wanted to make sure that we were doing that.

DR. BELSITO: Yeah. The reported use at 100 percent we felt would not be cosmetics. It would be what's sold for homeopathic or naturopathic therapy and would be not cosmetic because it's way out of line, that 100 percent. Carol said when she went out and queried industry, she did get that, so she had to report it. But I think we should clarify that our assumption was that that's not the way it's used in a cosmetic. The oil is not sold at 100 percent.

DR. BERGFELD: And, again, you're moving it to what area?

DR. BELSITO: Non-cosmetic use.

DR. BERGFELD: Non-cosmetic use. Is that agreeable to Dr. Cohen's team?

DR. COHEN: Yes.

DR. SLAGA: Yes.

DR. BERGFELD: All right. Was there a question that someone put forward that I didn't recognize them?

DR. LIEBLER: No. I'm emailing Priya about a little minor technical detail on the document.

DR. BERGFELD: Okay.

DR. LIEBLER: I'm making it hard for Priya, sorry.

DR. BERGFELD: Okay. Dr. Cohen, you have the next ingredient, acrylamide/acrylate copolymers.

JUNE 2022 MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – June 16, 2022

Dr. Belsito - OK. So we're moving on to Ginger. And we at the last meeting we said that all the root derived materials were sufficient when formulated to be non sensitizing.And insufficient for ginger leaf, cell extract for method of manufacture, composition, impurities and if the composition of the cell extract was notably different from the composition of the others 28 day dermal to assess for absorption. And depending upon that, tox data. We did receive some data on leaf cell extract in terms of irritation sensitization. But I don't think it really helped address any of the concerns. So I think our conclusion that we arrived at the last meeting should stand. And go from there.

Dr. Snyder -We did get a Wave 3 Don.

Dr. Belsito - Yeah, the Council comments. Do you want to address those? I thought they were all fine.

Dr. Snyder - Yeah, I did too. I just want to make sure you realize we did. Yeah.

Dr. Liebler - Yeah.

Dr. Belsito - Yeah.

Dr. Liebler - But as far as the conclusion, I agree we're in the same place we were, so.

Dr. Rettie - So move forward with an 8-9 split. Is that what you would do?

Dr. Belsito - Yes. Pryia, do you have any questions?

Priya Cherian (CIR) - So we have so we said that the ingredients would be safe as used for the root derived ingredients. Does that when from.

Dr. Belsito - When formulated to be nonsense utilized.

Priya Cherian (CIR) - Right. So does that include the ginger extract too?

Dr. Belsito - No.

Priya Cherian (CIR) - OK.

Dr. Belsito - Right.

Priya Cherian (CIR) - *(inaudible) or safe and then two or not.

Dr. Belsito -Mm-hmm.

Priya Cherian (CIR) - Thank you.

Dr. Belsito - Yeah, because the ginger extract could be presumably the whole plant, right? Where allowing only the root derived ingredients. What we actually eat. Any other questions?

Monice Fiume (CIR) - I'm sorry, So, how did you say it's three that are insufficient? Is it the extract leaf cell extract and water? Or do I have my list wrong?

Dr. Belsito - Yes. Yes.

Monice Fiume (CIR) - OK.

Dr. Belsito – Let me just go back. So. Look at the list again. Yeah. So the extract the leaf cell extract and the water or insufficient. The risen the root. All of the root derived ingredients and the risen are safe as used.

Monice Fiume (CIR) - Thank you.

Dr. Belsito - So yeah, there are three insufficient. The extract, the leaf cell extract in the water.

Priya Cherian (CIR) - So I did get some information stating that ginger water was produced by steam distillation of the roots. Of Ginger, if that makes a difference.

Dr. Liebler - Where did you get that Priya? Where do we have that?

Priya Cherian (CIR) - On page. It's in the composition section of the report. I mean method of manufacturing section. 26, page 27.

Dr. Liebler - OK, so the table one doesn't specify the roots, it just says is steam distillation of the zingiber officinale. If it's the root, then we're OK with the water's going to be OK if it's from the root. It's just that this and this is not consistent with the definition, but you know when the method of manufacture clarifies or further elaborates on the definition then we go ahead with the method of manufacture description as provided here. So this is this. I think this should be OK for the water then.

Monice Fiume (CIR) - Actually, can I jump in? I think the table is correct I think of the root was added here, unless that was additional data, Priya that were received separately?

Priya Cherian (CIR) - It was additional data from a manufacturer.

Dr. Snyder - Where was that data?

Dr. Belsito - Do we have not additional data in the report?

Priya Cherian (CIR) - This was included before because in the and I'm trying to look at the citations and it says received on May 19th, 2021.

Dr. Liebler - Yeah, reference 17 would appear to be the key thing here. From this whole Salafia group manufacturing process. That bio ginger. Ohh ginger water.

Priya Cherian (CIR) - It's also provided in a submission that we got on January 4th, 2022 on page 54 of this PDF.

Dr. Belsito - Yeah, there it is. It starts rooting Ginger.

Dr. Liebler - Makes. Yeah. So I think we're, we're good on that. So 2 insufficient.

Dr. Belsito - So root derived and water. Just root derived.

Dr. Snyder - We want to make sure we highlight that into discussion.

Priya Cherian (CIR) - OK.

Dr. Belsito - Whole plant and leaf cell extracted the two that are insufficient. Right?

Dr. Snyder - Correct.

Dr. Belsito - OK. Okey doke. So we have, I think 4 minutes, but let's try and knock off we want to try and knock off the Kojic Acid. That's *(inaudible) use area Monice?

Cohen Team – June 6, 2022

Dr. Slaga - Ginger.

Dr. Cohen - Ginger. OK, in December. We issued an IDA for this ingredient group for leaf cell extract. For method of manufacturing and composition and impurity. And I don't think we got further information. We have sensitization, irritation at Max use. Any other any comments about this one?

Dr. Shank - No, I think they're all safe, except the leaf cell extract.

Dr. Cohen - Because we just don't have the method of manufacturing or the composition or what it is?

Dr. Shank - Well, there's no toxicology, no sensitization, no use. So that's insufficient.

Dr. Cohen - Ohh let me see. OK, so it's insufficient because it's a tentative report. But safe is used for the others.

Dr. Shank - I have a question for Doctor Ross. Umm on page 38 Table 2. Uh, they list a property of the log KAW. What does that mean for a mixture? Can you have partition coefficient? For a mixture.

Dr. Ross - Generally, on a pure compound.

Dr. Slaga - Yes, I.

Dr. Shank - It's on page 38, page 2.

Dr. Ross - Yeah. Generally, on a pure compound, so I don't know why they. What is it?

Dr. Slaga - You can't have it on a mixture.

Dr. Shank - I don't. 100 years ago, when I took chemistry, that was the case, but things change.

Dr. Ross - Now I haven't looked at the reference, but that would be my at sensitive as well. Could I, could I ask you question the you know when I went through this and you know trying to catch up with these not being involved in the original discussions, the whole extract on new one the finding.

Dr. Cohen - Now you're bringing up an important point that it that I didn't discuss. You're talking about what part represents the extract we that was also a deficiency. Right? Right. Priya, that was.

Priya Cherian (CIR) - Yeah.

Dr. Cohen - That was a deficiency as well for the extract and I don't think we got anymore information about it, right.

Priya Cherian (CIR) - Not.

Dr. Ross - Yeah.

Dr. Cohen - So we're insufficient on that too.

Dr. Ross - Yeah. So that was my one issue. And then the other issue, this one made my grand were a little bit too when you when you actually were considering this the, you could educate me here the root extract versus the rise on extract. And these two things exactly the same? Are roots the same as rizos, Google says, maybe not, but, you know what, what are we dealing with here? Can someone sort of point me in the right direction there?

Dr. Cohen - I think this was did something come up in wave three about this?

Dr. Bergfeld - Doctor Peterson talked about them being the same.

Dr. Ross - That's what I got from the transcript. Yeah. And you got some data on the rise on Max track the HRIPT. you didn't get anything on the whole extract all the leaf extract.

Jay Ansell (PCPC) - So our notes say that they're used interchangeably and INCI will defer to the request of the supplier.

Dr. Ross - OK, so basically the using the terms interchangeably, definitionally they may not be, but we're probably are.

Jay Ansell (PCPC) - Yeah.

Dr. Ross - And this report said Grandma, I am no pun intended. Assuming Doctor Peterson *(inaudible).

Dr. Cohen - In. I think the PCPC sent a note to Bart saying the INCI names are used interchangeably, but is the method of manufacturing the same?

Dr. Ross - Look different when I don't. Let me just go back to that. I'm just scrolling down here.

Dr. Cohen - Yeah, Pryia put some new information about the ginger root method of manufacturing. One thing Pryia the ginger root discussion that you put in method of manufacturing. Would that be?

Priya Cherian (CIR) - Under composition.

Dr. Cohen - Yeah.

Priya Cherian (CIR) - I think I need to move that. I was thinking the same exact thing.

Dr. Bergfeld – Should she not be mentioning that in the discussion as well, that they discussion deals solely with the boilerplates. And inhalation where we have two ingredients that are insufficient, we need to say why in the discussion. And perhaps we need to mention that the possible sensitizers within these, I think, I think we have mixtures in the boilerplate. No. Yes, we have multiple botanicals. There's this third paragraph, OK. So the discussions missing something.

Dr. Cohen - We get another crack at this.

Dr. Bergfeld - But the discussions missing some things that we should add them now.

Dr. Cohen - So when the what was the last thing you wanted in the discussion?

Dr. Bergfeld - We have two ingredients that you're saying are insufficient. We need to put that into this discussion with the needs. And then if you, I'm retracting the one about desensitizers because, you have the mention in the discussion of the multiple botanicals within one product could be a problem. So you have already covered the sensitization problem there I think. That was my second one. But after the insufficient you know ones have to go into the discussion. What we need.

Dr. Cohen - And but the rest are we going to go out with safe as used when formulated to be non sensitizing.

Dr. Ross - And which ones are we going out on that?

Dr. Bergfeld - Did you?

Dr. Cohen - For the other components.

Dr. Ross - That's root and oil.

Dr. Cohen -Think do I have a?

Dr. Bergfeld - We had sensitization. It was anything but in the case report, should we? I mean anything that came up.

Dr. Cohen - I think it did. Alright, let me just maybe I'm confusing it.

Dr. Bergfeld – In the reports they did.

Dr. Cohen - I think the DPRA said sensitizing and Table 7. And then we had a discussion with Bart about when we're supposed to be using safe as used when non sensitized. Uh. Safe as used to be formulated to be not sensitizing. And we got into that discussion last time. Let me go back to Table 7.

Dr. Bergfeld - I don't have a Table 7 do. The table.

Dr. Cohen - I don't have a Table 7 either.

Dr. Bergfeld - Oh, here it is. The bottom here it.

Dr. Cohen - Ohh no there.

Dr. Slaga - OK.

Dr. Ross - You're not.

Dr. Cohen - Not used.

Dr. Ross - Not used.

Dr. Cohen - Hold on. I'm checking one other thing.

Dr. Ross - Sometimes checking. So DPR data was the on the ginger extract itself. The whole extract which was possible.

Dr. Cohen - OK so. Excuse me. I'm a. Thank you. I'm on the wrong.

Dr. Bergfeld - Ingredient. I've done that.

Dr. Cohen - I think so.

Dr. Bergfeld - I don't know.

Dr. Cohen - No, but we had this it's interesting. We had this discussion during the Ginger.

And in the group full panel in December. I think at one point. Don says well it's a botanical we'd be going formulation to be non sensitizing.

Dr. Bergfeld - So they have the concentration that you have, it's pretty low. And most of your sensitization occurs in your case reports.

Dr. Cohen - Let me read. Yep. Yeah. And we had. Point. I remember this conversation that we had .19691% at .19 and the max use was .2, so we had some good data on this. So I like, like we're going to go out of safe as used. Yeah.

Dr. Shank - Good.

Dr. Slaga - Right.

Dr. Shank - For including the Leaf cell extract?

Dr. Cohen - Thank you for. No, no, no, no. We're going insufficient on the leaf cell extract and the ginger and the extract.

Dr. Shank - OK.

Dr. Ross - Yeah.

Dr. Cohen -Because we didn't get our prior needs filled. So it's just going to be insufficient. And will this will get this will come back to us as a final report. Hopefully we can get some additional information.

Dr. Bergfeld - And at the present time you'll add to the discussion the insufficient to ingredients and the why?

Priya Cherian (CIR) - I can do that.

Dr. Bergfeld - Yeah, please. This keeps us focused.

Dr. Cohen – And discussion. Insufficiencies. It’s just a matter of protocol, so if we have in the discussion the reason for the insufficiencies and we go to final report and those insufficiencies have been met, does it just come out of the discussion?

Dr. Bergfeld - Editorial.

Dr. Cohen - OK.

Bart Heldreth (CIR) - Yeah, I mean, if so the old rule goes that if it's less restrictive, you know, things that were either unsafe or insufficient are now safe, that the panel can choose to have it just go final at that situation. But if the panel feels this was such a substantive change that they would like the public to have another 60 day comment period, you can ask for it to be a come back around again as a revised, report. So you have the you have the option there. But typically.

Dr. Cohen -You mean? As a tentative or as a final.

Bart Heldreth (CIR) - Yeah, it would get, so if you chose to have there be another comment period, it would go out as a revised kind of report and then it would come back to the panel table in a future meeting as a revised draft final report. So I basically just puts it through another cycle so that there's an opportunity for public to comment, but you don't have to do that. I just wanted you to know that that option is there if you feel that there were some reason that you wanted the public or somebody to have extra time to comment. Historically, when it's a less restrictive conclusion, we simply go final.

Dr. Cohen - And can you do that maneuver for a final that were reviewing?

Bart Heldreth (CIR) - Yes, that's actually what I'm talking about is so.

Dr. Cohen - Ohh OK I thought it was for tentative. It was going to come back as the tentative so final, so we might we could consider doing that for Sage if we wanted to or one of the others where we don't have enough.

Bart Heldreth (CIR) - Right. If that information comes in before the next time it hits the panel table and the panel feels as a whole that all the needs are met, yes, you can go safe with it and be done with it.

Dr. Cohen - OK. Alright, our last one is the Grass determination, the White Paper on Grass. I thought it was really well done, really well written. Put a lot of detail and color on what we should be doing and looking at, I think it was very clearly highlighting the issue that a no questions letter is very easy on its face to be misinterpreted. I mean, it's just that parts very confusing. So if I get it right, there are FDA affirmed Grass components. And that, and there's a different group of Grass self

determination. And we ought to know that when we're looking at Grass data as a surrogate for additional data for our toxicology assessment.

Dr. Bergfeld - Does that list exist somewhere? For the FDA, Grass approved?

Jay Ansell (PCPC) - Well, you know first, I thought it was very well written, but the issue before us is, Human exposure, a long history of human exposure. And so the grass status is only one place where we would look for a long history. We have a not only those, but the FDA keeps records on substances added to food. Their prior sectioned ingredients. They're their indirects, there's colors, there's products that come out of FEMA. The WHO check for process and grass. So grass is only one element in determining whether there's a long history of the ingredient being part of the diet. That distinction of, however well the distinction you measured mentioned is, is true, but it's relatively historical. The originally the grass status was a status for ingredients that were commonly used in food. When the 50's regulations were issued, there was a decision that FDA didn't need to go back and conduct a review of all the ingredients that were being used, that there were some which were generally recognized by experts as. And so they got to listed as a prior sanctioned and I think they're they were in use before, I think it's 1958. Following that, they established a mechanism for establishing grass affirmations and you would go through and you'd, you know, have your expert panels and you would submit a material claim demonstrating that that panel of experts generally recognized as safe. You know, basically it was recognized coming in through the 90s, that system was entirely broken. That FDA hadn't managed to affirm a material for a significant amount of time, and so they went from affirmation to notification. But the notification requirement is the same as the affirmation requirement. It requires that a group of experts that conform to FDA's of vision expert panel has a reviewed all of the data and concluded it was safe. And FDA then has a opportunity to opine whether they disagree with the grass status. So you know it's true, but it's only a part of the issue and understanding grass status and grass status is only one of a number of ways of determining whether there is a long history of human exposure. So I hope that adds a little clarity. I think the paper itself was fine, but the panel should remember that what we're looking for is human exposure. We're not looking for grass status uniquely.

Dr. Cohen - OK.

Dr. Slaga - Yeah.

Dr. Shank - This is the first time the panel has seen this document. I'd like to know if FDA has seen the document, reviewed it and comment on it because I don't see anything from FDA.

And until FDA has a chance to review the document, I think it's premature for the panel to discuss it. Has FDA seen it?

Dr. Cohen - I Bart has Bart. So it's something I could discuss tomorrow when we open the discussion, it's the I think it's.

Dr. Shank - OK.

Dr. Cohen - That's not the last thing tomorrow, it's.

Bart Heldreth (CIR) - It's towards the end though.

Dr. Cohen - Yeah.

Dr. Shank - But doesn't matter. Has FDA seen the report? The document.

Bart Heldreth (CIR) - We forwarded them this information for this resource document along with these along with all of the other reports.

Dr. Shank - Uh-huh. And have they responded?

Bart Heldreth (CIR) - No, not as of yet. I think Janet saying has her hand up. I think maybe should be able to shed some light on this.

Janet Zang (FDA) - Thank you. Thank you, Bart. This is Janet sang from the FDA. Yes, I believe that we've seen the white Paper after it's published on the CIR website. However, we're not quite sure about the status because I don't know if it's still under revision or this is finalized, so we haven't officially put up any comments or detailed review on that.

Dr. Shank - OK. Thank you, I think.

Dr. Bergfeld - How long does it take? Comments to come back usually. Doctor Zang?

Dr. Shank - Pardon me.

Dr. Bergfeld - I've just asked that like saying how long it takes for FDA to respond. Just so we have a time on this.

Janet Zang (FDA) - I think that would be a question to Doctor Linda Katz.

Dr. Bergfeld - OK.

Janet Zang (FDA) - Yeah.

Dr. Cohen - So Wilma.

Janet Zang (FDA) - And I think it will be. I'm sorry.

Dr. Cohen - No, go ahead, Janet.

Janet Zang (FDA) - Yeah.

Dr. Cohen - So Wilma.

Janet Zang (FDA) - Yeah, it will be helpful to inform Doctor Katz about the status of this document and what is the plan.

Dr. Bergfeld - So we can ask her?

Janet Zang (FDA) - Thank you.

Bart Heldreth (CIR) - Yeah, I can send a formal request to Linda for this to be reviewed and something we can provide to the panel and return.

Dr. Slaga - *(inaudible).

Dr. Cohen - So for tomorrow. I mean, I don't know if there's a lot to say in the in the recitation about it that it's well written. We we've gotten clarification about grass. There's caution on how we use grass information in our adjudication of each chemical group or plant group. And that where we're not finalizing it now, but we are discussing it and we would be very interested in FDA's comments. I'm in time that this is sitting as a draft document right now.

Dr. Bergfeld - Could I ask a Bart the difference between a draft document that's on our website and one that's a living document?

Bart Heldreth (CIR) - Well, I at this point, this document is only found in our panel meetings folders, so you go on to the website, you can find it there. It is not graduated to the resource and findings tab of the website where you will find things that the panel has marked as this is this is our verbiage, this is what we believe. So I'd say the difference is it's not yet validated.

Once the panel feels like it's final, even though it may still be living and may be changing as the science changes. Once it's finalized it to that extent, then it'll move to the findings.

Dr. Bergfeld - Could I ask you what's going to happen to the comment that were made by the Women's WV I does that have the I forgot?

Dr. Cohen - Now a Women's Voices for the Earth.

Dr. Bergfeld - I suppose yeah. WWE E.

Dr. Cohen - And it was a pretty thorough note about it. And I thought Jinqiu response was very thorough as well and reasonably addresses the issues and concerns brought up. I didn't want to get into every detail, but I thought the response was very thoughtful. I found that I found the letter helpful. I mean it I think Jay also you know resonated that you know just have to use the data in an appropriate way. And as far as I could remember, we don't just we might, in a discussion say it's grass and we're moving on, but it's not our only pathway for assessing safety. Not even close.

Bart Heldreth (CIR) - Right.

Dr. Bergfeld - Well, undoubtedly we're going to have a response to the Women's Voice's of the Earth. And we will respond on two documents. She commented on the airbrush, plus the grass.

Bart Heldreth (CIR) - Yes.

Dr. Cohen - That was my next thing.

Dr. Bergfeld - Sorry, sorry.

Dr. Cohen - No, no, no, no, no, no. So I just want to make sure we're closing grass because on the agenda I don't know if the airbrush boilerplate question will come up tomorrow, but right, but we will be. You think it will.

Dr. Bergfeld - It isn't listed.

Bart Heldreth (CIR) - Think it will. I know that I know that the other team is for is proposing to bring it up before we close tomorrow's meeting.

Dr. Cohen - OK. Yeah, I think it's it there's a potential for it to come up two ways. One, when we talk about Barley. We'll open with barley and the whole question about the verbiage for the reports is going to come up, and that speaks to the women's voices for the Earth letter of concern about the boilerplate and we did address that earlier today on how we would plan on doing it so we can amalgamate that all into the conversational make barley an awfully long conversation. But I think it'll get the job done appropriately.

Dr. Bergfeld - Yeah, yeah.

Bart Heldreth (CIR) - Yeah. And I think it's great that it'll set the tone for the day and we won't have to be revisiting the issue in different ways before we get through to the end of the items.

I think that's a great plan.

Dr. Cohen - Any advice on how? I should present the grass document other than what I said. I mean it's not going to be very long discussion.

Dr. Bergfeld - *(inaudible) all need to say is draft.

Bart Heldreth (CIR) - Yeah, right. I think the way we discussed it as perfectly great. We'll communicate formally with Linda Katz and see if we can get their input on it. And Jinqiu will take her comments and the comments from women's voices for the Earth, and you'll see another draft iteration of this document in the future.

Dr. Bergfeld - I think that's enough.

Bart Heldreth (CIR) - I think so too.

Dr. Cohen - No, I think there's is, is really, really good to discussion in the in the third wave and in the in the letters we received and our and the response is that were put together. I thought that was a really well done and I think makes everyone on the panel very contemplative about all those issues. Any other any other business? Questions, comments, or advice for tomorrow?

Dr. Bergfeld - Eat your Weedies!

Dr. Cohen - I always do. And David it, it's so nice to have you on the panel it it's amazing to bring your experience here. Your accomplishments are remarkable and it's just so important.

Dr. Ross - I found I felt like I knew after reading all those transcripts, I felt like I knew you all already. So. Uh, because I mentioned particularly the Zeolite one.

Dr. Cohen – Ah yeah, that might not have been the first one to start with.

Dr. Bergfeld - Now you've seen the real personalities.

Dr. Heldreth (CIR) - That's right.

Dr. Ross - Yes.

Dr. Bergfeld - OK.

Dr. Cohen - OK. See you tomorrow at tomorrow morning at 8:30. You guys open and we'll cut right into it. OK.

Dr. Heldreth (CIR) - Correct. Sounds great.

Dr. Bergfeld - But I know everyone have a good night.

Dr. Heldreth (CIR) - Thank you all.

Dr. Cohen - Bye.

Dr. Ross - Have a bye.

Dr. Shank - OK.

Full Panel – June 7, 2022

Dr. Cohen - OK, so in December, we issued an insufficient data announcement for the ingredients in the group. And we wanted the following information. On the leaf cell extract as method of manufacturing and composition and a purities and we also wanted additional information about the extract. I don't, we didn't get any information on the cell extract and I don't know if we have a good understanding of what Ginger quote, ginger extract close quote is, if we had clarity, it was it's the root. We could clear it, but I don't know if we have that. It's a very similar conversation to before we we're open to discussion. Our motion is safe as used when formulated to be non-sensitizing for all ingredients except the leaf cell extract and extract.

Dr. Bergfeld - Is there a comment or a second?

Dr. Belsito - No, there's a second I think before we had also excluded the water, but it was now pointed out that the water is made from the root.

Dr. Cohen - The root, the root? Yeah. And there was some information in the late breaking data about root and rye zone being inky equivalents in in some way and we were going to add that to the discussion or it's in the discussion now.

Dr. Liebler - So I think that ginger extract, is OK for method of manufacture. First of all it's described in table one as extract of the whole plant or as extract of the whole plant and then under method of manufacture on PDF 26 it indicates you know it

indicates that it's a pulverized percolated in 95% methanol etcetera. So that one I think is OK, it's the leaf cell extract where we've got nothing.

Dr. Belsito - But we don't know that it's just the root of the ginger Dan. We we're passing on systemic toxicity because the root is food.

Dr. Liebler - Yeah, right. But we ohh. OK, so you're not saying it's insufficient for method of manufacture.

Dr. Cohen - No, no.

Dr. Belsito - Just saying it's insufficient for other toxicity at the end points.

Dr. Ross - Yeah.

Dr. Liebler - Gotcha. OK.

Dr. Ross - There was a tox.

Dr. Liebler - Yep. OK. Thank you.

Dr. Bergfeld - Doctor Cohen did you want to say something?

Dr. Cohen - No, I just want to give some clarity and I could just use a hand on what we're going to ask Priya, what the insufficiencies for the extract are Dan, could you help with that?

Dr. Belsito - So the insufficiencies that we have, our method of manufacturing data on ginger leaf cell, extract composition and impurities of the leaf cell extract, and if they notice noticeably differ from the remaining ginger ingredients than 28 day dermal and depending upon that systemic toxicity endpoints such as dart or genotoxicity. And or carcinogenicity data may be needed and then dermal irritation sensitization on the ginger extract. That maximum concentration of use.

Dr. Cohen - So yeah, that's my that's the last part is the hanging part of it. So if we got dermal sensitization and irritation on the extract, not knowing it could be the whole plant, it's the same conversation as sage in some ways. won't we need? A whole portfolio of data on the extract?

Dr. Belsito - I mean, we're going insufficient for it anyway, if you want to add on other data points.

Dr. Cohen - Well, Dan, so you, you where you were OK with the method of manufacturing on the extract?

Dr. Liebler - Yeah. For the ginger extract, I'm OK on that. And then I also think that we've got composition, impurities, data on the ginger extract. It's not in a table, but it's in a couple of paragraphs on PDF 27. And I was looking at the tables just now double check to see if there was any side by side comparison of chemicals detected in the extract versus any of the root stuff and I didn't see any side by side. But you know it it's a listing of you know common phenolics and so, you know, flavonoids and so forth, no discussion of any well and get it if you terpenes too. So anyway it you know it's the usual kind of stuff that we get from chemical analysis, I can't say that it's completely different or identical to the rissone root types of ingredients, but there are common features certainly.

Dr. Cohen - I can't help but to draw the analogies of Sage. It says the ginger extract is the whole plant.

Dr. Liebler - Right.

Dr. Cohen - Right. And the majority of this report relates to the root.

Dr. Ross - Yeah.

Dr. Cohen - So.

Dr. Liebler - And it might be that the ginger extract, even though it's defined as the whole plant, what they actually do is work with the root, but we just don't know that.

Dr. Cohen - OK. Yeah, I do see, you know, I, see your point. And if you go through the report, there's discussions about the extract in general. So we could stick with dermal irritation and sensitization. Anyone from the team want to add any insufficiencies to the extract?

Dr. Shank - No.

Dr. Ross - No, I think as long as you had the turmoil sensitization and rotation considering the DPRA that's it was positive with the ginger extract.

Dr. Cohen - Yeah.

Dr. Bergfeld - So where are we ready to call the question on this? It sounds to me like we're having a split conclusion.

Dr. Belsito - Yes.

Dr. Bergfeld - Route the greetings and then are we doing insufficient on?

Dr. Cohen - It's insufficient data, insufficient.

Dr. Bergfeld - On the whole, on the whole document?

Dr. Cohen - No, no safe is used when formulated to be non-sensitizing for all ingredients except leaf cell extract and extract. And we discussed all those needs.

Dr. Bergfeld - OK and there has been a second. So I'm going to call the question unless there's more discussion. All those in favor of this conclusion? Uh, oppose things we sent me to the reverse by opposing this conclusion. Abstaining. Unanimous approval, then. Thank you. OK, we're off to the next set of items, which is other items called Hair Dyes. Doctor Belsito.

Safety Assessment of *Zingiber officinale* (Ginger) – Derived Ingredients as Used in Cosmetics

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

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ABBREVIATIONS

ALP	alkaline phosphatase
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BUN	blood urea nitrogen
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
cGMPs	current good manufacturing practices
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
DART	developmental and reproductive toxicity
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DNFB	dinitrofluorobenzene
DPPH	1,1-diphenyl-2-picryl-hydrazyl
DPRA	direct peptide reactivity assay
ECHA	European Chemicals Agency
FDA	Food and Drug Administration
GC	gas chromatography
GD	gestation day
GRAS	generally recognized as safe
HaCaT	human epidermal keratinocyte line
HDM	house dust mite
HeLa	human cervical cancer cells
HPLC	high performance liquid chromatography
HRIPT	human repeated insult patch test
IC_{50}	half-maximal inhibitory concentration
IgE	immunoglobulin E
IL	interleukin
kDa	kilodaltons
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LD_{50}	median lethal dose
MDA-MD-231	human breast cancer cells
MS	mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCE	normochromatic erythrocytes
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	no-observable-adverse-effect-level
NR	not reported
OECD	Organisation for Economic Cooperation and Development
OVA	ovalbumin
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PII	primary irritation index
RAST	radioallergosorbent
RIFM	Research Institute for Fragrance Materials
SDS-PAGE	sodium dodecyl sulphate-polyacrylamide gel electrophoresis
SIDS	screening information dataset
SPME	solid phase microextraction
$T_{1/2}$	elimination half life
TG	test guidelines
T_{max}	time to reach serum concentration
TNF-α	tumor necrosis factor alpha
US	United States
UV	ultraviolet
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 9 *Zingiber officinale* (ginger)-derived ingredients. The majority of these ingredients are reported to function in cosmetics as skin-conditioning agents. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. With *Zingiber officinale* (ginger)-derived ingredients, the Panel was concerned about the presence of potential sensitizers (e.g., citronellol) in cosmetics. Industry should continue to use good manufacturing practices to minimize impurities that could be present in botanical ingredients. The Panel reviewed the available data to determine the safety of these ingredients, and concluded that the 7 *Zingiber officinale* (ginger) root- and rhizome-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. In addition, the Panel concluded that the available data are insufficient data to make a determination that Zingiber Officinale (Ginger) Extract and Zingiber Officinale (Ginger) Leaf Cell Extract are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This is a safety assessment of the following 9 *Zingiber officinale* (ginger)-derived ingredients as used in cosmetic formulations:

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Leaf Cell Extract
Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the majority of these ingredients are reported to function in cosmetics as skin-conditioning agents – miscellaneous (Table 1).[1] Other reported functions include antioxidants, skin protectants, antimicrobial agents, fragrance ingredients, and flavoring agents. It should be noted that skin protectant and antimicrobial functions are considered drug, not cosmetic, functions in the United States (US), and therefore, use as such does not fall under the purview of the Panel.

Zingiber Officinale (Ginger) Water is reported to function only as fragrance ingredient. The 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). However, according to personal communications with RIFM, it is unknown when the safety assessment of this ingredient will be prepared; therefore, it will be reviewed herein.

The United States (US) Food and Drug Administration (FDA) has affirmed that *Zingiber officinale* is generally recognized as safe (GRAS) as a spice, natural seasoning agent, and flavoring agent [21CFR182.10]. In addition, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are considered GRAS for human consumption [21CFR182.2]. For the ingredients that are affirmed GRAS, systemic toxicity via the oral route will not be the focus of this safety assessment. Although oral exposure data are included in this report, the primary focus of this safety assessment is topical exposure and local effects.

Zingiber officinale contains many constituents. In this assessment, the Panel is evaluating the potential toxicity of each of the *Zingiber officinale* (ginger)-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 exhaustive search of the world's literature. 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.

Some of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[2] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited**.** The CAS No. used to identify the test material in the ECHA data (84696-15-1) is generic, and the ingredient that is being tested is not clearly identified; it could possibly correspond to several of the ingredients in this report, with the exception of Zingiber Officinale (Ginger) Root Oil (which has a different CAS No.). Therefore, it should be noted that when ECHA summary data are presented, it is possible that it may refer to any ginger-derived ingredient in which the CAS number 84696-15-1 is used.

Confusion exists between the distinction of ginger root versus ginger rhizome in both the *Dictionary* and published literature, and many times, it is possible that these plant names are used synonymously. Therefore, for the purposes of this report, research on the ginger rhizome juice, oil, and powder is placed under the closest root ingredient. For example, data regarding a *Zingiber officinale* (ginger) rhizome oil is placed under the name Zingiber Officinale (Ginger) Root Oil, as this name is included in the *Dictionary*.

CHEMISTRY

Definition and Plant Identification

All ingredients reviewed in this report are derived from the *Zingiber officinale* (ginger) plant. The definitions of the ginger-derived ingredients included in this review are provided in Table 1; the generic CAS number for the majority of these ingredients is 84696-15-1.[1]

Ginger is a tropical, flowering, 2 - 4 ft long perennial plant, with grass-like leaves that grow up to a foot in length.[3] The shoots and leaves grow directly from thick, underground, branched rhizomes, which have a corky, brown to golden outer skin.[4] The interior of the rhizomes are juicy, fleshy, and pale yellow in color.

Chemical Properties

According to ECHA data, a *Zingiber officinale* (ginger) extract (may refer to other ginger-derived ingredients reviewed in this report) is reported to be a liquid substance with a water solubility and log k_{ow} of 0.0004 g/l and 6.9, respectively.[2] Other chemical properties evaluated for this test substance and other ginger-derived ingredient mixtures can be found in Table 2.

Method of Manufacture

It is unknown if the methods found in the published literature apply to cosmetic ingredient manufacturing; however, data provided by suppliers do 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.

Zingiber Officinale (Ginger) Extract

Air-dried Zingiber Officinale (ginger) was pulverized and percolated in 95% methanol, multiple times, until extraction completion.[5] The extracts were concentrated under reduced pressure using a rotary evaporator. Concentrated extracts were kept at -20° C until use.

Zingiber Officinale (Ginger) Rhizome Extract

Ginger rhizome extracts were prepared by weighing 300 g of fresh rhizomes, and combining with a solvent (*n*-hexane or methanol) in a flask.[6] These samples were shaken for 48 h, and filtered with filter paper. The filtrate was subjected to rotary evaporation for removal of the solvent. The solvent was further removed under a purified nitrogen stream. A different *Zingiber officinale* (ginger) rhizome extract was prepared by first cleaning, peeling, chopping, and drying the rhizomes.[7] After drying, rhizomes were ground into a fine powder, and soaked in distilled water for 24 h. This aqueous extract was then filtered by double gauze and concentrated under reduced pressure.

Zingiber Officinale (Ginger) Root Extract

According to a supplier, Zingiber Officinale (Ginger) Root Extract is produced via maceration of the ginger root, followed by sterilizing filtration and evaporation.[8] Typical solvents include water, glycerin 50/50, glycerin 20/80, and refined sunflower oil. Another supplier reported that a Zingiber Officinale (Ginger) Root Extract is manufactured via extraction using a mixture of propylene glycol (68.5%) and water (30%), followed by filtration.[9,10]

Data were also submitted by a supplier regarding the manufacturing process of a trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)).[11] This mixture is created via the grinding/milling of the plant roots, followed by aqueous extraction, solvent dilution (with hexylene glycol and caprylyl glycol), and filtration.

An aqueous ginger root extract was prepared by first peeling ginger roots.[12] Peeled ginger root (50 g) was then cut into small pieces and homogenized in 75 ml of 0.9% sodium chloride, in the presence of crushed ice. Homogenization was performed using a blender for a total of 12 min. This mixture was then filtered through cheesecloth, and the filtrate was centrifuged for 10 min. The clear supernatant was made up to 100 ml with saline.

Zingiber Officinale (Ginger) Root Juice

Fresh rhizomes of ginger (1 kg) were obtained and crushed.[13] Crushed ginger rhizomes were then squeezed in muslin cloth to obtain juice, and stored in a refrigerator until use.

Zingiber Officinale (Ginger) Root Oil

In order to create a ginger root fixed oil (non-volatile), approximately 4023 g fresh ginger were reduced to a paste using a laboratory mortar, and macerated in n-hexane, for 72 h.[14] This solution was shaken for 15 min and filtrated with filter paper. The vehicle (n-hexane) was evaporated via a rotary evaporator, leaving an oily extract. This extract was cooled and stored in a tight-capped fitted container. In order to produce a ginger root essential oil, 1000 g of fresh ginger were ground using an electric blender. The sample was placed in a conical flask and connected to a Clevenger apparatus. Distilled water was added to the flask and heated. The steam in combination with the essential oils was distilled into a graduated cylinder for 5 h, and separated from the aqueous layer. The extracted oil was kept in a refrigerator until further use.

Zingiber Officinale (Ginger) Root Powder

Fresh ginger rhizomes were washed in water to remove dirt, and chopped into small pieces.[15] Pieces were allowed to dry for 5 d. Dried samples were milled into fine particles, and sieved. The powder was stored in an air-tight container until further use. Other methods of drying include oven drying, microwave drying, and solar drying.[16]

Zingiber Officinale (Ginger) Water

According to a supplier, Zingiber Officinale (Ginger) Water is produced by steam distillation of the roots of *Zingiber officinale*.[17] The distillate is then filtrated to produce the final product.

Composition and Impurities

Zingiber Officinale (Ginger) Extract

The main components of a *Zingiber officinale* (ginger) extract (solvent not stated) were determined by a solid phase microextraction (SPME) assay.[18] Identified components included camphene (7.27%), geranial (8.37%), α-zingiberene (14.50%), α-farnesene (9.14%), β-bisabolene (6.52%), and β-sesquiphellandrene (9.92%).

The total phenolic and flavonoid content of methanolic *Zingiber officinale* (ginger) leaf and stem extracts was evaluated via a 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay.[19] Two varieties of ginger in the *Zingiber officinale* family were evaluated (Halia Bentong and Halia Bara). The average phenolic content in the leaves of the Halia Bentong and Halia Bara varieties was 33.0 ± 1.13 and 39.1 ± 9.2 mg gallic acid/g dry plant material, respectively. The average flavonoid content in the leaves of the Halia Bentong and Halia Bara varieties was 5.54 ± 1.83 and 7.05 ± 7.4 mg quercetin/g dry plant material, respectively. In addition, the average phenolic content in the stems of the Halia Bentong and Halia Bara varieties was 7.8 ± 0.65 and 8.5 ± 0.81 mg gallic acid/g dry plant material, respectively. The average flavonoid content in the stems of the Halia Bentong and Halia Bara varieties was 1.36 ± 0.85 and 1.77 ± 0.75 mg quercetin/g dry plant material, respectively.

Zingiber Officinale (Ginger) Rhizome Extract

The major constituents of ginger rhizomes include carbohydrates (50-70%), lipids (3-8%), terpenes (zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene), and phenolic compounds (gingerol, paradols, and shogaol).[20] Maximum phenolic content in a methanolic and hexane extract of fresh ginger rhizomes was reported to be 95.2 mg/g dry extract and 87.5 mg/g dry extract, respectively.[6]

The levels of various metals in ginger rhizome samples in four different regions of Ethiopia were evaluated via flame atomic absorption spectrometry.[21] The mean metal concentration ranges (µg/g dry weight basis) in the ginger samples were: Ca (2000 - 2540), Mg (2700 - 4090), Fe (41.8 - 89.0), Zn (38.5 - 55.2), Cu (1.1 - 4.8), Co (2.0 - 7.6), Cr (6.0 - 10.8), Mn (184 - 401), Ni (5.6 - 8.4) and Cd (0.38 - 0.97). In a different study, an aqueous *Zingiber officinale* (ginger) rhizome extract was reported to contain 5.52% gingerol and 11.7% shogaol.[22]

Zingiber Officinale (Ginger) Root

Ginger root contains a lipophilic oleoresin, including essential oil with mainly sesquiterpenes.[23] Furthermore, the oleoresin contains different phenylpropanoids and gingerols, mainly 6-gingerol; further, there are homologues with longer side chain, e.g., 8- and 10-gingerol.

Zingiber Officinale (Ginger) Root Extract

According to a supplier, a mixture consisting of Zingiber Officinale (Ginger) Root Extract (1 - 5%) and helianthus annus (sunflower) seed oil (> 50%) contained potential allergens at concentrations less than 0.4%.[24] These potential allergens include citral (< 0.4%), citronellol (< 0.2%), geraniol (< 0.01%), limonene (< 0.03%), linalool (< 0.05%), and α-pinene (< 0.06%). A trade name mixture consisting of Zingiber Officinale (Ginger) Root Extract (≤ 1.5%), propylene glycol (68.5%), and water (30%) was reported to be free from diethylene glycol, dioxin, formaldehyde, formol, gluten, glycol ether, and phthalate.[25]

Another supplier reported that a trade name mixture containing Zingiber Officinale (Ginger) Root Extract (12 – 17%) also comprised hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%).[26] According to this supplier, this trade name mixture did not contain the following heavy metals in levels exceeding their specifications: total heavy metals (< 20 ppm), chromium (< 20 ppm), lead (< 10 ppm), nickel (< 10 ppm), cobalt (< 10 ppm), antimony (< 5 ppm), arsenic (< 2 ppm), mercury (< 1 ppm), and cadmium (< 1 ppm). In addition, fragrance allergens listed in Annex III of EU Cosmetic Regulation (EC) No. 1223/2009 and pesticides were not known to be present in this trade name mixture.

The chemical composition of *Zingiber officinale* (ginger) root extract in various solvents (water at 100°C and 30°C, ethanol, methanol, acetone, 80% methanol, 80% ethanol) was evaluated.[27] Total polyphenols, flavonoids, and tannins were highest in the aqueous extract (0.84 mg/g, 2.98 g/100 g, and 1.51 g/100 g, respectively). Antioxidant components and total antioxidant activity of each ginger extract can be found in Table 3. The average total amounts of protein, fat carbohydrate, vitamin C, and carotenoids from all samples were 5.09, 3.72, 38.35, 9.33, and 29 g/100g, respectively. Phosphorous, calcium, manganese, and iron were present in all samples in average amounts of 1.74, 0.88, 0.09, and 0.008 g/100g, respectively.

Zingiber Officinale (Ginger) Root Oil

A *Zingiber officinale* (ginger) oil, prepared from ginger rhizomes using hydrodistillation and extracted with pentane, was evaluated via gas chromatography (GC) and GC-mass spectrometry (MS).[28] The oil, for which the yield was 2.52%, contained 64.4% sesquiterpene hydrocarbons, 6.6% carbonyl compounds, 5.6% alcohols, 2.4% monoterpene hydrocarbons, and 1.6% esters. The main compounds were zingiberene (29.5%) and sesquiphellandrene (18.4%). Specific amounts of hydrocarbons and oxygenated constituents identified in the ginger rhizome oil are provided in Table 4.

Zingiber Officinale (Ginger) Root Powder

The compositions of *Zingiber officinale* (ginger) powders prepared by various drying methods are summarized in Table 5.[16] Polyphenol contents were similar among all samples (average amount of 12.3 mg/100 g powder). The phytochemical and mineral composition of a *Zingiber officinale* (ginger) rhizome powder was evaluated.[15] Phytins, tannins, saponins, oxalates, and glycosides were present in amounts of 0.28, 0.02, 4.01, 0.26, 0.81 mg/100 g, respectively. The following minerals were present in the ginger rhizome powder: Zn (4.19 µg/g), Mn (18.9 µg/g), Cu (0.86 µg/g), Ca (34.55 µg/g), P (26.70 µg/g), Fe (1.59 µg/g), Na (38.96 µg/g), and K (36.34 µg/g).

Zingiber Officinale (Ginger) Water

According to a supplier, a trade name mixture containing Zingiber Officinale (Ginger) Water consisted of 98.5% Zingiber Officinale (Ginger) Water and phenoxyethanol (1.5%).[29] This mixture was reported to be free from diethylene glycol, dioxin, formaldehyde, formol, gluten, glycol ether, and phthalate.[30]

USE

Cosmetic

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

According to 2022 VCRP survey data, Zingiber Officinale (Ginger) Root Extract is reported to be used in 244 formulations (154 leave-on formulations; 84 rinse-off formulations; 2 formulation diluted for bath use) and Zingiber Officinale (Ginger) Root Oil is reported to be used in 135 formulations (95 leave-on formulations; 36 rinse-off formulations; 7 formulations diluted for bath use; Table 6).[31] All other in-use ingredients are reported to be used in 7 formulations or less. The results of the concentration of use survey conducted by the Council in 2020 indicate Zingiber Officinale (Root) Extract also has the highest concentration of use in a leave-on formulation; it is used at up to 0.2% in face and neck formulations.[32] The 3 ingredients not in use according to the VCRP and industry survey can be found in Table 7.

Incidental ingestion and mucous membrane exposure of these ginger-derived ingredients may occur due to use in lipstick, dentifrices, and other oral hygiene product formulations (e.g. Zingiber Officinale (Ginger) Root Extract is used at up to 0.02% in lipsticks). In addition, Zingiber Officinale (Ginger) Root Extract is reported to be used in one eye lotion formulation (concentration for this formulation type was not provided).

Some of these ginger-derived ingredients are used in cosmetic sprays and powders, and could possibly be inhaled; for example, Zingiber Officinale (Ginger) Root Extract is reported to be used in other fragrance preparations (up to 0.1%), and Zingiber Officinale (Ginger) Root Oil is reportedly used pump spray body and hand formulations (up to 0.001%), and in face powders (concentration not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

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

All of the ginger-derived ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[33]

Non-Cosmetic

Zingiber officinale (ginger) is used worldwide as a food and flavoring agent.[34] Ginger rhizomes are consumed fresh, dried, pulverized into a spice, candied, or pickled. Ginger is also incorporated into baked goods, or steeped in boiling water to make ginger tea. According to the US FDA (21CFR182.10), *Zingiber officinale* is GRAS as a spice, natural seasoning agent, and flavoring. Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are GRAS for human consumption (21CFR182.20), and in animal drugs, feeds, and related products (21CFR582.20). According to 2020 concentration of use data provided by the Council, Zingiber Officinale (Ginger) Root Oil is reported to be sold at a concentration of 100% in "other fragrance preparations" as an essential oil, in which a few drops are used per teaspoon of carrier oil. It is unlikely that essential oils at concentrations of 100% would be used in cosmetic products; therefore, the Panel considered this use to be a non-cosmetic use.[32]

Ginger is commonly consumed as an over-the-counter remedy for nausea and dyspepsia, and has been listed as an inactive ingredient in two orally-ingested, FDA-approved drug products.[34,35] In Asian cultures, ginger is used as a traditional medicine to treat various ailments such as arthritis, hypercholesterolemia, baldness, toothache, and respiratory conditions. Historically, ginger has been used to improve appetite, reduce nausea, and as a topical counter-irritant.

TOXICOKINETIC STUDIES

Penetration Enhancement

In Vitro

Zingiber Officinale (Ginger) Root Extract

The influence of an aqueous *Zingiber officinale* (ginger) root extract on the transdermal absorption of hydrophilic ([^{14}C]caffeine) and hydrophobic ([^{14}C]salicylic acid) penetrants was evaluated via a flow-through in vitro porcine skin system.[36] Skin samples were placed into a two-compartment diffusion cell, and the dermal side of the skin sections were perfused using the receptor fluid consisting of a buffer solution, dextrose, and bis(trimethyl)acetamide. The flow rate of the flow-through receptor solution was 4 ml/h. A 10% solution of the ginger root extract prepared in ethanol was applied to the porcine skin, with either caffeine or salicylic acid, to an area of 1 cm^2. Control samples were exposed to ethanol combined with either caffeine or salicylic acid. All doses were occluded following topical application. Receptor fluid was collected 0, 15, 30, 45, 60, 75, 90, 105, and 230 min after application, and then 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24 h after application. Flux and permeability of caffeine with ginger root extract (flux: 1.67 ± 0.28 $\mu g/cm^2/h$; permeability: 0.78 ± 0.13 $cm/h*10^3$) was compared to the flux and permeability of caffeine with ethanol (flux: 0.58 ± 0.08 $\mu g/cm^2/h$; permeability: 0.29 ± 0.04 $cm/h*10^3$). No significant differences were observed in the absorption of [^{14}C]salicylic acid with the ginger root extract compared to the control.

Absorption, Distribution, Metabolism, and Excretion

Human

Oral

Zingiber Officinale (Ginger) Root Extract

The pharmacokinetics of active constituents found in a *Zingiber officinale* (ginger) root extract (6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol) were evaluated in humans.[37] Nine healthy volunteers received a 2 g oral dose of the ginger root extract.[37] Blood was drawn from participants at baseline, and at 0.25, 0.75, 1, 2, 4, 6, 10, 24, 48, and 72 h after ingestion. Plasma was separated from blood and evaluated via a liquid chromatography-mass spectrometry (LC-MS) analysis. Free 10-gingerol was detected in plasma with a peak concentration of 9.5 ± 2.2 ng/ml at 1 h, but was undetectable after 2 h post-dosing. Free 6-shogaol was detected in plasma at a peak concentration of 13.6 ± 6.9 ng/ml at 1 h, and was undetectable after 4 h post-dosing. No free 6-gingerol or 8-gingerol was detected in the plasma samples from 0 to 24 h post-dosing. In a multiple-dose assay, 23 healthy human subjects received either placebo (n = 11) or ginger root extracts (2.0 g/d; n = 12), for 24 d. Blood samples were drawn within 24 h of the last dose. No free 6-, 8-, or 10-gingerol and no 6-shogaol was detected in the plasma of all the subjects 24 h after the last dosing, suggesting that there was no accumulation of free 6-, 8-, or 10-gingerol or 6-shogaol in plasma after multiple daily dosing. Low levels of 6-gingerol glucuronide, 6-gingerol sulfate, and 10-gingerol glucuronide were observed in 4 subjects.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Zingiber Officinale (Ginger) Extract

No toxicity or lethality was observed in male Wistar rats (5/group) given a single oral dose of a *Zingiber officinale* (ginger) extract (concentrations ranging from 100 – 1000 mg/kg).[38] In a different study, Sprague-Dawley rats (5 rats/sex/group) were given a single oral dose of up to 5000 mg/kg steamed and dried ginger extract via gavage.[39] No mortalities or adverse effects were reported.

Zingiber Officinale (Ginger) Rhizome Extract

Five Syrian golden hamsters (5/sex/group) were given an ethanolic *Zingiber officinale* (ginger) rhizome extract via gavage in doses of 1000, 3000, or 5000 mg/kg bw.[40] Control hamsters were fed a mixture of distilled water and a polysorbate surfactant. Lethality, body weight changes, histopathology, and clinical signs of toxicity were evaluated. No deaths were observed throughout the study and body weight was similar among control and treated groups. No signs of toxicity were observed.

Zingiber Officinale (Ginger) Root Powder

Sprague-Dawley rats (5/sex/group) were given either 5000 mg/kg bw *Zingiber officinale* (ginger) rhizome powder, or distilled water, via gavage.[41] Body weight changes, food and water intake, and histopathology was evaluated in animals. Reversible stomach irritation was observed directly after administration. No other signs of toxicity were observed.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

An acute toxicity assay on a *Zingiber officinale* (ginger) extract in an olive oil vehicle was performed according to Organisation for Economic Cooperation and Development (OECD) test guidelines (TG) 423.[2] Three female Wistar rats were given a single administration of the test substance (2000 mg/kw bw ginger extract in olive oil) via drinking water. Animals were inspected daily for the next 14 d. The LD_{50} was determined to be greater than 2000 mg/kg bw.

Short-Term Toxicity Studies

Animal

Oral

Zingiber Officinale (Ginger) Rhizome Extract

Syrian golden hamsters (5/sex/group) were given an ethanolic *Zingiber officinale* (ginger) rhizome extract via gavage in doses of 1000, 3000, or 5000 mg/kg bw, for 30 d.[40] Control hamsters were fed a mixture of distilled water and a polysorbate surfactant. At the end of the treatment period, animals were sacrificed and vital organs were examined. Body weights and water and food intake were similar among control and treated groups. No abnormal histopathology was observed.

Zingiber Officinale (Ginger) Root Extract

Female Sprague-Dawley rats (6/group) were given 0.5 ml of saline or a *Zingiber officinale* (ginger) root extract (50 or 500 mg/kg), daily, via gavage, for 4 wk.[12] Mortality, hematological parameters and systemic toxicity was evaluated. No mortalities were reported throughout the study period. Total lactate dehydrogenase levels in serum was statistically significantly higher in rats treated with 500 mg/kg ginger root extract compared to controls. Histopathological examinations revealed similar results in the lungs and liver in control and treated rats.

Zingiber Officinale (Ginger) Root Oil

Male Wistar rats (10/group) were given either 0.02 or 0.002 ml/kg bw of a *Zingiber officinale* (ginger) root fixed oil, or 0.04 ml/kg bw *Zingiber officinale* (ginger) root essential oil, via gavage, for 60 d.[14] (The production of the essential and fixed oils are provided in the Method of Manufacture section of this report.) A control group received 0.5 ml/kg bw corn oil over the same time period. Behavioral, morphological, macroscopic, hematological, and histomorphological parameters were evaluated. A statistically significant ($p < 0.05$) increase in weights of the kidneys, lungs, liver, and spleen was observed in animals treated with the fixed ginger root oil, at both doses, compared to controls. A statistically significant decrease in alkaline phosphatase (ALP; $p < 0.05$) and increase in alanine transaminase was recorded in animals treated with 0.002 ml/kg bw ginger root fixed oil. Some forms of pathologies in the liver and spleen were observed in rats treated with ginger root fixed oil; however, these effects were not observed in animals treated with ginger root essential oil. No significant organ weight differences were observed in animals treated with ginger root essential oil, compared to controls. Aspartate aminotransferase (AST) values were significantly reduced in animals treated with 0.04 ml/kg bw ginger root essential oil, compared to controls. No observable differences in the histology of the heart, lung, and kidney, were observed, in either ginger-treated group, compared to the control group. Following the main study, a 14-d reversibility study was performed using 4 rats/group (14 d of no treatment). Test effects that were observed in the main study were observed to be reversible.

Zingiber Officinale (Ginger) Root Powder

Sprague-Dawley rats (5/sex/group) were given either 500, 1000, or 2000 mg/kg bw *Zingiber officinale* (ginger) rhizome powder, via gavage, each day, for 28 d.[41] A control group received distilled water. Results were similar among ginger-treated and control rats regarding body weight, behavior, histopathology, and laboratory parameters. Statistically significant increased numbers of white blood cells, neutrophils, and lymphocytes were noted in all ginger-treated groups, compared to controls.

A *Zingiber officinale* (ginger) root powder (5 ml/kg) in 5% gum arabic was given to Sprague-Dawley rats (5 rats/sex/group) at doses of 500, 1000, and 2000 mg/kg bw, via gavage, for 35 d.[42] Five males and 5 females were given the vehicle (5% gum arabic), only. Mortality, behavior, growth, food and water consumption, hematological parameters, and histopathological parameters were evaluated. All parameters evaluated were similar between control and treated groups,

however, a dose-related decrease in serum lactate dehydrogenase activity in males was observed. Treatment with 2000 mg/kg of the ginger powder led to slightly reduced absolute and relative weights of the testes.

Human

Oral

Zingiber Officinale (Ginger) Extract

The potential toxic effects of a steamed ethanolic *Zingiber officinale* (ginger) extract was evaluated in a 12-wk, randomized, double-blind, placebo-controlled trial.[43] Seventy healthy obese participants were given an oral dose of either steamed ginger extract (200 mg in capsule form; n = 36), or a placebo (n = 34), daily. Blood pressure, pulse, and hematological and biochemical parameters (white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet, ALP, gamma-glutamyl transferase, total bilirubin, total protein, albumin, blood urea nitrogen, creatinine, glucose, creatinine kinase, lactate dehydrogenase) were evaluated. All clinical test results were normal, and all participants completed the study. No extract-related adverse effects were observed.

Subchronic Toxicity Studies

Oral

Zingiber Officinale (Ginger) Root Oil

A 13-wk oral toxicity assay was performed in Wistar rats (5 rats/sex/group).[44] Animals were either left untreated, treated with the vehicle control (paraffin oil), or treated with 100, 250, or 500 mg/kg *Zingiber officinale* (ginger) oil (containing 31.08% zingiberene). Administrations occurred via gavage once per day. Mortality, body weight, food consumption, hematological parameters, and histopathological parameters were similar in control and treated groups. The no-observed-adverse-effect level (NOAEL) was determined to be greater than 500 mg/kg/d.

Chronic Toxicity Studies

Oral

Zingiber Officinale (Ginger) Root Powder

The potential chronic toxicity of a *Zingiber officinale* (ginger) rhizome powder was evaluated in Sprague-Dawley rats (20 rats/sex/group).[41] Animals were given the powder, via gavage, in doses of either 250, 500, or 1000 mg/kg bw, for 12 mo. Control animals were given distilled water. On day 366, animals were euthanized, and histopathological and hematological parameters were evaluated. No treatment-related, serious, adverse clinical effects were noted during the treatment period. Body weights and food and water consumption were similar amongst all dose levels. The NOAEL was considered to be 1000 mg/kg bw. Hematological and biochemical parameters were generally similar among control and treated groups. However, statistically significant differences were observed in hemoglobin, white blood cell, neutrophil, lymphocyte, cholesterol, triglyceride, and glucose numbers, in rats treated with 500 and 1000 mg/kg bw ginger rhizome powder, compared to controls (further details were not provided). Histopathological examination revealed no apparent adverse effects after ginger rhizome treatment (at any dose) compared to controls.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Zingiber Officinale (Ginger) Rhizome Extract

Reproductive effects of an aqueous *Zingiber officinale* (ginger) rhizome extract were evaluated in female ICR mice, at different dosing intervals.[7] At each dosing interval, mice were given either 250, 500, 1000, or 2000 mg/kg bw of the test article via gavage. A control group was treated with distilled water. For the main study, female mice (25/group) were dosed with the test substance for 90 d, and throughout mating and gestation. On gestation day (GD) 20, mice were killed and fetuses were evaluated. For estrous cycle evaluation, mice (10/group) were treated for 2 wk before evaluating vaginal cytology, and throughout a 20-d evaluation period (35 d total). During the evaluation period, estrous cycle phases were screened daily, and vaginal cytology was assessed. Pre-implantation loss (anti-fertility effects) was evaluated in 10 mice/group treated for 20 d throughout gestation. Post-implantation loss (abortifacient effects) were evaluated in mice (10/group) treated 20 d before, and throughout gestation. All pregnant females survived until necropsy, except for one female treated with 1000 mg of the extract in the pre-implantation loss group, and in 2 females treated with 2000 mg of the extract in the post-implantation loss group. High doses of the ginger rhizome extract significantly reduced the number of live fetuses, and increased fetal death and resorption, compared to controls ($p \leq 0.05$). Mice treated with 2000 mg/kg bw in the post-implantation loss group displayed significant decreases in implantation sites, compared to control animals ($p \leq 0.05$). At the highest dose level, estrous cycles were prolonged, with a significant decrease in the duration of the luteal phase, compared to control animals. The NOAEL was determined to be 500 mg/kg bw.

Zingiber Officinale (Ginger) Root Powder

The effect of prenatal exposure to a *Zingiber officinale* (ginger) rhizome powder on pregnancy outcome and postnatal development of Sprague Dawley rats was evaluated.[45] Pregnant rats were given dry powder extracts (500 mg/kg/d ; n = 4 or 1000 mg/kg/d; n = 5) of ginger rhizomes via gavage on GD 5-15. A negative, untreated control group consisted of 6 rats. Daily food and water intake, and total weight gain was significantly reduced in ginger-fed rats compared to controls ($p < 0.05$). Significant embryonic loss was observed in ginger-treated rats ($p < 0.05$), however, growth and physical

maturation parameters of offspring (pup body weight and length) exposed to ginger were unaffected. No external congenital anomalies were found in either treated or control groups.

The effect of *Zingiber officinale* (ginger) rhizome powder (50 or 100 mg/kg/d) on spermatogenesis and sperm parameters were evaluated in male Wistar rats (10 rats/group).[46] Animals were treated orally for 20 d. The method of oral administration was not stated. A control group consisting of 10 rats received treatment with distilled water, only. Serum total testosterone levels was significantly increased in the group treated with 100 mg/kg/d ginger rhizome extract, compared to the control group ($p < 0.05$). Sperm viability and motility were significantly increased in the ginger-treated groups compared to controls ($p < 0.05$). Luteinizing hormone levels, follicle stimulating hormone levels, sperm concentration, morphology, and testes weights were similar in both ginger-treated and control groups.

ANTI-REPRODUCTIVE TOXICITY STUDIES

Treatment with *Zingiber officinale* (ginger) in rats resulted in an ameliorating effect against several reproductive toxicants.[47-51] Toxicants evaluated in these studies included aluminum chloride, ethanol, cisplatin, sodium arsenite, and cadmium chloride.

GENOTOXICITY STUDIES

In Vitro

Zingiber Officinale (Ginger) Root Oil

A *Zingiber officinale* (ginger) essential oil prepared from the rhizomes of ginger was tested for the induction of reverse mutations in *Salmonella typhimurium* strains TA1535, TA98, TA100, and TA102, with and without metabolic activation.[52] The oil was tested at concentrations of 10, 50, 100, 1000, and 3000 µg/plate. No indication of mutagenic activity was observed.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

An Ames assay was performed on a *Zingiber officinale* (ginger) extract (up to 5 µl/plate) using *S. typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102, with and without metabolic activation.[2] This assay was performed according to OECD TG 471. The test substance was considered to be non-genotoxic.

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

In Vitro

Zingiber Officinale (Ginger) Rhizome Extract

The anticancer activity of a *Zingiber officinale* (ginger) rhizome extract (12.5, 25, 50, 100, 200, and 400 µg/ml) against human cervical cancer (HeLa) cells and breast cancer (MDA-MD-231) cells was evaluated via a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) and colony formation assay.[53] The rhizome extract inhibited proliferation in both cell lines in a dose- and time-dependent manner. The effect of a *Zingiber officinale* (ginger) rhizome extract (0, 10, 50, 100, 200, 500, 800, 1000, and 1500 µg/ml) on the proliferation and apoptosis of colon cancer cell lines (HCT 116 and HT 29) was also evaluated via an MTT assay.[54] The ginger extract inhibited proliferation of HCT 116 and HT 29 cells with an half-maximal inhibitory concentration (IC_{50}) of 496 ± 34.2 µg/ml and 455 ± 18.6 µg/ml, respectively. Ginger extract also caused an increase in apoptosis of the cancer cell lines in a dose-dependent manner.

Animal

Zingiber Officinale (Ginger) Extract

Potential anti-prostate cancer activity of a whole *Zingiber officinale* (ginger) extract was evaluated in male Balb/c nude mice (6 mice/group).[55] Human prostate (PC-3) xenografts were subcutaneously implanted in all test mice. Animals were fed 100 mg/kg/d ginger extract in phosphate buffered saline for 8 wk. A control group received the vehicle only. Tumors in vehicle-treated control animals showed unrestricted progression, while ginger extract treatment resulted in a time-dependent inhibition of tumor growth over the 8-wk study period. A reduction in tumor burden by 56% was observed after 8 wk of ginger extract treatment. The mean final tumor volume was significantly less in ginger extract treated mice compared to control mice ($p < 0.05$).

The effect of an ethanolic *Zingiber officinale (*ginger) extract on ethionine-induced hepatoma was evaluated in male Wistar rats (6 rats/group).[56] Rats were randomly divided into 5 groups based on diet: i) control (given normal rat chow), ii) olive oil, iii) ginger extract (100 mg/kg body weight), iv) choline-deficient diet + 0.1% ethionine to induce liver cancer (positive control) and v) choline-deficient diet + ginger extract (100mg/kg body weight). A significant reduction in positive staining of tumor necrosis factor (TNF)-α and expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) was observed in rats treated with ginger ($p < 0.05$), compared to rats in the positive control group. In addition, treatment with ginger lowered liver nodule incidence by 17%, compared to the positive control group.

OTHER RELEVANT STUDIES

Ultraviolet (UV)-Protective Effects of Ginger

Zingiber Officinale (Ginger) Rhizome Extract

The following study is included in this report as it may be helpful in addressing cosmetic safety concerns regarding phototoxicity. Male C57BL/6 mice (5 mice/group) were subjected to mid-wavelength ultraviolet light (UVB) exposure (200 mJ/cm^2) every alternate day for 2 wk, and then given different oral doses of an aqueous *Zingiber officinale* (ginger) rhizome extract (1% and 2.5%), following each UVB exposure.[22] A control group received UVB radiation followed by distilled water. The method of oral administration was not stated. Mice were killed 24 h after the last irradiation, and blood was collected. The dorsal skin was removed and measured for cytokines and hematoxylin and eosin staining. Treatment with the ginger rhizome extract reduced the effects of UVB-induced hyperplasia, infiltration of leukocytes, and dilation of blood vessels in the dermis of mice, in a dose-dependent manner. The protective effects of *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol, were also evaluated in human epidermal keratinocyte (HaCaT) cells. HaCaT cells were UVB-irradiated (100 mJ/cm^2) and cultured with test substances. Treatment with *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol at concentrations up to 10 μg/ml or 10 μM had an insignificant effect on the toxicity of irradiation. However, all test substances inhibited production of cytokines in UVB-irradiated HaCaT cells.

Immunomodulatory Effects

The following studies were included as they may be helpful in addressing cosmetic safety concerns regarding allergenicity/ hypersensitivity of the ginger-derived ingredients evaluated in this report.

Zingiber Officinale (Ginger) Extract

Anti-inflammatory effects of a whole *Zingiber officinale* (ginger) extract were evaluated in a murine asthma model.[57] Lung inflammation was induced in C57/B16 mice, via house dust mite (HDM) sensitization (intranasally), for 10 d. Throughout this period, mice also received a ginger extract (40 mg/kg) via gavage in 2% hydroxypropyl methylcellulose and 2.5% polyethylene glycol, twice daily. A positive control group was given intranasal HDM plus the vehicle. Bronchoalveolar lavages (BAL) and histologic analyses were performed following study completion. In addition, lung homogenate interleukin-4 (IL-4) concentrations were evaluated. Significant lung inflammation and increases in BAL total cell counts were evaluated after HDM administration. Co-administration of ginger extracts significantly decreased BAL cell counts compared with positive control mice ($p < 0.05$). The ginger extract also decreased lung concentration of IL-4 ($p < 0.05$), by 59%, compared to positive control animals.

Zingiber Officinale (Ginger) Powder

The anti-allergic effects of *Zingiber officinale* (ginger) powder was evaluated using a mouse allergy model.[58] Female Balb/c mice (8-10/group) were sensitized via an injection of ovalbumin (OVA), twice, in a 2-wk interval. Mice were fed diets containing 2% *Zingiber officinale* (ginger) powder, or a control diet, from 2 wk before the first injection of OVA until the end of the experiment. Two wk after the second injection, sensitization was followed by intranasal challenges, daily, for 6 d, with OVA, in all groups. Mice with OVA-induced allergic rhinitis and treatment with ginger displayed a reduction in the severity of sneezing and nasal rubbing by nasal sensitization of OVA and suppressed infiltration of mast cells in nasal mucosa and secretion of OVA-specific IgE in serum, compared to control animals.

Zingiber Officinale (Ginger) Rhizome Extract

Four patients with IgE-mediated allergy to *Zingiber officinale* (ginger) were evaluated in a study to analyze specific allergens of the ginger rhizome.[59] Two patients reported previous dyspnea and gastrointestinal symptoms following ingestion of ginger. One patient reported palpitations, hyperhidrosis, and loss of consciousness after consumption of raw ginger. Another patient reported facial angioedema and conjunctival irritation after handling ginger powder, but no symptoms after ingestion of ginger. Skin prick tests with a raw ginger extract were positive in all patients. Three healthy control subjects had negative skin prick tests to raw ginger. The ginger extract showed protein bands ranging from 90 kilodaltons (kDa) to 8 kDa. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) IgE immunoblotting assays were performed using individual patient sera. IgE-reactivity bands with molecular weights of approximately 30 and 32 kDa were observed in all patient sera. Serum from one patient revealed bands of 8-10 kDa, and serum for another patient revealed a band of 8 kDa. The 8-, 10-, 30-, and 32-kDa protein bands of the raw ginger extract were excised and analyzed. The analysis of the peptides by mass spectrometry corresponded to the cysteine protease GP-1, for the 30- and 32-kDa band. No matches were found for the 8- and 10-kDa bands.

Zingiber Officinale (Ginger) Root Oil

The anti-hypersensitivity effect of a volatile oil of *Zingiber officinale* (ginger) was evaluated in female ICR mice (12/group).[60] Mice were sensitized with 0.5% dinitrofluorobenzene (DNFB) in absolute acetone and olive oil, onto shaved abdominal skin, at the beginning of the experiment. Five days after initial sensitization, animals were challenged with 10 μl DNFB on both sides of the left ears. The right ear was treated with the vehicle (acetone and olive oil). Mice were then treated with the vehicle, ginger oil (0.125, 0.25, and 0.5 g/kg bw), or dexamethasone sodium phosphate (0.005 g/kg), via gavage, daily, for 5 d. Following the 5-d test substance administration, a DNFB challenge was performed, and mice were sacrificed. Ear swelling, thymus, and spleen weights were noted. The ginger oil, at all doses, weakened the delayed type of hypersensitivity response to DNFB in sensitized mice ($p < 0.05$), in a dose-dependent manner.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details on the dermal irritation and sensitization studies summarized below can be found in Table 8.

In vitro dermal irritation assays performed using reconstructed human epidermis on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded negative results.[2,61] An acute dermal toxicity assay on steamed and dried *Zingiber officinale* (ginger) extract (0.5 ml) was performed in 6 New Zealand White rabbits.[39] No erythema or edema was observed 24 and 72 h after treatment on intact or abraded skin. Similarly, no irritation was noted in a 48-h patch test performed on 10 subjects, using a product containing 0.0995% Zingiber Officinale (Ginger) Root. [62]

A KeratinoSens™ ARE-Nrf2 luciferase assay and direct reactivity peptide assay (DPRA) performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract yielded negative results. [63,64] A DPRA performed using a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded positive results.[2] Assays performed in humans yielded negative results (human repeated insults patch tests (HRIPTs) performed using a moisturizer containing 0.1% Zingiber Officinale (Ginger) Rhizome Extract (n = 54), a serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract (n = 104), and a product containing 0.2% Zingiber Officinale (Ginger) Root Extract (n = 53).[65-67]

OCULAR IRRITATION STUDIES

In Vitro

Zingiber Officinale (Ginger) Root Extract

An EpiOcular™ was performed on a trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%).[61] Two tissue inserts (corneal epithelial models) were incubated with the test material for 30 min. The test article was considered to be non-irritating.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

Potential ocular irritancy of a *Zingiber officinale* (ginger) extract was evaluated in an in vitro assay performed according to OECD TG 437.[2] Bovine corneas (3/group) were incubated with the test substance (ginger extract) for 10 minutes, and evaluated. Negative controls were incubated with a balanced salt solution, and positive controls were incubated with dimethylformamide. The concentrations of the test agents used were not reported. Corneal opacity values were similar among the negative control and treated groups.

CLINICAL STUDIES

Case Reports

In 2013, a woman took an herbal medicine containing ginger for motion sickness and felt full-body pruritus soon after ingestion.[68] The woman reported use of this herbal medicine for 20 yr prior, with no symptoms. Several hours after ingestion, the woman lost consciousness and was taken to the emergency department. The patient was diagnosed with anaphylactic shock. A year later, the woman reported dyspnea and itchy rash following ingestion of a different herbal medication, also containing ginger. A skin prick test was performed using powdered zedoary, powdered ginger, powdered turmeric, powdered Japanese kelp, and microcrystalline cellulose, in order determine the causative agent. Reactions were apparent after zedoary, turmeric, and ginger skin pricks. The patient was diagnosed with immediate-type allergy to zedoary/turmeric/ginger-containing drugs and foods.

A 43-yr-old man reported interrupted urinary stream associated with dysuria, perineal, and flank pain, for 4 yr.[69] The patient also reported a feeling of warmness, chest heaviness, and palpitations. History analysis revealed that the patient had been consuming ginger tea (2 - 3 tsp dry ginger) each day, for 15 yr. One week after eliminating ginger from the diet, symptoms began to recede. All symptoms were completely cleared after 8 wk without ginger consumption.

Four subjects with reported occupational allergic contact dermatitis from spices were evaluated using patch testing and prick testing.[70] Eleven spices (including powdered ginger), were put on a filter paper in a test chamber, moistened with a drop of water, and placed on the back, under occlusion. Each spice was tested in different chambers. Patches stayed in placed for 2 d. One patient elicited a strong (2+) reaction to the ginger powder spice. No patients displayed reactions to skin prick testing.

A 26-yr-old man employed at a spice factory reported shortness of breath and rhinitis approximately 2 yr after starting the job.[71] By the third year, the patient reported serious attacks of dyspnea with wheezing. When assigned a different job that did not require exposure to spices, all symptoms of atopic disease diminished. Total IgE, and allergen-specific IgE, radioallergosorbent (RAST) inhibition were evaluated using various powdered spices. Specific IgE antibodies against all evaluated spices were observed in patient sera. Percent IgE binding to coriander, curry, mace, paprika, ginger, white pepper, and mugwort were reported to be 45, 44, 26, 30, 27, 13, and 5%, respectively. IgE-binding components from coriander did not cross-react with the IgE-binding components from ginger and paprika.

Forty-five female spice-factory workers were recruited to evaluate possible allergenicity to various spices (chili pepper, paprika, pepper, parsley, garlic, onion, parsnip, ginger, turmeric, salt, and dextrose). Forty-five women without constant exposure to spices were also recruited as controls. Intradermal skin tests were performed with an aqueous extract

of the individual spices, in exposed and control workers. Skin reactions were read after 20 min. The most frequent positive dermal reactions occurred with chili pepper (13.3%), followed by paprika and parsnip (11.1%), pepper and turmeric (6.7%), and onion and ginger (2.2%). Among control workers, only 1 of 45 reacted to individual allergens, specifically with the chili pepper extract.

Spice Allergy in Spice-Sensitive Patients

Scratch tests with powdered commercial spices were performed in 70 atopic subjects with positive skin tests to birch and/or mugwort pollens and celery.[72] Scratch tests were also performed on 12 healthy controls. Anise seed, fennel, coriander, and cumin caused the highest number of positive reactions (46, 28, 26, and 24 patients, respectively). Ginger caused a positive scratch test in 3 of 70 patients.

SUMMARY

The safety of 9 *Zingiber officinale* (ginger)-derived ingredients as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, the majority of these ingredients are reported to function in cosmetics as skin-conditioning agents – miscellaneous; additional functions were also reported. *Zingiber officinale* is GRAS in the US as a spice, natural seasoning, and flavoring agent. In addition, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are considered GRAS for human and animal consumption.

According to 2022 VCRP survey data, Zingiber Officinale (Ginger) Root Extract is reported to be used in 244 cosmetic formulations (154 leave-on formulations; 84 rinse-off formulations; 2 formulations diluted for bath use). Zingiber Officinale (Ginger) Root Oil is reported to be used in 135 total formulations. All other in-use ingredients are reported to be used in 7 formulations or less. The results of the concentration of use survey conducted by the Council indicate Zingiber Officinale (Root) Extract also has the highest concentration of use in a leave-on formulation; it is used at up to 0.2% in face and neck formulations.

The influence of a *Zingiber officinale* (ginger) root extract on the transdermal absorption of [^{14}C]caffeine and [^{14}C]salicylic acid was evaluated in porcine skin. The dermal absorption of [^{14}C]caffeine was significantly higher with the ginger root extract compared to the control (ethanol). No significant differences were observed in the absorption of [^{14}C]salicylic acid with the ginger root compared to the control.

Nine healthy volunteers were given a 2 g dose of *Zingiber officinale* (ginger) root extract in order to evaluate metabolism. Plasma was evaluated at various intervals following ingestion. Metabolites found in the plasma included 10-gingerol and 6-shogaol. In a multiple-dose assay, 23 healthy volunteers received a placebo or 2 g *Zingiber officinale* (ginger) root extract, once a day, for 24 d. No free 6-, 8-, and 10-gingerol or 6-shogaol were detected in the plasma of any the subjects 24 h after the last dosing, suggesting that there was no accumulation of free 6-, 8-, and 10-gingerol or 6-shogaol in plasma after multiple daily dosing.

No adverse effects were reported in oral toxicity assays on *Zingiber officinale* (ginger) extracts performed in rats at up to 5000 mg/kg. Similarly, no adverse effects were reported in an acute oral toxicity assay involving Sprague-Dawley rats given up to 5000 mg/kg *Zingiber officinale* (ginger) rhizome powder. Reversible stomach irritation was observed in an acute oral toxicity assay performed in Syrian golden hamsters given *Zingiber officinale* (ginger) root powder. No other toxic effects were observed.

In a short-term oral toxicity assay, Syrian golden hamsters were given an ethanolic *Zingiber officinale* (ginger) rhizome extract, via gavage, at up to 5000 mg/kg bw/d, for 30 d. No signs of toxicity were observed. Female Sprague-Dawley rats were given up to 500 mg/kg of a *Zingiber officinale* (ginger) root extract, daily, via gavage, for 4 wk. Elevated total lactate dehydrogenase levels in the serums of high-dosed animals were observed; however, no other adverse effects were reported. In a 60-d study, male Wistar rats were given either 0.02 or 0.002 ml/kg bw of a *Zingiber officinale* (ginger) root fixed oil, or 0.04 ml/kg bw *Zingiber officinale* (ginger) root essential oil, via gavage, daily. Reversible, statistically significant increases in kidney, lung, liver, and spleen weights, and pathologies in the liver and spleen, were observed in animals treated with fixed ginger oil. These effects were not observed in animals treated with ginger root essential oil. In a 28-d study, Sprague-Dawley rats were given up to 2000 mg/kg bw of a *Zingiber officinale* (ginger) rhizome powder, daily, via gavage. Statistically significant increased numbers of white blood cells, neutrophils, and lymphocytes were noted in all ginger-treated groups, compared to controls. No other adverse effects were reported. In a different study, a *Zingiber officinale* (ginger) root powder was orally administered to Sprague-Dawley rats at doses of up to 2000 mg/kg bw/d, via gavage, for 35 d. All parameters evaluated were similar between control and treated groups, however, a dose-related decrease in serum lactate dehydrogenase activity in males, was observed. In a 13-wk oral toxicity assay, a *Zingiber officinale* (ginger) root oil was administered to Wistar rats, each day, via gavage, at doses up to 500 mg/kg/d. The NOAEL was determined to be greater than 500 mg/kg/d. The potential chronic toxicity of a *Zingiber officinale* (ginger) rhizome powder was evaluated in Sprague-Dawley rats. Animals were treated via gavage in doses up to 1000 mg/kg bw, for 12 mo. No treatment-related, serious, adverse clinical effects were noted during the 12 mo.

In a human assay, an ethanolic *Zingiber officinale* (ginger) extract (200 mg) was given to 36 healthy, obese participants via a capsule, each day, for 12 wk. No extract-related adverse effects were observed.

The reproductive effect of an aqueous Zingiber officinale (ginger) rhizome extract (up to 2000 mg/kg bw/d; gavage administration) was evaluated in ICR mice. Estrous cycles, pre-implantation loss, and post-implantation loss were evaluated. High doses of the ginger rhizome extract significantly reduced the number of live fetuses, and increased fetal

death and resorption, compared to controls ($p \leq 0.05$). Mice in the post-implantation loss group, treated with 2000 mg/kg bw, displayed significant decreases in implantation sites, compared to control animals ($p \leq 0.05$). The NOAEL was determined to be 500 mg/kg bw. The effect of prenatal exposure to a *Zingiber officinale* (ginger) rhizome powder on pregnancy outcome and postnatal development of Sprague Dawley rats was evaluated. Pregnant rats were given dry powder extracts (500 mg/kg/d ; n = 4 or 1000 mg/kg/d; n = 5) of ginger rhizomes via gavage on GD 5-15. Significant embryonic loss was observed in ginger-treated rats ($p < 0.05$); however, growth and physical maturation parameters of offspring (pup body weight and length) exposed to ginger were unaffected. The effect of a *Zingiber officinale* (ginger) rhizome powder (up to 100 mg/kg/d; 20 d oral administration) on sperm parameters were evaluated in male Wistar rats. Serum total testosterone levels, sperm viability, and sperm motility were statistically increased in ginger-treated rats compared to controls ($p < 0.05$). Treatment with *Zingiber officinale* (ginger) resulted in an ameliorating affect against several reproductive toxicants (aluminum chloride, ethanol, cisplatin, sodium arsenite, and cadmium chloride) in several anti-reproductive toxicity assays.

No mutagenicity was observed in an Ames assay performed using a *Zingiber officinale* essential oil (up to 3000 µg/plate; with and without metabolic activation), on *S. typhimurium* strains TA1535, TA98, TA100, and TA102. An Ames assay was performed using a *Zingiber officinale* (ginger) extract (may refer to other ginger-derived ingredients; up to 5 µl/plate; with and without metabolic activation) on *S. typhimurium* strains TA1535, TA1537, TA98, TA100, TA102. The test substance was considered to be non-mutagenic.

The anti-cancer effect of a *Zingiber officinale* (ginger) rhizome extract (up to 400 µg/ml) on human cervical and breast cancer cells was evaluated in vitro. The rhizome extract inhibited proliferation in both cell lines in a dose- and time-dependent manner. A similar assay was performed in order to evaluate the effect of *Zingiber officinale* (ginger) rhizome extract (up to 1500 µg/ml) in colon cancer cell lines. The ginger rhizome extract inhibited proliferation and increased apoptosis in the human colon cancer cell lines, in a dose-dependent manner. In a mouse assay, the potential anti-prostate cancer effect of a whole *Zingiber officinale* (ginger) extract (100 mg/kg/d; 8-wk oral administration) was evaluated in male Balb/c nude mice with subcutaneously implanted human prostate xenografts. A reduction in tumor burden by 56% was observed after 8 wk of ginger extract treatment. The effect of an ethanolic *Zingiber officinale (*ginger) extract (100 mg/kg bw) on ethionine-induced hepatoma was evaluated in male Wistar rats. Treatment with ginger lowered liver nodule incidence by 17%, compared to the positive control group.

The potential UV-protective effects of an aqueous *Zingiber officinale* (ginger) rhizome extract (1 and 2.5%) was evaluated in male C57BL/6 mice. Treatment with the ginger rhizome extract reduced the effects of UVB-induced hyperplasia, infiltration of leukocytes, and dilation of blood vessels in the dermis of mice, in a dose-dependent manner. An in vitro assay was also performed using UVB-irradiated HaCaT cells to evaluate the potential protective effects of *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol. All test substances inhibited production of cytokines in UVB-irradiated HaCaT cells.

The anti-inflammatory effects of a whole *Zingiber officinale* (ginger) extract was evaluated in C57/B16 mice. Lung inflammation was induced via intranasal HDM sensitization, for 10 d. Mice also received the ginger extract (40 mg/kg/d) via gavage, twice daily. Ginger extracts resulted in a statistically significant decrease in BAL cell counts and lung concentrations of IL-4, compared to positive control animals ($p < 0.05$).

The anti-allergic effects of a *Zingiber officinale* (ginger) powder was evaluated in female Balb/c mice. Mice were sensitized via OVA injection, and fed diets containing 2% *Zingiber officinale* (ginger) powder. Mice with OVA-induced allergic rhinitis and treatment with ginger displayed a reduction in the severity of sneezing and nasal rubbing by nasal sensitization of OVA and suppressed infiltration of mast cells in nasal mucosa and secretion of OVA-specific IgE in serum, compared to control animals.

The anti-hypersensitivity effect of a volatile oil of *Zingiber officinale* (ginger) was evaluated in female ICR mice. Mice were initially dermally sensitized with DNFB in acetone and olive oil. Treated mice were given ginger oil (up to 0.5 g/kg bw), via gavage, daily, for 5 d. Following the 5-d test substance administration, a DNFB challenge was performed, and mice were sacrificed. The ginger oil, at all doses, weakened the delayed type of hypersensitivity response to DNFB in sensitized mice ($p < 0.05$), in a dose-dependent manner.

Four patients with IgE-mediated allergy to *Zingiber officinale* (ginger) were evaluated to analyze the specific allergens of the ginger rhizomes via IgE immunoblotting assays. IgE-reactivity bands with molecular weights of approximately 30 and 32 kDa were observed in all patient sera. The analysis of the peptides by mass spectrometry corresponded to the cysteine protease GP-1, for the 30- and 32-kDa band.

In vitro dermal irritation assays performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded negative results. An acute dermal toxicity assay on steamed and dried *Zingiber officinale* (ginger) extract (0.5 ml) was performed in 6 New Zealand White rabbits. No erythema or edema was observed 24 and 72 h after treatment on intact or abraded skin. Similarly, no irritation was noted in a 48-h patch test performed on 10 subjects, using a product containing 0.0995% Zingiber Officinale (Ginger) Root. A KeratinoSens™ ARE-Nrf2 luciferase assay and direct reactivity peptide assay (DPRA) performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract yielded negative results. A DPRA performed using a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded positive results. Assays performed in humans yielded negative results (HRIPTs performed using a

moisturizer containing 0.1% Zingiber Officinale (Ginger) Rhizome Extract, a serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract, and a product containing 0.2% Zingiber Officinale (Ginger) Root Extract).

In vitro ocular irritation assays performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract yielded negative results.

Full-body pruritus and loss of consciousness was reported in a woman after consumption of an herbal medication containing ginger. The patient reported prior 20-yr use of this medication with no adverse effects. One yr after the initial incident, the patient reported dyspnea and an itchy rash following a different herbal preparation containing ginger. Skin prick tests confirmed allergy to zedoary, turmeric, and ginger. A 43-yr-old man reported dysuria, perineal and flank pain, for 4 yr. History analysis revealed that the patient had been ingesting ginger tea, each day, for 15 yr. The patient's symptoms resolved after eliminating ginger from the diet.

Four subjects with reported occupational allergic contact dermatitis from spices were evaluated using patch testing and prick testing. One patient elicited a strong (2+) reaction to the ginger powder spice. No patients displayed reactions to skin prick testing. A 26-yr-old spice factory-worker reported increasingly exacerbated dyspnea and wheezing 2 yr after starting the job. Total IgE, and allergen-specific IgE, RAST inhibition were evaluated using various powdered spices. Percent IgE binding to coriander, curry, mace, paprika, ginger, white pepper, and mug wort were reported to be 45, 44, 26, 30, 27, 13, and 5%, respectively. Forty-five female spice-factory workers were recruited to evaluate possible allergenicity to various spices (chili pepper, paprika, pepper, parsley, garlic, onion, parsnip, ginger, turmeric, salt, and dextrose) via intradermal skin tests. Only 2.2% of patients reported a positive reaction to ginger. In a different study, scratch tests with powdered commercial spices were performed in 70 atopic patients with positive skin tests to birch and/or mugwort pollens and celery. Ginger caused a positive scratch test in 3 of 70 patients.

DISCUSSION

This assessment reviews the safety of 9 *Zingiber officinale* (ginger)-derived ingredients as used in cosmetic formulations. The Panel reviewed the available data and concluded that the 7 *Zingiber officinale* (ginger) root- and rhizome-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing. It should be noted that the Panel found the available data to be sufficient to conclude safety for Zingiber Officinale (Ginger) Water, as this ingredient, according to manufacturers, is reported to be prepared via the distillation of ginger roots.

The Panel also concluded the available data are insufficient to make a determination that Zingiber Officinale (Ginger) Extract and Zingiber Officinale (Ginger) Leaf Cell Extract are safe under the intended conditions of use in cosmetic formulations. In order to determine safety for Zingiber Officinale (Ginger) Leaf Cell Extract, the Panel requires method of manufacturing, composition, and impurities data. If the composition of Zingiber Officinale (Ginger) Leaf Cell Extract notably differs from the root-derived ginger ingredients, systemic toxicity data (e.g., 28-d dermal toxicity, genotoxicity, developmental/reproductive toxicity, and carcinogenicity data) would also be required. Insufficiencies for Zingiber Officinale (Ginger) Extract are irritation and sensitization data at the maximum use concentration.

The Panel expressed concern about pesticide residues, heavy metals, and other plant species that may be present in these *Zingiber officinale*-derived ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities in final formulation.

Because final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For the *Zingiber officinale*-derived ingredients, the Panel was concerned about the presence of potential sensitizers (e.g., citronellol) in cosmetics. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., Zingiber Officinale (Ginger) Root Extract is reported to be used in other fragrance preparations at up to 0.1%). Inhalation toxicity data were not available; however, inhalation toxicity concerns were mitigated due to low concentrations of use, high NOAELs in subchronic, chronic, and reproductive oral toxicity assays, and the use of these ingredients in foods. In addition, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which the ingredients are used in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

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

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 7 *Zingiber officinale* (ginger)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root*
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice*
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

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

Additionally, the Panel concluded the available data are insufficient to make a determination that the following 2 ingredients are safe under the intended conditions of use in cosmetic formulations:

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Leaf Cell Extract**

** There are currently no reported uses for this ingredient.*

TABLES

Table 1. INCI names, definitions, and functions of the *Zingiber officinale* (ginger)-derived ingredients in this safety assessment[1]

Ingredient (CAS No.)	Definition	Function
Zingiber Officinale (Ginger) Extract [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Extract is the extract of the whole plant, *Zingiber officinale*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Leaf Cell Extract	Zingiber Officinale (Ginger) Leaf Cell Extract is the extract of a culture of the leaf cells of *Zingiber officinale*	Antioxidants, Skin Protectants
Zingiber Officinale (Ginger) Rhizome Extract	Zingiber Officinale (Ginger) Rhizome Extract is the extract of the rhizomes of *Zingiber officinale.*	Antimicrobial Agents
Zingiber Officinale (Ginger) Root	Zingiber Officinale (Ginger) Root is the root of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Extract [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Root Extract is the extract of the roots of the ginger, *Zingiber officinale.*	Fragrance Ingredients; Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Juice [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Root Juice is the juice expressed from the roots of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Oil [CAS No. 8007-08-7]	Zingiber Officinale (Ginger) Root Oil is obtained from the dried rhizomes of *Zingiber officinale*. (The chemical class for this ingredient is essential oils and waters.)	Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Powder	Zingiber Officinale (Ginger) Root Powder is the powder obtained from the dried, ground roots of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Water [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Water is an aqueous solution of the steam distillate obtained from *Zingiber officinale.*	Fragrance Ingredients

Table 2. Physical and chemical properties of a *Zingiber officinale* (ginger)-derived ingredients and trade name mixtures

Property	Value	Reference
Zingiber officinale (ginger) extract		
Physical Form	liquid	2
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.878	2
Vapor pressure (mmHg@ 20 ºC)	63.76	2
Boiling Point (ºC)	229.9	2
Water Solubility (g/L)	0.0004	2
log K_{ow}	6.9	2
Zingiber Officinale (Ginger) Water (98.5%), phenoxyethanol (1.5%)		
Physical Form	transparent solution	73
Color	colorless	73
Odor	characteristic	73
Refraction Index (@ 20 ºC)	0.332 – 1.339	73
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.999 – 1.002	73
Water Solubility	miscible	73
Alcohol Solubility	miscible	73
Mineral/Vegetable Oil Solubility	non-miscible	73
Zingiber Officinale (Ginger) Root Extract (1-5%) and helianthus annuus hybrid oil (> 50%)		
Physical Form	clear – slightly turbid liquid	24
Color	yellow – brown	24
Odor	characteristic	24
Refraction Index (@ 20 ºC)	1.445 – 1.489	24
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.891 – 0.924	24
Water Solubility	10%; not soluble	24
Alcohol Solubility	10%; not soluble	24
Zingiber Officinale (Ginger) Root Extract (1.5%), propylene glycol (68.5%), and water (30%)		
Physical Form	translucent liquid with slight precipitate	74
Color	orange yellow to orange	74
Odor	characteristic	74
Refraction Index (@ 20 ºC)	1.410 – 1.420	74
Density/Specific Gravity (g/cm^3 @ 20 ºC)	1.045 – 1.055	74
Water Solubility	miscible	74
Alcohol Solubility	miscible	74
Mineral/Vegetable Oil Solubility	non-miscible	74
Zingiber Officinale (Ginger) Water (98.5%) and phenoxyethanol (1.5%)		
Physical Form	transparent solution	73
Color	colorless	73
Odor	characteristic	73
Refraction Index (@ 20 ºC)	0.332 – 1.339	73
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.999 – 1.002	73
Water Solubility	miscible	73
Alcohol Solubility	miscible	73
Mineral/Vegetable Oil Solubility	non-miscible	73

Table 3. Antioxidant components and antioxidant activity of various ginger extracts[27]

Solvent	Total Polyphenols (mg/100 g)	Tannins mg/100 g	Flavonoids (mg/100 g)	Total antioxidant activity (µmol/g of sample)
Water (100 °C)	840	1510	2980	73,529.4
Water (30 °C)	838	1340	1371	79,400
Methanol	510	1120	685	98,822.5
Ethanol	565	980	278	91,176.25
Methanol (80%)	780	1280	404	85,294
Ethanol (80%)	800	1150	352	80,000
Acetone	325	670	249	32,056

Table 4. Hydrocarbons and oxygenated compounds in a *Zingiber officinale* (ginger) rhizome essential oil[28]

Constituent	Amount (%)	Constituent	Amount (%)
(*E*)-farnesene	0.73	pinanol	amount undermined
(*E,E*) α-farnesene	1.92	sabinene	trace
(*Z*)-β-Farnesene	amount undermined	santalene	trace
2,6-dimethylhepen-1-ol	0.01	terpinolene	0.09
2-ethyl hexanol	amount undermined	toluene	0.03
2-methyl butanal	amount undermined	*t*-muurolene	amount undermined
2-methyl-2-hepten-6-one	0.09	*t*-muurolol	0.14
2-pentanone	amount undermined	*trans*-2-octanol	trace
acetic acid	0.03	*trans*-isouegenol	0.60
acetone	0.02	vetivinene	0.57
allaromadendrene	trace*	zingiberene	29.54
bergametene	0.23	α-bisabolol	amount undermined
borneol	1.27	α-copaene	amount undermined
cadinol	amount undermined	α-cubebene	0.11
calamenene	amount undermined	α-eudesmol	0.11
camphene	0.61	*α*-eugenol	trace
camphor	0.06	α-gurjumene	0.01
cintronellal	0.14	α-himachallene	amount undermined
cintronellol	0.60	α-humulene	0.22
elemol	0.36	α-phellandrene	0.03
eremophyllene	0.09	α-pinene	0.21
eudesmol	0.36	α-terpineol	0.61
farnesene	6.46	α-ylangene	0.55
geranial	3.46	β-caryophyllene	0.35
geraniol	0.77	β-phellandrene	0.95
geranoic acid	0.24	β-pinene	0.61
geranylacetone	amount undermined	β-selinene	0.16
germacrene D	3.58	β-sesquiphellandrene	18.42
hexanal	0.02	β-sesquiphellandrol	0.34
ionone	amount undermined	γ-elemene	0.12
isovaleraldehyde	amount undermined	δ-elemene	1.14
lauric acid	amount undermined	δ-terpinene	0.01
limonen-10-ol	0.02	*ρ*-cymene	0.03
limonene	0.34	geranic acid	amount undermined
linalool	0.40	isobornyl acetate	0.03
methyl-*n*-heptylketone	0.03	citronelly acetate	0.39
methyl-*n*-undecylketone	0.09	geranyl acetate	amount undermined
Myrene	0.11	neryl acetate	1.22
n-butylaldehyde	Trace	1,8-cineole	0.41
neral	2.50	linalool oxide	amount undermined
nerolidol	0.54	caryophyllene oxide	0.18
n-heptanol-2-ol	0.02	acetyl furan	amount undermined
perillene	amount undermined	methyl pyrrole	amount undermined

*trace - < 0.01%

Table 5. Composition of *Zingiber officinale* (ginger) powders dried via different methods (mg/100 g ginger powder)[16]

Ginger Powder	Shade dried	Solar dried	Oven dried	Microwave dried
Moisture	3.7±0.08	3.5±0.08	3.6±0.07	3.7±0.09
Protein	5.8±0.09	5.5±0.10	5.0±0.05	5.7±0.09
Crude Fiber	5.4±0.08	4.9±0.07	5.4±0.09	5.6±0.10
Fat	0.90±0.02	0.76±0.04	0.78±0.02	0.80±0.02
Ash	3.5±0.04	3.4±0.07	3.3±0.04	3.6±0.05
β-carotene	0.81±0.01	0.68±0.02	0.71±0.05	0.78±0.07
Ascorbic acid	3.8±0.07	2.2±0.08	2.3±0.09	3.5±0.10
Polyphenols	12.5±0.13	11.8±0.15	12.4±0.10	12.4±0.12
Calcium	69.2±1.02	65.3±1.04	64.4±1.02	67.6±1.03
Iron	1.8±0.05	1.6±0.06	1.5±0.03	1.6±0.02
Copper	0.75±0.03	0.46±0.06	0.68±0.03	0.70±0.02

Table 6. Frequency (2022)[31] and concentration (2020)[32] of use according to duration and exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Zingiber Officinale (Ginger) Extract		**Zingiber Officinale (Ginger) Rhizome Extract**		**Zingiber Officinale (Ginger) Root Extract**	
Totals*	**7**	**0.000042 – 0.0009**	**2**	**NR**	**244**	**0.0000033 – 0.22**
Duration of Use						
Leave-On	*3*	*0.000042*	*2*	*NR*	158	*0.0001 – 0.2*
Rinse-Off	*4*	*0.0009*	*NR*	*NR*	84	*0.0001 – 0.22*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	2	*0.0000033 – 0.001*
Exposure Type						
Eye Area	NR	NR	NR	NR	4	NR
Incidental Ingestion	NR	NR	NR	NR	13	0.0072 – 0.02
Incidental Inhalation-Spray	1[a]; 1[b]	0.000042[a]	2[a]	NR	1; 57[a];42[b]	0.001 – 0.1; 0.009[a]
Incidental Inhalation-Powder	1[b]	NR	NR	NR	42[b]	0.0001 – 0.2[c]
Dermal Contact	5	NR	2	NR	151	0.0000033 – 0.22
Deodorant (underarm)	1[a]	NR	NR	NR	1[a]	NR
Hair - Non-Coloring	NR	0.000042 – 0.0009	NR	NR	80	0.0001 – 0.018
Hair-Coloring	NR	NR	NR	NR	NR	0.0016
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	22	0.0000033 – 0.02
Baby Products	NR	NR	NR	NR	NR	NR
	Zingiber Officinale (Ginger) Root Oil		**Zingiber Officinale (Ginger) Root Powder**		**Zingiber Officinale (Ginger) Water**	
Totals*	**135**	**0.000046 – 0.004**	**5**	**NR**	**2**	**NR**
Duration of Use						
Leave-On	*95*	*0.000046 – 0.003*	1	*NR*	NR	*NR*
Rinse Off	*36*	*0.001 – 0.004*	4	*NR*	1	*NR*
Diluted for (Bath) Use	*4*	*0.001*	NR	*NR*	1	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	2	NR	1	NR	NR	NR
Incidental Inhalation-Spray	16; 28[a]; 21[b]	0.00032 – 0.001; 100**	1[b]	NR	NR	NR
Incidental Inhalation-Powder	1; 21[b]	0.001 – 0.003[c]	1[b]	NR	NR	NR
Dermal Contact	109	0.000046; 100**	4	NR	1	NR
Deodorant (underarm)	5[a]	0.000046 – 0.0021	NR	NR	NR	NR
Hair - Non-Coloring	22	0.004	NR	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	19	0.001	3	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
**Essential oil: diluted for use; a few drops used per tsp of carrier oil
[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
NR – not reported

Table 7. Ingredients not reported to be in use according to 2022 FDA VCRP and 2020 concentration of use data[31,32]

Zingiber Officinale (Ginger) Leaf Cell Extract
Zingiber Officinale (Ginger) Root
Zingiber Officinale (Ginger) Root Juice

Table 8. Dermal irritation and sensitization studies

Ingredient	Test Article	Dose/Concentration	Test Population	Procedure	Results	Reference
IRRITATION						
In Vitro						
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	100	3 tissue inserts	EpiDermTM assay; reconstructed human epidermis; tissue inserts incubated for 60 min	Non-irritating	[61]
Zingiber Officinale (Ginger) Extract*	*Zingiber officinale* (ginger) extract*	NR	3 tissue inserts	OECD TG 439; reconstructed human epidermis	Non-irritating	[2]
Animal						
Zingiber Officinale (Ginger) Extract	*Zingiber officinale* (ginger) extract (dried)	0.5 ml; concentration not reported	6 New Zealand white rabbits	The test substance was applied to intact and abraded skin (level of occlusion not reported), and kept in place for 24 h	Non-irritating; PII = 0	[39]
Human						
Zingiber Officinale (Ginger) Root Extract	Product containing 0.0995% Zingiber Officinale (Ginger) Root Extract	0.02 ml; 100%	10 subjects	48-h application; occlusive conditions; evaluations made 30 min after patch removal	Non-irritating	[62]
SENSITIZATION						
In Vitro						
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	0.00098 - 2 mM	HaCaT cells	KeratinoSens™ ARE-Nrf2 luciferase test; OECD TG 442D	Non-sensitizing; IC_{50} > 1000 µm	[63]
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	100 mM	cysteine- and lysine-containing peptides (3 replicates)	DPRA; OECD TG 442C	Non-sensitizing; mean percent depletion of 1.89% (minimal reactivity)	[64]
Zingiber Officinale (Ginger) Extract*	*Zingiber officinale* (ginger) extract*	100%	cysteine- and lysine-containing peptides (3 replicates)	DPRA; OECD TG 442C	Sensitizing; mean percent depletion pf 27.81% (moderate reactivity)	[2]
Human						
Zingiber Officinale (Ginger) Rhizome Extract	Moisturizer containing 0.1% Zingiber Officinale (Ginger) Rhizome Extract	concentration and application area not reported; 0.1 – 0.15 g	54 subjects	HRIPT; occlusive conditions; test article was volatized for 30-90 min prior to application	Non-sensitizing	[67]
Zingiber Officinale (Ginger) Root Extract	Serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract	100%; dose and application area not reported	104 subjects	HRIPT; occlusive conditions	Non-irritating and Non-sensitizing	[65]
Zingiber Officinale (Ginger) Root Extract	Product containing 0.2% Zingiber Officinale (Ginger) Root Extract	100%; 2 cm x 2 cm application area	53 subjects	HRIPT; semi-occlusive conditions	Non-irritating and Non-sensitizing	[66]

*potential inference source for one or more ginger-derived ingredients

DPRA = direct peptide reactivity assay; HaCaT = immortalized human keratinocytes; HRIPT = human repeat insult patch test; IC_{50} = half-maximal inhibitory concentration; OECD TG = Organisation for Economic Cooperation and Development test guidelines; PII = primary irritation index

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2022 FDA VCRP DATA – Zingiber officinale (ginger)-derived ingredients

Zingiber Officinale (Ginger) Extract

Shampoos (non-coloring)	1
Tonics, Dressings, and Other Hair Grooming Aids	1
Deodorants (underarm)	1
Other Personal Cleanliness Products	1
Cleansing	1
Body and Hand (exc shave)	1
Paste Masks (mud packs)	1

Total: 7

Zingiber Officinale (Ginger) Rhizome Extract

Moisturizing	1
Other Skin Care Preps	1

Total: 2

Zingiber Officinale (Ginger) Leaf Cell Extract

Total: 0

Zingiber Officinale (Ginger) Root

Total: 0

Zingiber Officinale (Ginger) Root Extract

Bath Oils, Tablets, and Salts	1
Bubble Baths	1
Eye Lotion	2
Other Eye Makeup Preparations	2
Cologne and Toilet waters	1
Hair Conditioner	28
Shampoos (non-coloring)	29
Tonics, Dressings, and Other Hair Grooming Aids	9
Wave Sets	1
Other Hair Preparations	13
Foundations	1
Lipstick	11
Makeup Bases	2

Other Makeup Preparations	2
Dentifrices	1
Other Oral Hygiene Products	1
Bath Soaps and Detergents	5
Deodorants (underarm)	1
Feminine Deodorants	1
Other Personal Cleanliness Products	1
Beard Softeners	1
Cleansing	13
Face and Neck (exc shave)	29
Body and Hand (exc shave)	12
Moisturizing	42
Night	1
Paste Masks (mud packs)	5
Skin Fresheners	5
Other Skin Care Preps	23

Total: 244

Zingiber Officinale (Ginger) Root Juice

Total: 0

Zingiber Officinale (Ginger) Root Oil

Bath Oils, Tablets, and Salts	4
Perfumes	2
Other Fragrance Preparation	14
Hair Conditioner	3
Shampoos (non-coloring)	10
Tonics, Dressings, and Other Hair Grooming Aids	2
Other Hair Preparations	7
Face Powders	1
Lipstick	4
Bath Soaps and Detergents	11
Deodorants (underarm)	5
Beard Softeners	2
Other Shaving Preparation Products	1
Cleansing	10

Face and Neck (exc shave)	5
Body and Hand (exc shave)	16
Moisturizing	22
Paste Masks (mud packs)	1
Skin Fresheners	4
Other Skin Care Preps	11

Total: 135

Zingiber Officinale (Ginger) Root Powder

Other Oral Hygiene Products	1
Bath Soaps and Detergents	1
Other Personal Cleanliness Products	1
Cleansing	1
Body and Hand (exc shave)	1

Total: 5

Zingiber Officinale (Ginger) Water

Other Bath Preparations	1
Shampoos (non-coloring)	1

Total: 2