Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 15, 2020
Panel Meeting Date:	June 8-9, 2020

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer, CIR.

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Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst, CIR
Date: May 15, 2020
Subject: Draft Final Safety Assessment on *Punica granatum* (Pomegranate)-Derived Ingredients

Enclosed is the Draft Final Report of the Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics. (It is identified as *pomegr062020rep* in the pdf document.)

At the December meeting, the Panel issued a Revised Tentative Report with the conclusion that the following 8 ingredients are safe in the present practices of use and concentration described in the safety assessment.

Punica Granatum Fruit Extract
Punica Granatum Fruit Juice
Punica Granatum Fruit Water
Punica Granatum Juice Extract
Punica Granatum Pericarp Extract
Punica Granatum Seed
Punica Granatum Seed Extract
Punica Granatum Seed Powder

However, the Panel also concluded that the data were insufficient to make a determination of safety for the following 10 ingredients:

Punica Granatum Extract
Punica Granatum Bark Extract
Punica Granatum Bark/Fruit Extract
Punica Granatum Callus Culture Extract
Punica Granatum Flower Extract
Punica Granatum Fruit/Root/Stem Powder
Punica Granatum Fruit/Sucrose Ferment Filtrate
Punica Granatum Leaf Cell Extract
Punica Granatum Peel Extract
Punica Granatum Seed Cell Culture Lysate

The additional data needed for these cosmetic ingredients are:

- Method of manufacture, especially with regard to solvent used for the extracts
- Composition and impurities data
- Systemic toxicity data
- Dermal irritation and sensitization data

Since the December Panel meeting, no new data have been received. CIR staff did receive comments from the Council on the Revised Tentative Report; these comments and the comments provided by the Council prior to the December meeting on the draft Tentative Report have been addressed (*pomegr062020pcpc1 and pomegr062020pcpc2*).

The Use Table (Table 5) was updated with 2020 VCRP data (*pomegr062020fda*). Use for Punica Granatum Extract has increased from 312 total uses to 334; the changes to the number of uses in the other pomegranate ingredients were minimal. As a reminder, Punica Granatum Extract, which was defined as an extract of the "whole plant," is no longer listed in the *Dictionary*. Trade names that were associated with this ingredient are now included for the monographs associated with Punica Granatum Fruit Extract or Punica Granatum Pericarp Extract, as suppliers have indicated that extracts are not made from the "whole plant." However, Punica Granatum Extract is still included in the list of ingredients named in this report because it has the highest number of uses reported in the VCRP database, and because concentration of use data are still associated with this name.

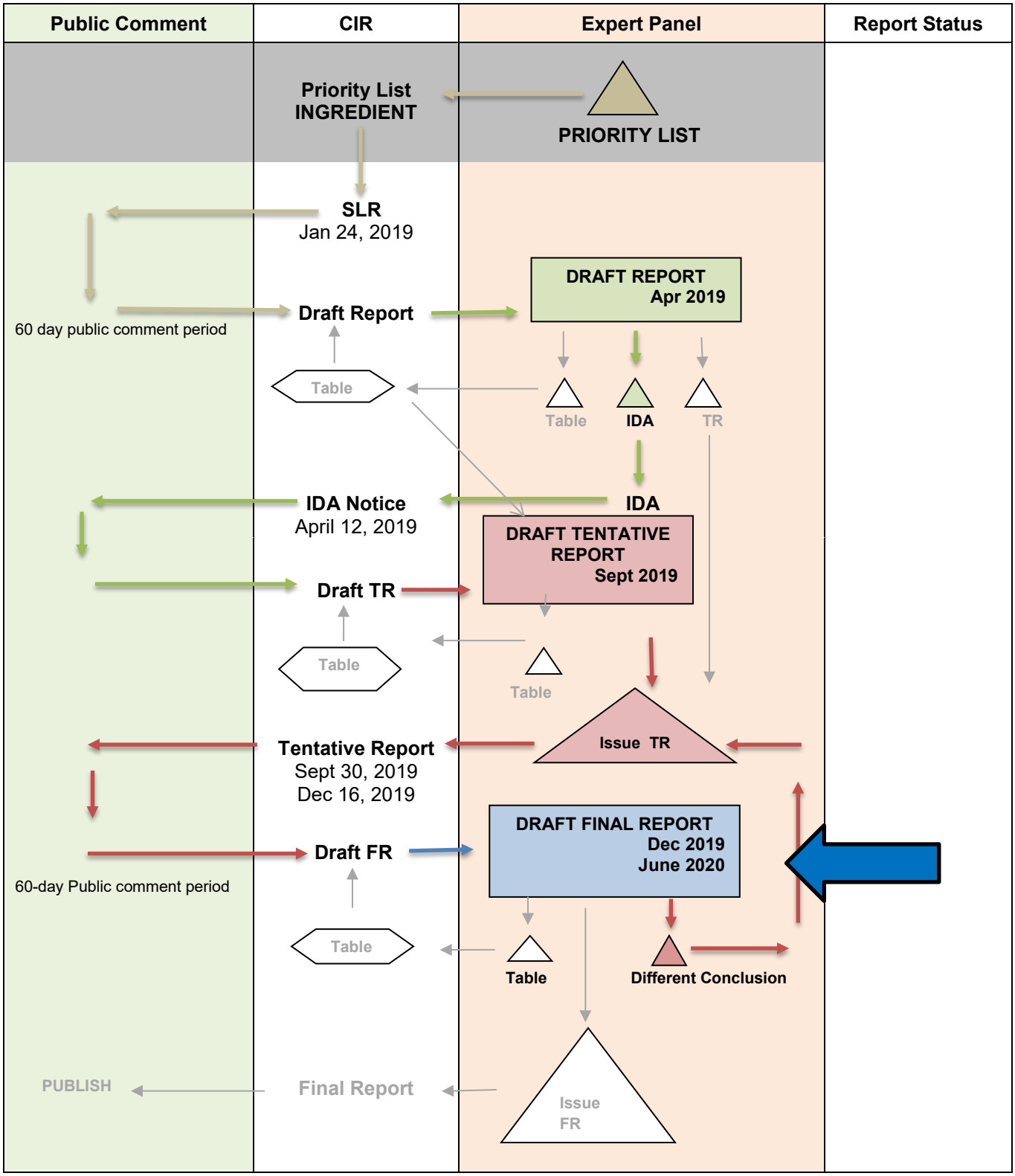
Other supporting documents for this report package include a flow chart (*pomegr062020flow*), report history (*pomegr062020hist*), transcripts from the previous meeting (*pomegr062020min*), a search strategy (*pomegr062020strat*), and a data profile (*pomegr062020prof*).

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

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Punica granatum* (Pomegranate)-Derived Ingredients

MEETING June 2020



Punica granatum **(Pomegranate) History**

January 24, 2019 – Scientific Literature Review announced.

April 2019 - The Panel issued an Insufficient Data Announcement for these 18 ingredients. The Panel's data needs were:

- Dermal irritation and sensitization data at maximum leave-on use concentrations for all ingredients, except Punica Granatum Pericarp Extract
- A no-observed-effect-level (NOEL) for skin lightening effects
- The generally recognized as safe (GRAS) status for the pomegranate plant parts not usually consumed (e.g., the bark, flower, root, stem, and leaf)
- Method of manufacturing for the extracts, especially with regard to solvent-type used
- Composition and impurities data for Punica Granatum Bark Extract, Punica Granatum Bark/Fruit Extract, Punica Granatum Callus Culture Extract, Punica Granatum Flower Extract, Punica Granatum Fruit/Root Stem Powder, and Punica Granatum Leaf Cell Extract.

September 2019 – The Panel issued a tentative report for public comment with the conclusion that the data were insufficient to support a determination of safety for these 18 ingredients. The additional data needed for these cosmetic ingredients are:

- A no-observed-effect-level (NOEL) for skin lightening effects for all ingredients
- Method of manufacturing for the extracts with regard to solvent-type used
- For Punica Granatum Bark Extract, Punica Granatum Bark/Fruit Extract, Punica Granatum Callus Culture Extract, Punica Granatum Flower Extract, Punica Granatum Fruit/Root/Stem Powder, Punica Granatum Leaf Cell Extract, and Punica Granatum Peel Extract
    - Composition and impurities data
    - Systemic toxicity data
    - Dermal irritation and sensitization data

December 2019 – The Panel issued a Revised Tentative Report with the conclusion that the following 8 ingredients are safe in the present practices of use and concentration described in the safety assessment.

Punica Granatum Fruit Extract
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Punica granatum-Derived Ingredients, June 2020 – Christina Burnett																																
						Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents	Impurities	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
Punica Granatum Extract	X																															
Punica Granatum Bark Extract	X																															
Punica Granatum Bark/Fruit Extract																																
Punica Granatum Callus Culture Extract																																
Punica Granatum Flower Extract	X			X																												
Punica Granatum Fruit Extract	X		X	X	X				X			X	X	?	?	X	X								X							
Punica Granatum Fruit Juice	X														X							X										
Punica Granatum Fruit/Root/Stem Powder																																
Punica Granatum Fruit/Sucrose Ferment Filtrate																																
Punica Granatum Fruit Water	X																															
Punica Granatum Juice Extract	X			X											X																	
Punica Granatum Leaf Cell Extract																																
Punica Granatum Peel Extract				X								X																				
Punica Granatum Pericarp Extract	X		X	X	X				X							X				X			X	X	X	X	X					
Punica Granatum Seed	X																															
Punica Granatum Seed Cell Culture Lysate																																
Punica Granatum Seed Extract	X			X					X						X																	
Punica Granatum Seed Powder	X		X																													
Pomegranate or Punica Granatum natural extractives including distillates (plant part not defined)		X																														

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

Punica granatum-Derived Ingredients

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Punica Granatum Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Bark Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Bark/Fruit Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Callus Culture Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Flower Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Fruit Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Fruit Juice	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Fruit/Root/Stem Powder	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Fruit/Sucrose Ferment Filtrate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Fruit Water	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Juice Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Leaf Cell Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Peel Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Pericarp Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Seed	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Seed Cell Culture Lysate		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Seed Extract	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Punica Granatum Seed Powder	84961-57-9 (generic)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	EMA	AGRICOLA	SSA	IFRA	RIFM
Punica Granatum (generic search)		√	√	√	√	√	√	√	√	√	√

Search Strategy

SciFinder – Search utilized generic CAS No. and INCI names. Search resulted in a single entry for an "unspecified pomegranate, ext." No reference hits were associated with this entry.

PubMed
Punica Granatum Extract – 536 hits, 65 relevant
Punica Granatum Bark Extract – 14 hits, 1 relevant
Punica Granatum Bark/Fruit Extract – 5 hits, 0 relevant
Punica Granatum Callus Culture Extract – 0 hits
Punica Granatum Flower Extract – 34 hits, 6 relevant
Punica Granatum Fruit Extract – 239 hits, 34 relevant
Punica Granatum Fruit Juice – 233 hits, 14 relevant
Punica Granatum Fruit/Root/Stem Powder – 0 hits
Punica Granatum Fruit/Sucrose Ferment Filtrate – 0 hits
Punica Granatum Fruit Water – 103 hits, 7 relevant
Punica Granatum Juice Extract – 82 hits, 15 relevant
Punica Granatum Leaf Cell Extract – 13 hits, 2 relevant
Punica Granatum Peel Extract – 147 hits, 31 relevant
Punica Granatum Pericarp Extract – 16 hits, 4 relevant
Punica Granatum Seed – 229 hits; exclude "oil" = 137 hits, 33 relevant
Punica Granatum Seed Cell Culture Lysate – 0 hits
Punica Granatum Seed Extract – 73 hits; exclude "oil" = 56 hits, 24 relevant
Punica Granatum Seed Powder – 6 hits, 2 relevant

Search updated January 2020 – No new relevant studies.

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- additional terms will be used as appropriate

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

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;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- 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
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- 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/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- 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
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.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
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- 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) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM) - http://rifm.org/

APRIL 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito's Team Meeting – April 8, 2019

DR. BELSITO: Okay. Pomegranate. This is the first time we're seeing this as well. Another one of our favorite botanicals. So the highest leave-on is in a lipstick at .11 and we've got Wave 2 data on HRIPT, right, that supported that?

MS. BURNETT: No, the Wave 2 was the updated use.

DR. BELSITO: Oh, updated use. Okay. So that's what the Wave 2 is. So from Wave 2, the highest leave-on use in lipstick at .11.

MS. BURNETT: This is the ingredient where the dictionary has deleted the whole tree extract, the main -- what we based the priorities on, that ingredient has been deleted and reassigned.

DR. BELSITO: Okay. So basically our composition is on page 12. And I didn't know if you thought that was adequate, and whether there were any molecules that were identified that caused issues. But it's really sort of very general. Other polyphenols, 28 percent ellagitannins and other polyphenols.

So we really don't have much in the way of composition for this. The concentrations are low. Page 13, again, we have some composition data.

DR. SNYDER: I like the way that you did the genus and species. It was a cosmetic ingredient and just pomegranate. I thought it was helpful to read the report; and you could tell when you wrote in specifically. I think we should do that for all botanicals, so we know we're actually looking at cosmetic one.

MS. BURNETT: Okay.

DR. SNYDER: I thought it was a good strategy.

DR. BELSITO: So the seed extract, from what I gather, is essentially fatty acids. And that's .3 in a cuticle softener. And then we have .11 in a lipstick. The repro data was well above cosmetic level use, with abnormal sperm.

DR. SNYDER: And they're pretty good.

DR. BELSITO: And then I didn't know what to make of the in vitro genotox data. This is page 16, PDF.

DR. SNYDER: Yeah, I had a plus/minus on that. So probably defer to Tom on his interpretation.

DR. LIEBLER: I had a note about that and the carcinogenicity, which we don't have anything on. And do we feel we need that with this kind of mixed genotox -- in vitro geno --

DR. BELSITO: But then we have anti-genotox data, where it seemed to protect --

DR. LIEBLER: It's not surprising. Many of these botanicals are protective in mouse skin protocols, or even in vivo -- let's see. This is -- oh, this is the mouse bone marrow micronucleus assay in vitro. Oh, no, in vivo. Okay.

DR. BELSITO: Then we have the issue with the biological effect in terms of skin pigmentation.

DR. SNYDER: Skin lightening?

DR. BELSITO: No, it was actually darkening. No?

DR. SNYDER: Lightening. Page 17.

DR. BELSITO: Yes, skin lightening effect. Sorry. But the doses for that are pretty high. 100 milligrams per kilogram per day in water. But we don't have a no effect level.

I have a question about the pericarp being okay. Do we have enough data on that?

DR. SNYDER: I mean, almost all of this is unknown source material, the pomegranate. And it's not the cosmetic. That's why when she did that, I think it was because also it's unknown source material, just pomegranate.

MS. BURNETT: Correct. If it's in the proper capitalization for an INCI product, then that's data that we received from Council.

DR. LIEBLER: It looks like the fruit extract is just an aqueous extract of the fruit. And the pericarp extract is an alcohol water extract of the dried fruit. Well, the dried raw material, which I'm assuming is the fruit**.**

MS. BURNETT: Learned a lot about the biology of the pomegranate plant, and I'm still confused. What's the pericarp and what's the inside? Because I think the pericarp -- I'm not 100 percent sure, but it's the white membrane that goes through the middle, I think.

DR. LIEBLERR: The pericarp is loosely defined as the part of a fruit formed by the wall of the ripened ovary.

MS. BURNETT: Right. So there's like when you open one up, there's all those chambers that have all the little arils, which is essentially a juice sack and the seed.

DR. LIEBLER: Right, and then the dividers are the pericarp?

MS. BURNETT: I believe that's how I understand it to be. Yes. Then like the skin would be called the mesocarp.

DR. HELDRETH: Unfortunately, pericarp can mean something different in different fruits.

MS. BURNETT: Yes. Each fruit --

DR. LIEBLER: Different plants.

MS. BURNETT: Because I remember when I looked at it at citrus it was different. Like I think the segments where maybe the pericarp, if not it’s the (inaudible).

DR. LIEBLER: The reason I'm asking about that is an aqueous versus an aqueous butanol mixture extract of the fruit would, in my view, be pretty much equivalent; and we could use safety data on one to support the other.

If the starting material for these extracts is really different, then maybe we can't. And so, I guess it does hinge on the difference between what is the pericarp in pomegranate versus the fruit. Because the fruit, I think, contains the juicy stuff and then all the surrounding packaging basically.

MS. BURNETT: That's how I interpret it to be, is the whole ball and --

DR. LIEBLER: But if we could get that issue resolved, then we can have a lot more freedom to use the data from pericarps for food extract and vice versa. Right now we're kind of assuming about the nature of these without knowing.

MS. BURNETT: Right.

DR. BELSITO: Right. But do we have enough data to say that pericarp is okay?

MS. BURNETT: I did want panel input on one of the data submissions that was an anonymous source that gave a pretty short summary without a whole lot of detail. That is under pericarp extracts, PDF page 76-77. Especially when you get down to like human patch test could be interpreted as an irritation test or a sensitization test, but there's no detail stating length of time and occlusiveness or anything like that**.**

DR. BELSITO: What page are you on, Christine?

MS. BURNETT: It's the data submission, 76-77.

DR. SNYDER: Sensitization, we have a pericarp extract at 10 percent negative on in vitro. Pericarp extract at 20 percent on a guinea pig maximization test negative. And a pericarp extract at 20 percent negative HRIPT. So we actually have pretty good data on that.

MS. BURNETT: But there's no detail. Like if you go to Page 77, you'll see.

DR. LIEBLER: 44 subjects, negative 20 percent of the trade name mixture in 44 subjects. That's all.

MS. BURNETT: So it does have .5 percent solids in this trade name mixture. The page before 76 gives the characterization of this.

DR. BELSITO: So this data, Christine, just came from a manufacturer without the actual details of the study and the individual reports like we sometimes see?

MS. BURNETT: And as I understand, it most likely is all we're going to get.

DR. BELSITO: I mean, they state they did 50 odd people in HRIPT at 30 percent and it was negative. Right? So your question is how much do we trust the data in the absence of not seeing raw data?

MS. BURNETT: Right.

DR. SNYDER: I mean, if it was one study, but it was three, and they were all negative. I mean it's -- there's not a hint of a signal there.

DR. BELSITO: Right.

DR. SNYDER: It does have Kersitin (phonetic) in it, right?

DR. BELSITO: Very low levels only.

DR. LIEBLER: So you think we should ask for additional documentation of those human test data, Don?

DR. BELSITO: I mean, it's always nice.

DR. LIEBLER: It's customary to submit a report that's redacted. It's the rage. It's all the rage now.

DR. BELSITO: Well, we need to see what Slaga and the other team is going to say about the genotox studies. We have some crazy DART studies, and we have this pigment issue that we don't have a NOAEL for, for the fruit. So we don't have that kind of data for the pericarp. What we have for the pericarp is good HRIPT data. And we have fruit extract. We have a 90-day oral, with nothing. 600 milligrams was the NOAEL.

DR. SNYDER: And that was highest dose tested, so it could be actually higher. I mean, I thought we had a pretty good swath of data for botanical; composition wise and -- I think you raised the issues for me were related to the skin lightening effect. We don't have a no effect level. Concentration of use are pretty low. The tox data we have; we have oral acute for the fruit extract, pericarp seed extract. We've got short term on the peel extract, the fruit extract, subchronic, repro and developmental -- and any effects for the high doses.

So the only extra for me was really the skin lightening and the (inaudible) the genotox. But if you want to ask for more data on the pericarp, I'm not certain --

DR. BELSITO: Well, I thought the pericarp was okay. I was wondering about more data on the others. Then also the data that we have on the seed extracts, they seem to be just essentially fatty acids.

DR. LIEBLER: Well, that's all that was measured.

DR. BELSITO: Okay.

DR. LIEBLER: There's probably lots more stuff in there.

DR. SNYDER: There were developmental repro study on the seed extract.

DR. BELSITO: Right.

DR. SNYDER: Fruit juice extract, seed extract and a mixed extract are the two together, and fruit juice.

DR. BELSITO: And then this is the one where we really don't have human data. We have animal data on the pericarp extract for sensitization, was negative at 20 percent in guinea pigs.

DR. SNYDER: We have the HRIPT.

DR. BELSITO: Oh, yeah. We have an HRIPT for the pericarp.

DR. LIEBLER: So, I'm looking at some images from various texts, and lecture notes, and journal articles on the anatomy of pomegranate. And this picture is sort of illustrative. The little red things that are the things that we think of as being fruity are the seeds. And then sort of the dividers in between are the pericarp. And I think the fruit is the whole thing.

DR. BELSITO: So those dark things are --

DR. LIEBLER: Are the seeds. The dark red things.

DR. SNYDER: They're in little packages in there.

DR. LIEBLER: Those are the seeds.

DR. BELSITO: Then the pericarp is the lighter red?

DR. LIEBLER: Yeah, it's the stuff around it. In fact, there's other photos here.

MS. BURNETT: Sometimes it's red or pink or white.

DR. LIEBLER: Like this. The dividers are the pericarp. And there was another. It's a cartoon, but it even points to it and says pericarp, skin, seeds, calyx. But the thing is, it seems to me, all of these say this is the fruit and then the subdivided components of the fruit. So the fruit is everything.

So we actually have a lot of data on fruit, which I think would tend to clear the subconstituents of the fruit, which include the seeds and the pericarp. Because when the fruit is extracted, you get all that stuff.

DR. SNYDER: So, Christine, on page 15 on the developmental repro study, it says the results at greater than or equal to 70 milligrams per kilogram for the effects.

MS. BURNETT: Yes. It was written and I cannot make that any clearer. It was kind of a weird --

DR. SNYDER: But in the summary section, you say fruit extract dose was up to 700 milligrams.

MS. BURNETT: That was probably a typo.

DR. SNYDER: Okay, so that was my question. Is it 70 or 700?

MS. BURNETT: My number keys stick on my computer. I will fix.

DR. SNYDER: She needs a new computer, Bart.

MS. BURNETT: Well, I got this. My main one is my desktop.

DR. SNYDER: Okay. We've just got to make sure we have the right number, whether it's 70 or 700.

MS. BURNETT: I appreciate it.

DR. BELSITO: So that correction is on the summary, Paul?

DR. SNYDER: It's in the results section under --

DR. BELSITO: Page 15.

DR. SNYDER: Correct. It says 70, and then on page 19 in the summary, abnormal sperm were observed in male mice at doses up to 700.

DR. BELSITO: Right. But the summary is wrong? Because here it says that frequency of abnormal sperm was significant at doses greater than 70.

MS. BURNETT: Yeah.

DR. BELSITO: So that's correct. So it's the summary that's incorrect.

MS. BURNETT: I must have sticky keyed it and hit 700. I'll fix it.

DR. SNYDER: Okay. So I think we have a fair bit of data here, other than the genotox and -- the plus minus genotox and then the skin lightening. We don't have a no effect level for that. For the fruit extract. Was that all three, the fruit extract, the peel extract and the juice?

DR. BELSITO: It was the fruit extract that was the genotox, no?

DR. SNYDER: No, I mean, I was looking for the skin lightening.

DR. BELSITO: Fruit extract, as well, I think.

DR. SNYDER: Peel extract.

MS. BURNETT: Fruit, peel and juice. They looked at fruit, peel and juice for the skin lightening.

DR. SNYDER: The fruit, the peel and juice, yeah.

DR. BELSITO: Just to clarify the 7700, Christine, so on page 19 in the summary, the third paragraph down, it will say, "Abnormal sperm were observed in males treated with a hydroalcoholic pomegranate fruit extract at doses greater than 70 milligrams per kilogram." Is that right?

MS. BURNETT: I believe so. Now that I'm reading it, I wrote it was tested up to 700, I believe. But the results were for abnormal at 70 and above.

DR. SNYDER: I just want to make sure.

DR. KLAASEN: Don, I think it's 70 and above.

DR. BELSITO: Right. That's what I said.

DR. KLAASEN: Sure you didn't say above 70?

DR. BELSITO: No, it's on page --

DR. SNYDER: Said 70 or higher, didn't it? 70 or above?

MS. BURNETT: The summary says, "Abnormal sperm were observed in male mice treated with a hydroalcoholic" --

DR. BELSITO: A dose greater than equal to 70, right. So it's 70 and above.

MS. BURNETT: I'll fix it.

DR. BELSITO: So 7 was the NOAEL. So we've been dancing around this for a while. So, are we saying that our only insufficiencies are to find out from Slaga what he thinks of the in vitro genotox, and then a NOAEL for the skin lightening effects?

DR. SNYDER: It's what I think.

DR. LIEBLER: I think we're also insufficient for method of manufacture, composition and impurities for the leaf, bark and cell culture ingredients.

MS. BURNETT: The nonedible portions?

DR. LIEBLER: Yeah, right. Leaf, bark and cell culture.

DR. BELSITO: And then I guess this always raises the question, and Carol's not here, but -- so none of these are pure, they're all sort of a certain percentage of pomegranate and a bunch of other stuff. Right? I mean, it's not supplied to the consumer product company for blending as 100 percent pomegranate.

MS. BURNETT: No. I don't believe so.

DR. BELSITO: I mean, they're usually like in --

DR. SNYDER: Mixtures.

DR. BELSITO: Mixtures. So the concentrations that we have, are those the concentrations of pomegranate per se, or what was supplied to the consumer product company that used this? Because then, I mean, this could potentially be a worst-case scenario in which the levels are misrepresented as being too high.

Or is this actually what the amount of pomegranate extract -- is it really used up to .13 in a leave on? Or is it 20 percent of .13 or whatever that pomegranate is, in that mixture that was supplied?

DR. LIEBLER: That's a good point. We don't have sufficient information in our --

DR. BELSITO: And usually what Carol ends up saying -- go ahead, Don.

DR. BJERKE: It's the botanical fraction.

DR. BELSITO: It is.

DR. BJERKE: We're requesting the report. So it's not the raw materials, it's the botanical fraction.

DR. BELSITO: Okay. So I can get rid of that question. So, our insufficiencies: Manufacture, composition, impurities of nonedible fractions?

DR. LIEBLER: Right, the leaf, bark and cell culture.

DR. SNYDER: On the Table 4, the leaf is not listed, the cell culture is not listed, and the bark and the flower are listed.

DR. LIEBLER: So even if they're not used, if they're in the report we needed --

DR. BELSITO: So leaf, bark. Do we need flower? That's not edible**.**

DR. LIEBLER: Flower. Yes, the flower is not listed in method of manufacture, I believe. I can look again.

DR. BELSITO: Leaf, bark, you said stem?

DR. SNYDER: Leaf, bark, cell culture and flower.

DR. LIEBLER: Yeah. Correct.

MS. BURNETT: There's also a fruit root stem powder and the callus culture.

DR. LIEBLER: Right.

DR. BELSITO: Do we need those?

DR. LIEBLER: That's the cell culture.

MS. BURNETT: Yeah, there's a leaf cell culture too. Or a leaf cell extract.

DR. LIEBLER: I used those terms descriptively. The cell culture involved ingredients are insufficient.

DR. BELSITO: So cell culture, that is the callus culture?

DR. LIEBLER: Right.

DR. BELSITO: And the flower? What was the flower one?

DR. SNYDER: Flour extract.

MS. BURNETT: Flower extract.

DR. BELSITO: But you said there was another culture?

DR. SNYDER: A root something, you said.

MS. BURNETT: Fruit, root and stem powder.

DR. SNYDER: Fruit, root, stem.

DR. HELDRETH: Seed cell culture and lysate.

DR. BELSITO: So there are three cultures?

DR. HELDRETH: Two.

DR. BELSITO: There's the callus culture.

DR. HELDRETH: And the seed cell culture lysate.

DR. SNYDER: So, it's a fruit root stem culture?

DR. LIEBLER: No, fruit, root, stem powder.

DR. SNYDER: Powder.

DR. BELSITO: So then we need the fruit, root, stem powder.

DR. SNYDER: Yeah.

DR. LIEBLER: Yeah. And then both bark ingredients, the bark extract and the bark fruit extract.

DR. SNYDER: So there are six of them for method of manufacture and composition.

DR. BELSITO: Okay. So, what I have for method, composition, impurities is the leaf, the bark extract, the bark fruit extract, the flower, a callus culture and the seed culture lysate, and the fruit root stem powder.

DR. LIEBLER: Right.

DR. BELSITO: And then the others, we need Tom's input on genotox. And we need a NOAEL for skin lightening. Anything else?

MS. BURNETT: Did you need any sensitization data?

DR. BELSITO: Well, we have the HRIPT. Let me just save this. Let me link it. I think that's the problem, I don't link them.

DR. KLAASEN: You only have it for the pericarp extract. Basically.

DR. BELSITO: Well, we have the pericarp extract -- we have a mixture of pericarp extract that was negative in the DPRA. And we have pericarp extract that was negative in carotenosis (phonetic). So if you use the two out of three as not posing a hazard for sensitization, the pericarp extract should not pose a hazard for sensitization based upon in vitro data.

And then we have HRIPTs for the pericarp extract, right. So the only ones we have any sensitization on is pericarp extract. So do we need sensitization and irritation --

DR. SNYDER: Concentration of use.

DR. BELSITO: -- concentration of use for the others?

DR. LIEBLER: If we could get the fruit, it would probably cover everything.

DR. BELSITO: But it wouldn't cover bark, flower.

DR. LIEBLER: No, no. But it would cover the most used --

DR. SNYDER: I think at the – if this is the first thing to go out, let's ask for more than we need and go from there.

DR. BELSITO: So we need sensitization and irritation on all except for pericarp extract?

DR. LIEBLER: Right.

DR. SNYDER: The concentration of use of these are ridiculously small.

DR. BELSITO: Right.

DR. SNYDER: Ridiculously small. Seven zeros. Okay. You got it, boss?

DR. BELSITO: Yeah, I think so. So then, given the ridiculously low concentrations, and the ridiculously high concentrations for skin whitening, do we need a NOAEL for that?

DR. SNYDER: We don't know.

DR. BELSITO: We don't know.

DR. SNYDER: We don't know.

DR. BELSITO: So we're going to ask for it.

DR. SNYDER: We have to.

DR. BELSITO: Okay. Just making sure. Let me save this. Absence of data.

Marks' Team Minutes – April 8, 2019

DR. MARKS: Okay. If no other discussion points, we'll move on to the next ingredients. So pomegranate is the next. Let me see here. That's, of course, the common name. So this is the first review of these 18 pomegranate ingredients, also known as punica granatum. Is that how you pronounce it? Who's the botanist in here?

MS. BURNETT: I don't know. I've been calling it punica granatum, but pomegranate works. Let's call in pomegranate.

DR. MARKS: So the first thing, Ron and Tom, Ron Shank gave his opinions on these ingredient groups that are new, so I'll read his in a minute. First of all, are the ingredients okay, that are listed here -- these 18 pomegranate ingredients? I might mention, in Wave 2, there's been a change. Is that right?

MS. BURNETT: Correct.

DR. MARKS: We deleted punica granatum extract, and apparently, that's going to be -- that ingredient is rolled into -- and I'm not sure which is which -- into the fruit extract and the pericarp extract. Is that right, Christina?

MS. BURNETT: We were notified that, yes, it might be more than one ingredient that it falls into. So the data that we received before -- unfortunately, it hasn't been totally cleared up. So in the VCRP database -- and this was the original basis for the report -- punica granatum extract was the most uses. We've been informed that that is no longer an ingredient in the dictionary, and those uses are being divvied up; not through the VCRP, but the Concentrations Council has gone back to the suppliers to find out where the concentrations belong.

Unfortunately, with the VCRP database, we don't know if or when that will be updated to reflect that these now belong to the fruit extract pericarp extract. So for future dates, the main extract might reflect the most reported uses.

DR. MARKS: How many ingredients do we have now? If we get rid of the punica granatum extract, is it still 18? Usually, I change the numbers -- or is it 17 now?

MS. BURNETT: It'll go down by one.

DR. MARKS: So it's 17?

MS. BURNETT: Right.

DR. HILL: But we would have to keep it in here in some level, right? Because the labels on whatever's out there on the market aren't going to change overnight.

MS. BURNETT: Correct.

DR. HILL: The problem for us, as I saw it, was, if we have data on something -- frequently, with botanicals anyway, we're not quite sure what that is, except if it's very specific. Anyway. I wanted also clarification about the seeds for pomegranate because I don't -- maybe I've eaten pomegranate once, twice in my life. So if it's the whole fruit and they're grinding, milling, that's including the seeds and everything, right? And these must not be oily seeds like an apple or a pear, I'm guessing.

DR. MARKS: Well, we've reviewed in the seed oil and the hydrogenated seed oil, and that was safe, in the past, correct?

MS. BURNETT: Correct. So I did as much botanical research as I could understand. And when you take apart a pomegranate, the little juice part is called the aril, and it's like a pouch with juice around the actual seed. We eat both the juice and the seed when we eat those little arils, if I understand that correctly.

DR. HILL: So when people eat pomegranate, they eat the seeds?

DR. SADRIEH: Yes. I eat most of them, so yes.

DR. MARKS: So as far as the ingredients -- we have the complication of the extract alone, not the extract of the different parts of pomegranate. That's been rolled into, it sounds like, the fruit and the pericarp. Were the ingredients okay, Ron and Tom? I mean, I don't see how we could eliminate any of them.

DR. SLAGA: Yeah. I thought they were fine.

DR. MARKS: And then what are the needs? Now, should I read Ron Shank's comments at this point? Would you like that?

DR. SLAGA: I would enjoy that. It's very close to what I have, too.

DR. MARKS: Oh, good. Yes. I forwarded Ron Shank's memo on to both of you.

DR. HILL: You did?

DR. MARKS: Yeah, I did.

DR. HILL: When did you send that?

DR. SLAGA: A couple weeks ago.

DR. HILL: If it was from sometime Saturday afternoon until now, I probably didn't -- no, I didn't see it.

DR. MARKS: That's correct. I think it was Saturday. Ron sent it to me on Friday, so it's sort of late breaking.

DR. HILL: Okay.

DR. MARKS: So actually, Tom, Ron, and I probably all -- and Ron Hill are probably all on the same page. I said we would be seconding an insufficient data announcement, and the main needs are sensitization. So Ron Shank, hello out there. I'm going to quote you. "Need skin sensitization data on, one, the whole extract." Well, now we know that the whole extract has been rolled into others at 0.1 percent in face and neck products -- 0.13 percent in moisturizers and hair products.

"Two, the fruit extract used up to 0.1 percent face, neck, and nights products. Fruit juice used up to 0.1." So he was naming various extracts and juice -- and the seed extract. All of them are right around sensitization data at the 0.1. So it's the whole extract, which now has been rolled into the fruit and pericarp, and the fruit juice and the seed extract.

"Skin lightening was not a problem in humans treated with 4 percent juice for 60 days." I had actually had skin lightening as a discussant point. "Does grass status apply to all ingredients?" And obviously, that's for the suspended toxicity.

I actually felt that we needed the use concentration on pericarp. That was important. We have a 30 percent HRIP, which is okay, but we don't know the concentration it's used. Presumably, it's a low concentration if it's similar to the other ingredients. To read across, I felt what we could do is use the extracts for bark, flower, fruit, juice, leaf, cell, peel, and seed. And if we had sensitization data for all those, then we could read across for everything with the idea the extract is going to contain other components of, say, similar -- like fruit. If you had the fruit extract HRIP, then that could be read across for the fruit juice side. If you had the seed, then it could be read across. So that was my needs. Tom and Ron?

DR. HILL: What about leaf?

DR. MARKS: I had leaf cell. Is there leaf alone?

DR. HILL: Yeah. But I don't see -- no, it's leaf cell --

DR. MARKS: -- Yeah. Leaf cell extract. That's what I mean.

DR. HILL: And there's no data right now on it?

DR. MARKS: Yeah. That's what I said. Well, I said from sensitization point of view. I guess the question is, if they're grass, do you need it for other toxicologic endpoints?

DR. HILL: I can't imagine the leaf is grass, in this case. It's a tree.

DR. SLAGA: Well, animals eat it.

DR. HILL: Animals eat it. Some animals eat it, probably. What animals eat it? Animals eat lots of things and don't get killed, that if I eat, I will get killed. That's a fact. I'm not making that up.

MS. BURNETT: I did want to point out that there is a concentration of use for the pericarp extract at up to 0.1 percent. That was in the Wave 2 data. Originally, I don't think there was concentration of use, but once we -- the new survey went out, we received that. The only thing I could find for grass designation just was a general pomegranate natural extractives, including distillates. Plant part not defined.

DR. HILL: I'm thinking that this would all be from the fruit, or at least I would infer the fruit. So not bark, not whole plant, not leaves. I don't know about leaf cell. What information we have -- here's what I wrote. For the leaf extract, they've got constituents but no percentages. The other key point is there's no reason to expect that this extract corresponds to any commercially available extract, because it matters a lot what you extract with. Is it hexane? Is it water? Is it ethanol? Is it ethanol water? Is it butylene glycol? Is it supercritical fluid -- or supercritical carbon dioxide?

What you extract with, and then what the dilution is, that's the whole problem with anything extract -- is if you don't standardize -- so if you look at even dietary supplements, which right now is a wild, wild west, at least in many cases, the reputable companies typically standardize. We don't have anything comparable here in most of our cases when we just write extract.

So we have to read across -- what we do is conclude based on what we know about some extract that's tested, and what constituents are in there and if there's anything of concern. But I can't read across from what I assume is fruit extracts to bark. And I doubt leaf cell without knowing something more about comparability of constituents.

DR. MARKS: Yeah. That's what I put. We would need a sensitization data if we knew that they were all similar composition. So Tom, your comments?

DR. SLAGA: No, I agree. I agree with you, that we have sensitization data on the subgroups that you talked about would be great -- the extract.

DR. MARKS: And Ron Hill, then, you raised a question of toxicity of the leaf. What would you want for that?

DR. SLAGA: But that's the leaf cell.

DR. MARKS: Yeah. Leaf cell.

DR. HILL: Yeah. So I think I would need either something showing comparability of constituents and concentrations to fruit extract. So if we're using the fact that people eat these things as part of our safety clearance, then I don't think people eat pomegranate leaf cell extract. Or if they do, we don't know that.

And then the other thing is there are places where we have data, so we have a single dose of pomegranate fruit extract, solvent not reported at zero, 50, 500 or 5,000 milligrams per kilogram bodyweight. Is the milligram administered of the overall extracts, that's solvent and all, including butylene glycol and water? Or does it contain dry weight of pomegranate extractives or what?

So when there's big gaps in what's being tested and how we evaluate, then we're back to what can humans eat safely and in large quantities? And does that preclude anything that might go on in the skin that wouldn't relate to the fact that we're eating this stuff?

MS. FIUME: So then, Ron, would one request be method of manufacture of all of the extracts with specific regard to the solvent?

DR. HILL: Yes. Then, while I might not know everything that's on the market, I can see if there's an array or we otherwise review based on the assumption that it's being done this way. If somebody's doing it some other way, support that.

DR. MARKS: Okay. Any other comments?

MS. BURNETT: Before we move on, we did want the panel to comment on one of the data submissions that we received. It was anonymous for punica granatum pericarp extract. They were extremely brief summaries with not a whole lot of detail.

DR. EISENMANN: They did say the extract contained 0.5 percent solids, which is sometimes better information than saying it's a certain percent of the extract. So that information needs to be added to the report.

I understand, yeah, it's limited information, but I think, as to the overall weight of evidence that you've got -- information that you have, I know it's coming from a company that doesn't speak English. So that might be an issue, too. The original reports aren't in English, and they might not be in a language that's easily translatable, either.

MS. FIUME: So I guess the guidance for the writer, and for CIR, is if you simply have a piece of data that's unpublished, that says a human patch test was negative with no details, is that acceptable and usable information for the panel members?

DR. EISENMANN: You do have a number of subjects, and you do have a concentration that's 0.5 percent solids.

MS. FIUME: But no details as to how long the patches were left, if they were occlusive or not, how many patches were applied, when the readings were done.

DR. HILL: I would think that our dermatologists who are heavily familiar with patch testing would find that fairly sketchy.

MS. FIUME: And it's not only the patch testing. It's on PDF page 76 and 77 --

DR. EISENMANN: But they're going to use the standard method, so it's not -- if they say it's a HRIPT, I don't think they would do something that's not a standard method, like patches break challenge period. That's what they mean.

MS. BURNETT: It just says human patch test, though. We're not even sure if that's a sensitization or an irritation test.

DR. EISENMANN: I think it should clearly say it's a summary, and this is all the information you have. So you don't mislead that you've seen the whole study.

DR. HILL: Is it unreasonable to think that, if they send us information, that they could be contacted to get what details we think would be enlightening here?

DR. MARKS: I think, Ron Hill and Carol, you're both correct. If I wasn't sure that it was a HRIPT, then I would be questioning what the sensitization is. Because on occasion, you'll see reports where it says sensitization, but really, it's an irritation patch.

They apply it once for 24 or 48 hours, and they'll say no irritation and no sensitization. I agree, as far as irritation, it hasn't -- that's adequate, say, but not for predicting sensitization. They can say, yeah, the subject isn't sensitized with one patch, but, as you said Carol, it's got to be a HRIPT to feel comfortable that this test really evaluates the sensitization potential of the ingredient. I think we're asking, actually, for a lot of that with these extracts in the insufficient data assessment.

DR. HILL: Is the solvent specified there? The solvent would be very important.

MS. FIUME: It's water, butylene glycol, and then the pericarp extract.

DR. HILL: Okay. And it doesn't give the percentage of butylene glycol, but I think we could assume, then, 20?

MS. BURNETT: So the trade name mixture is composed of that, and it says it was 20 percent of the trade name mixture.

DR. HILL: Okay. So 20 percent of the trade name mixture, which would then be 0.5 percent solids. So they're putting in 20 percent of this extract that's 5 percent solids and then doing patch testing. And the extract is probably butylene glycol, water, phenoxyethanol, I think, is -- well, we don't know about that for sure.

MS. BURNETT: It says under the method of manufacturing it was extracted from the raw material with a 50 percent ethanolic solution. Then, it goes through all the filtrations and gets down to adding 30 percent of the butylene glycol solution.

DR. HILL: So what we need to know is it's 0.5 percent solids in the final preparation, and they're testing that at 20 percent level in the patch.

MS. FIUME: And part of the bigger question was the data will simply say photosensitization test negative. Twenty percent of the trade name mixture, guinea pig. Or human patch test negative. Twenty percent of the trade name mixture 44 subjects. Is that information acceptable to the panel for use in the document for making a decision without any of the details?

DR. MARKS: I'm sorry. I was typing. If the references Carol says are standard tests, then yes. But if they don't state that it's standard testing, then, yeah, it's a problem. I think I was sort of multitasking here, and I'm not sure I heard your point.

MS. FIUME: So two of the tests -- so the HRIPT, we can assume, if we wanted to, what the procedure was. But for the photosensitization test, where it just says negative in guinea pigs and it was tested at 20 percent of the test article are a human patch test, which was negative in 44 subjects -- 20 percent was tested but then none of the details as far as what the patch was or is that negative for irritation, would be the assumption because it doesn't say sensitization test. It just says human patch test.

DR. EISENMANN: I assume it was a single insult patch test because that's how it's presented in the summary.

DR. MARKS: Yeah. Okay.

DR. BERGFELD: Did you conclude what you're going to do with that?

DR. MARKS: No. I think we conclude if it references standard testing methodology, like HRIPT. I think as far as a photosensitization, we might need more details on that, in terms of what was the actual photosensitization test used.

DR. HILL: Well, the other thing is it's 20 percent in water. Can we assume that? Because if it's just water, that's one thing. If it's ethanol there's greater chance -- something that gives more skin penetration or less. In terms of propensity for sensitizing what's it in matters.

MS. FIUME: The vehicle is not stated.

DR. HILL: Yeah.

DR. MARKS: Okay. So tomorrow, I will be seconding a motion, and presumably that'll be an insufficient data announcement. And our needs are sensitization data or HRIPTs for a number of extracts, the bark, flower, fruit juice, leaf cell, peel, seed, unless we have composition, which is similar to the pericarp extract, which we already have HRIPT, which is okay. We question on is this grass for all the ingredients. We assume it is, but maybe we can confirm that. And then under the method of manufacture, what were the solvents used? And is there anything else that we should list as our needs?

DR. HILL: I'm so sorry. Can you read that again?

DR. MARKS: Basically, sensitization data, grass for all the ingredients -- Ron Shank raised that -- and then method of manufacture for the extracts -- what solvents did they use?

DR. HILL: Well, if we're going to try to read across without further data to leaf cell extract, then something about the composition as to how it relates to these fruit ingredients that we're trying to read across from.

DR. MARKS: Yeah. That's what I said, unless the composition is similar. And then skin lightening, which was on page 17 -- there's a reference to four percent juice was not an issue, so I think that can be handled in the discussion. But that's a whole section on skin lightening and an important, obviously, effect.

DR. HILL: Well, so that goes, again, to knowing what constituents are if you're trying to read across to something else. Because if there's something or some combination of somethings, if we've got a skin lightening effect --

DR. MARKS: The concentration of the other ingredients is really quite low -- below that four percent.

DR. HILL: That was my assurance here, in looking at the whole big picture.

DR. MARKS: And again, Ron Hill, you're absolutely right. We assume the composition is going to be similar, but we need some data to support that.

DR. HILL: And so if you've got an ingredient that's not in use and you ultimately conclude it to be safe, which I don't like doing without some further data --

DR. MARKS: I think I brought this up. I was going to bring it up with another ingredient, but the asterisk at the conclusion where we say similar use in concentration -- when not in use, similar use and concentration as the other ingredients. You bring up a point that maybe we should put, also, similar in composition, too.

DR. HILL: Well, for botanicals, I think there might need to be something added. At least, we should consider that because, again, dilution matters when you've got an extract and what it's being extracted in and how can make massive differences in concentrations of what's there.

Full Team Meeting – April 9, 2019

DR. BELSITO: Yeah, so this is our first look at it, and we thought that the information was insufficient. At this point, we wanted manufacturing, composition, impurities of the leaf, the bark extract and the bark fruit extract, the flower and the cell culture, the callus culture and seed culture lysates, the fruit root stem powder. We also wanted sensitization and irritation for all of the various components except the pericarp. And we wanted a NOAEL for the skin lightening effect. And we wanted Tom's input on the genotox studies.

DR. BERGFELD: Is there a second, for insufficient?

DR. MARKS: Second. Yes, insufficient data announcement. We agree completely with that. And I might mention that we got Ron Shank's comments. We miss Ron Shank, we look forward to having him join us in June, and his review of this was similar.

The only other question we had is are all these GRAS ingredients? So we would like to know whether GRAS is appropriate. And then the other, Ron Hill brought up, in the method of manufacture for all the extracts he was concerned about what solvent was being used.

And we agree that the pericarp extract, the HRIPT at 30 percent, was fine, so we don't need any sensitization. I kind of use their approach looking at the sensitivity issue is, unless we know the composition is similar with all these different botanicals, if we had the sensitivity for all the extracts, the bark, the flower, the fruit, the juice, the leaf cell peel and seed, that we could read across to other ingredients that are derived from those particular parts of the plant, so just a nuance.

But that doesn't change your insufficient data and Christina's put the two of our comments together.

DR. BERGFELD: So we've had a second on the insufficient data announcement and the list of needs. Hopefully we have those.

DR. MARKS: Mm-hmm.

DR. BERGFELD: Yeah. And so I'll need to call the question. All those in favor of an insufficient data? Okay, report. Thank you. And that will return next meeting or?

DR. BELSITO: No, too soon.

DR. BERGFELD: Too soon?

MS. BURNETT: Yes. I'm sorry, the follow-up to Dr. Slaga on the genotoxicity? Did you want him to comment?

DR. BELSITO: Yeah, we wanted his comment, because we were confused by the genotox data.

DR. SLAGA: Come again?

DR. BELSITO: The genotox data on the materials?

DR. SLAGA: Yeah, there is a mixture, some both positive and negative genotoxicity. And there's really no weight of evidence here, so it's kind of difficult to decide positive or negative. But the majority of these type of extracts generally will give some positive now and then -- I mean, other extracts and from different plants and that.

So I didn't really have a concern, you know, we're dealing with very small amounts. And I don't think that -- I guess I put more weight on the one negative than I do the positive.

DR. LIEBLER: Tom, I noticed a couple of these had tests that I didn't really recognize, for example, on page 16, under the first paragraph on in vitro punica granatum fruit extract. There's a reference to *Saccharomyces cerevisiae* strain D7, which I was really unfamiliar with. And an increased frequency of reverse mutations was observed.

So I don't know if that's a system that was used at one point and fell by the wayside in the wake of the Ames assay, or what. Is that something that is a red flag test to you?

DR. SLAGA: No, no. It’s not a red flag.

DR. LIEBLER: Okay.

DR. HILL: I did have another question while we're on that topic, though, about that, which is, my comment was we needed info on as to how much weight of pomegranate ends up in what volume of extract, because it gives that we're testing it at 0.4512, and four milligrams per plate. Is that milligrams of the extract? And so then, if that's the case, the concentration of that extract matters massively. If it were very dilute, we're not testing much substance. If it was fairly concentrated, we’d get good data.

DR. BERGFELD: Any other comments? So that will be reflected in the minutes; and if it can be resolved, it will be resolved. Anything else?

MS. BURNETT: I'm not sure I can get further concentration data out of that. If there is concentration data, I usually put that in. With these, these were not cosmetic ingredients, so they took fruit and mushed it up in a lab and did it that way. So, whatever details I got, were put in the report.

I did want to clarify then; you do not have a genotoxicity need to go out with the IDA?

DR. HILL: No.

MS. BURNETT: Okay. Thank you.

DR. HILL: Yeah, I mean, in terms of the fruit itself, and the parts of pomegranate that the people eat routinely, and have been for centuries, who knows how many centuries, probably 20,000 years, at least, maybe more, I have no concern.

It's just ability to read across to anything else. Because depending on how the extraction is done, that's really method of manufacture; but then the test material exactly what's in there would affect, and then do you need activation or not? Because --

DR. BERGFELD: Well said, taken into the minutes. All right. So this is going out as an insufficient data announcement. We also have the needs that have been clarified for Christina, and there is no need for genotox, is what I understand. All right.

SEPTEMBER 2019 PANEL MEETING – SECOND REVIW/DRAFT TENTATIVE REPORT

Belsito's Team Minutes – September 16, 2019

DR. BELSITO: Pomegranate. Okay. So, at the 2019 meeting, we issued an IDA for 18 ingredients. We wanted dermal irritation and sensitization of maximum leave on use for all the ingredients except the pericarp extract. A NOAEL for this skin-lightening effect. Wanted to figure out the GRAS status of the different parts. Method of manufacture for the extracts, especially with regard to solvent type. Composition and impurities for the bark extract, bark/fruit extract, callus culture extract, flower extract.

So basically the extracts, the stem powder and the leaf cell extract. And since that time, we got an HRIPT for a leave-on product of the fruit extract and method of manufacture with a solvent type for the pericarp extract. And then we got some additional published literature --

DR. SNYDER: Composition.

DR. BELSITO: -- on composition. So I had a question to you, Paul, about the DART studies on fruit juice.

DR. SNYDER: The sperm affect, yeah.

DR. BELSITO: Page 32 of the PDF. Significant increases in the percentage. No, that was Curt's question. Increases in epidermal sperm concentrations, sperm motility, yadda, yadda, yadda, abnormal sperm rate.

DR. SNYDER: There was abnormal sperm at greater than 70 milligrams per day, but the root was not provided. And we had an oral DART study that was negative. So I was okay with the repro data. This looks like a positive effect, increases in sperm concentrations, increases in motility, increases in sperm density.

DR. BELSITO: But a decreased abnormal sperm. Okay.

DR. SNYDER: Decrease in abnormal. Yeah. It's all positive. Yeah. Yeah. Yeah. I say no more.

DR. BELSITO: Viagra for sperm.

DR. SNYDER: Say no more.

DR. BELSITO: Okay. And then Curt and the genotox where they saw in the Chinese hamster ovary, increase in the percentage of chromosomal aberrations at greater than 45 micrograms without metabolic activation. That's in the fruit extract.

DR. KLAASSEN: I don't know. I didn't catch this before as a positive, but I'd have to reread it.

DR. SNYDER: That's the last one, the fruit extract?

DR. KLAASSEN: Yeah.

DR. SNYDER: Yeah, it's over 70 milligrams per kilogram.

DR. LIEBLER: Right. It's really high.

DR. SNYDER: It's off the charts.

DR. BELSITO: Okay.

DR. SNYDER: You'd probably get cytotoxicity just with -- yeah. I didn't see an issue with that.

DR. LIEBLER: The CHO cell test.

DR. EISENMANN: It's typical for antioxidants to be not genotoxic at low doses but genotox at the high doses.

DR. LIEBLER: At high doses, right.

DR. BELSITO: Okay. So is that something even worthy of the discussion?

DR. SNYDER: No.

DR. BELSITO: Okay. So, in terms of the skin lightening effects -- this is page 33 of the document.

DR. KLAASSEN: Yeah.

DR. BELSITO: So there's obviously an effect of the phenolics, right? And the maximum per gram of fruit extract is 498 milligrams, assuming all of that is phenolic. And all the phenolic is the punicalagin.

Does that help us with lightening? And then I said you could also use whatever argument for the ellagic acid below in the peel extract. The peel has the highest phenolic content at least according to Table 3; but we still don't have a no observed adverse effect level for the lightening.

DR. LIEBLER: That's the problem.

DR. KLAASSEN: And we had asked for that.

DR. BELSITO: Yes.

DR. LIEBLER: And where we are is that we have -- the in vitro inhibition of tyrosinase, for example, or melanin production in cells doesn't necessarily mean anything unless you have an animal endpoint. In the animal endpoint the treatment concentrations are pretty high. So we don't have anything below, which there isn't an observed effect, so that's our problem.

DR. BELSITO: So we're still insufficient for NOAEL for skin lightening.

DR. LIEBLER: Right, particularly when we've got this human study, punica granatum juice, although there's no details, provided on test method and other data. It just said that significant decreases in skin melanin content were observed.

DR. BELSITO: Okay. So then, in terms of sensitization and irritation, we have -- for the pericarp we just have two in vitro studies, DPRA and the KeratinoSens. But according to current model, if 2 or 3 of those are negative, it shouldn't be a sensitizer. So we don't have actual studies but in vitro we predicted not desensitized.

For the pericarp extract, theoretically, even assuming this was a guinea pig maximization test, which is not stated, you need to really have 20 animals in the treatment group for OECD guidelines. And it doesn't say what kind of study this is.

DR. LIEBLER: That's the five-animal study you're referring to?

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah.

DR. BELSITO: For the pericarp extract.

DR. LIEBLER: Right.

DR. BELSITO: But we have the negative in vitro data for that. And then in the HRIPT, it was not occluded, so I don't know how valid the study is for the fruit extract. They were supposed to occlude it. Occlusion or semi-occlusion, here it just says the patches were air-dried and were not occluded at all. The patches are supposed to be occluded or semi-occluded, according to the protocol for an HRIPT. So it's really not a valid HRIPT.

And then, for the pericarp extract, I mean, again, we don't have -- theoretically, it's supposed to be a hundred patients all in the same group. But I think we sort of have enough data to cover pericarp extract from sensitization and irritation based upon the in vitro -- some type of guinea pig study and then these two HRIPTs, but that would be

the only one we can even come close to covering sensitization for. Unless you want to take the fruit extract that wasn't occluded.

DR. SNYDER: Well, even though it wasn't occluded, if there's no indication of anything, that does give you some sense of confidence that it's a hundred subjects.

DR. LIEBLER: So, if it's not occluded, it just means that it could be accidentally rinsed off or rubbed off or something.

DR. BELSITO: I don't understand this at all. Was allowed to air dry, the test patches were not occluded. I've never heard of that kind of HRIPT.

DR. LIEBLER: So, I mean, if you feel it's got a significance -- if it will be unreliable, then it's not --

DR. SNYDER: If it's not valid -- I mean, I would do it on a tox study if I didn't think it was valid. I mean, I do that all the time if it's not a valid study.

DR. LIEBLER: I agree with Paul.

DR. BELSITO: I presume that's what they said. Is that report in here?

DR. LIEBLER: Reference 74.

DR. HELDRETH: Yeah, PDF page 56.

DR. SNYDER: Open patch test.

MS. BURNETT: Fifty-six. It's just a summary. We don't have any test.

DR. SNYDER: No data.

DR. BELSITO: Yeah. I mean they would say it was covered with Webril or whatever. Honestly, I've never heard of anything like that.

DR. LIEBLER: So this is all you've got, Christina, this text you have in front of you?

MS. BURNETT: Yeah.

DR. LIEBLER: And it doesn't say that it wasn't occluded, or does it?

DR. BELSITO: It says open patch --

DR. LIEBLER: Open patch conditions, I see. Sorry.

DR. SNYDER: Well, we need sensitization data. It's going to be insufficient anyway.

DR. BELSITO: Yeah, I know.

DR. SNYDER: So we might as well --

DR. BELSITO: Well, I think the pericarp extract has enough studies even though none of them are terribly good to clear that. All right.

DR. LIEBLER: So the 44-subject patch test, negative?

DR. BELSITO: Yeah. The two in vitros are negative. The DPRA and the KeratinoSens are negative. And then you have some undefined guinea pig study on five animals that's negative. I think you can clear the pericarp extract for sensitization and irritation, but you can't clear the others.

DR. LIEBLER: It's only five uses.

DR. BELSITO: Well, we actually had already excluded the pericarp extract in our initial request too. So then we had asked for GRAS status on the parts not usually concerned, which we haven't gotten.

DR. SNYDER: We asked for GRAS for all components, my notes say. Irritation and sensitization --

DR. BELSITO: Bark, flower, root, stem, and leaf. Is there another component? So we didn't ask for the fruit because we know that's a food.

DR. SNYDER: Okay. Well, I just said you need the GRAS statement for all components.

DR. BELSITO: Well, there's not typically a GRAS statement for a food.

DR. HELDRETH: Right. If it was eaten in this country before a certain timeframe, it's just essentially grandfathered in, in most cases. There is no CFR entry for apples or pomegranates or things like that.

DR. BELSITO: Right.

MS. BURNETT: There is a GRAS entry for the essential oils, oil resins and natural extracts derived from pomegranate. That's the only official wording we have.

DR. BELSITO: I mean, we're not going to get a GRAS statement on bark, I don't think.

DR. SNYDER: Or stem.

DR. BELSITO: Or root. Okay, basically none of our data needs have been met.

DR. SNYDER: Correct.

DR. BELSITO: So insufficient for everything we said before.

DR. EISENMANN: But is pericarp okay? Are you going to say it's safe in conclusion for pericarp? Or is that still insufficient for --

DR. BELSITO: It's insufficient for what -- I mean, a pericarp extract is okay for sensitization and irritation, but it's not okay for --

DR. LIEBLER: Method of manufacturing.

DR. BELSITO: -- method of manufacturing. And it's not okay because we don't have a GRAS status on it. So I guess for the pericarp we need method of manufacture and 28 dermal, and if absorbed --

DR. SNYDER: Well we have method of manufacturing on the pericarp extract.

DR. LIEBLER: Yes, we do.

DR. BELSITO: Okay. So then we need a 28-day dermal on the pericarp extract, right, because we don't have GRAS status for that?

DR. SNYDER: Yeah.

DR. EISENMANN: But the skin lightening effects, the studies were all on the fruit; but I guess that includes pericarp so you're also applying the NOAEL for the skin lightening effects to all them. Is that correct?

MS. BURNETT: The lightening effects were on the fruit extract, the peel extract, and juice.

DR. EISENMANN: But if you had composition on the pericarp that showed it did not contain the phenolics, would that suffice?

DR. BELSITO: Mm-hmm.

DR. SNYDER: Mm-hmm.

DR. BELSITO: So, for the pericarp extract, to clear that, we would need a 28-day dermal. And, if absorbed -- or do we have the good DART for that?

DR. SNYDER: I don't know. I'd have to see what was it? I don't know what that is -- yup. I didn't write it. I just wrote DART.

MS. BURNETT: No DART.

DR. LIEBLER: Fruit extract, fruit juice.

DR. BELSITO: And what about mutagenicity? Which ones were those on?

DR. LIEBLER: Fruit extract, pericarp extract.

DR. BELSITO: Okay. So we would need a 28-day dermal and if absorbed some DART data?

DR. SNYDER: Yeah. Just if absorbed, additional data needs.

DR. BELSITO: And then we'd also need the phenolic concentration.

DR. SNYDER: Composition, yeah. If we get composition and it doesn't have the phenolics, that could clear it.

DR. BELSITO: And the others are insufficient for all the previously stated reasons.

DR. LIEBLER: In a 28-day dermal, that's a toxicity test, not an absorption test. I mean, it implies absorption but -- because an absorption test with these botanicals is impractical.

DR. BELSITO: Right.

DR. LIEBLER: We don't know what to measure so you can't --

DR. BELSITO: Right. We're just looking to see if there's any and/or toxicity that we need to be aware of.

DR. SNYDER: Systemic effect. Systemic effect.

DR. LIEBLER: Yeah. Okay. But if it's clean on the 28-day dermal tox, then we're not asking for DART?

DR. SNYDER: No.

DR. LIEBLER: Okay.

DR. BELSITO: Okay. So the entire group is insufficient for all the previously stated reasons. And for the pericarp extract, 28-day dermal, if absorbed, DART. And we also want to know the composition, so we get an idea of the concentration of the phenolics.

DR. SNYDER: I got the .1 leave-on fruit extract. Was that the one that was not occluded? Was that the one we discussed already because we did get data on that?

DR. BELSITO: Hold on.

DR. SNYDER: Yep, never mind. That's the one. Not occluded. Just checking.

DR. BELSITO: Okay. Anything more on pomegranate?

Marks' Team Minutes – September 16, 2019

DR. MARKS: Okay. We'll move onto punica granatum-derived ingredients, aka pomegranate. At the April 2019 meeting, we issued an insufficient data announcement for these 18 ingredients. Those needs were listed in the

August 22nd memo from Christina. We did, since that meeting, receive method of manufacturing with solvent type for the pericarp extract, and we got an HRIPT on the fruit extract.

So it's time to issue a tentative report and most of the data that were requested we did not receive. It looks like the irritation and sensitization data for the pericarp extract, the fruit extract are okay. And by read-across I would think that since the fruit extract is okay the fruit juice would be okay. We didn't get any skin lightening NOEL.

So do we move forward with an insufficient conclusion for the needs that are listed below instead of the irritation and sensitization for all the ingredients except for the pericarp extract? I would now say that fruit extract and the fruit juice are okay.

We didn't get the NOEL for the lightening. We didn't get the GRAS status for the plant parts not usually consumed, like the bark flour. We did get method of manufacturing for the pericarp extract; and composition and impurities we don't have. So, Ron and Tom, how would you like to see the tentative report conclusion formulated?

DR. SHANK: I'd say issued it as insufficient data and the needs are listed there. The fruit extract in an HRIPT at .1 percent was negative. Can we use that as a read-across for the rest of the extracts except for the bark, was the only question I had?

DR. MARKS: So you're saying it could also be used for the flower? Fruit is okay, so that would be the flower, the leaf cell, seed. What's the pericarp? Is that the covering around the seed?

DR. BERGFELD: I think so. That's part of the germ.

DR. MARKS: Yeah. I don't know. Can you use that for leaf and seed?

DR. BERGFELD: No.

DR. MARKS: What else is in the seed? It would be nice if we had the seed because then, presumably, although the pericarp could be shed off and only the seed be the extract. It depends on how it's manufactured.

MS. BURNETT: The seed is part of what you eat, if I understand it. It's what's in the little juice capsules.

DR. ANSELL: Yeah, we put the pericarp with the fruit.

DR. SHANK: Right. Okay. But the fruit is the whole thing.

DR. ANSELL: Including the pericarp.

DR. SLAGA: Yes, with the seed.

DR. SHANK: With the seed. You just crush the whole --

DR. SLAGA: You could eat the seed with the fruit.

DR. SHANK: Yes.

DR. SLAGA: There are probably some people who probably do.

DR. MARKS: Okay.

DR. SHANK: The seed is what I think they use most. But the fruit extract was an extract of the whole fruit.

DR. MARKS: So you said by read-across we could do all the extracts with the exception of bark.

DR. SHANK: Certainly with the exception of bark. Now, maybe the flower you can argue you need it for -- you need sensitization for the flower.

DR. MARKS: Yeah, I guess. And we deal with this repeatedly with the botanicals. We don't have composition to say that it's the same. Do we, so that we could say bark and flower have the same composition so therefore we -- or

similar composition, not same. Similar composition of chemical constituents so, therefore, we can read across for the bark and flower too? But we don't have that, do we?

DR. ANSELL: We focused on the fruit and excluded the bark, the stem, root, and put the pericarp with the fruits.

DR. MARKS: Right. That's where we have the irritation sensitization data which would support their safety. And, as I said, I think it's an easy read-across to the fruit juice when we have the fruit extract. So, which could we read across, the peel, seed? And what other extracts do we have here?

DR. BERGFELD: Do you eat the peel on a pomegranate? No.

DR. MARKS: I don't know.

DR. BERGFELD: You eat the inner parts.

DR. ANSELL: No, you open them up and --

DR. BERGFELD: You eat the --

DR. ANSELL: -- you eat the --

DR. MARKS: Seeds and the fruit.

DR. BERGFELD: Seeds and the surrounding stroma, so to speak.

DR. ANSELL: Yeah, that's more or less where we drew our lines. It was all the fruit and the fruit extracts and the juices, nothing from the stem, bark, or root.

DR. BERGFELD: Or fruit or peel.

DR. SHANK: Peel's part of the fruit, is it not?

MS. BURNETT: I'm looking at --

DR. BERGFELD: You don't eat the peel.

MS. BURNETT: I'm looking up a botanical site. It says the pomegranate fruit is berry-like with a leathery rind or husk including many seeds surrounded by juicy arils which comprise the edible portion of the fruit. Skipping some of this.

DR. MARKS: It doesn't sound like you eat the peel.

DR. BERGFELD: No, you do not eat the peel.

MS. BURNETT: No. The husk is comprised of two parts: the pericarp which provides a cuticle layer in a fibrous mat and the mesocarp, which is a spongy tissue and inner fruit wall where the arils attach.

DR. HELDRETH: So you don't eat the pericarp.

MS. BURNETT: You don't eat the pericarp.

DR. ANSELL: We have data on the pericarp.

MS. BURNETT: Yeah.

DR. MARKS: So the pericarp, fruit, seed extracts are okay. And the fruit juice is okay.

MS. BURNETT: So the pericarp and the peel would be the same thing? Is that how you read it?

DR. MARKS: Ooh, there you go. No, I thought the pericarp was part of the seed, not the whole fruit.

MS. BURNETT: Jay?

DR. SHANK: The white part is the fruit, isn't it?

MS. BURNETT: No, it's the outside of it. It's the red part. The inside is -- when you open one up, if you know what they look like, the white part that surrounds the seeds is the mesocarp. So it's the pericarp is the outer peel and the husk. Is that what they called it?

DR. MARKS: Well, the problem here -- and then there are the INCI names.

DR. BERGFELD: The pericarp is the outer part in the red area?

MS. BURNETT: Yeah. So my question to Jay would be, would the peel extract and the pericarp extract be the same thing? Is the pericarp considered to be the peel of the fruit?

DR. MARKS: Exactly, because they're listed as separate ingredients. And I was thinking the pericarp represented that outer lining of the seed.

DR. SHANK: That's what I thought too.

DR. MARKS: Not the outer lining of the fruit.

DR. BERGFELD: So it's -- the safe part of the seed.

DR. HELDRETH: And that's called an aril, right?

DR. BURNETT: Yeah, the seed and the juice around the seed -- aril.

MS. BERGFELD: Is the what?

DR. BURNETT: Aril.

MS. BERGFELD: How you spell that?

DR. BURNETT: A-R-I-L.

DR. MARKS: I think we can clarify that on the next rendition. We're going to certainly see the next rendition. And that will be -- for the time being, I'm going to say that sensitization is okay for the pericarp fruit seed extracts and the fruit juice. And we'll find out whether we need the peel whether that's the same as the pericarp. But I assume it's different since it's listed as a different ingredient. And then obviously the bark, flower, stem, and root we need.

We received nothing for the skin lightening, so we still need that for all of them. Do we need GRAS status for bark, flower, root, stem, leaf?

DR. SHANK: Well, this is a food.

DR. SLAGA: I don't think you're going to get it.

DR. MARKS: Yeah.

DR. SHANK: So I don't know that GRAS applies.

DR. MARKS: Right. If it's a food, whether ingested by humans or animals, do we need systemic tox data on the bark, the flower, root, stem, leaf?

DR. SLAGA: If it's consumed as a food by either I would say we don't need it.

DR. SHANK: Well, the bark, flower, root are not food, just the fruit. So, yes, we would need genotox, repeat dose tox, possibly DART.

DR. MARKS: So systemic tox data. What we normally --

DR. SHANK: Yes.

DR. MARKS: Method of manufacturing we got just for the pericarp, so we'd still need that for others, correct or not?

DR. SHANK: You have it for the fruit extract.

DR. MARKS: So do we need it just for again, though, the peel, bark, flower, stem, root that are not foods?

DR. SHANK: Yes.

DR. MARKS: Just the manufacturer?

DR. SHANK: Yes.

DR. MARKS: Need systemic tox, method of manufacture. And then composition and impurities. It looks like we have basically the same for the nonfoods; get the composition and impurities, and that way we can read across if we have the composition. Does that sound reasonable?

DR. SHANK: Yes.

DR. SLAGA: Yeah.

DR. MARKS: Okay. Let me go back and make sure that I have captured. So tomorrow our team will move -- or I'll move that a tentative report be issued. It'll be an insufficient data. And the pericarp, fruit extract, the seed extract and the fruit juice is okay. The seed extracts are okay.

What we need though is irritation/sensitization for the nonfood ingredients, the peel, bark, flower, stem, root. And the systemic tox, method of manufacture, composition and impurities. And we need skin lightening NOEL for everything, right? Because we didn't receive anything on that?

DR. SHANK: Correct.

DR. MARKS: So it's an insufficient conclusion. Comments?

DR. SLAGA: Good.

DR. HELDRETH: So then the conclusion is insufficient data for all ingredients, the pericarp, and other fruit extracts? Or only insufficient for skin lightening data, then the rest are insufficient for that plus irritation/sensitization and systemic?

DR. MARKS: Yes, if I heard you correctly, Bart. I'll need to clean up my notes here a little bit. But, basically, the pericarp, fruit and seed extracts, and fruit juice, are okay for sensitization. And they would also be okay for the systemic toxicology since they're foods. And it's the nonfoods that we need the systemic toxicity, method of manufacture, composition, and impurities. And the skin lightening NOEL for all of them. Sound good? Tom, Ron?

DR. HELDRETH: Good.

DR. SHANK: Yes.

DR. MARKS: Okay.

Full Team Meeting – September 17, 2019

DR. MARKS: In April of this year the panel issued an insufficient data announcement for these 18 pomegranate ingredients. The needs include dermal irritation, sensitization, the NOAEL for skin-lightening, what was the GRAS status, method of manufacturing, especially with regard to solvents, the composition and impurities.

We move that a tentative report be issued with an insufficient conclusion. We need the skin-lightening NOAEL for all of the ingredients, we didn't receive that data. The irritation and sensitization was okay; and food for the pericarp extract and fruit extract, and we read across for the fruit juice and seed extract, but we need sensitization, systemic toxicity if they're not foods. For peel, bark, flower, stem, and root, method of manufacturing, the composition, and impurities.

And, we suggested a table be created similar to the brown algae, that we'd have GRAS, food, tox sensitivity and sensitization so that we could kind of compare these in one table. So, we move, again, an insufficient conclusion, a tentative report with the needs that I outlined.

DR. BERGFELD: Belsito Team, any comment, or second the motion?

DR. BELSITO: We were also insufficient for all the reasons. And, I have a note that we wanted a 28-day dermal on the pericarp extract.

DR. SNYDER: No, pericarp was okay.

DR. BELSITO: Okay.

DR. MARKS: Yeah, irritation, sensitization, and it's a food so pericarp extract -- fruit extract. And from those two you can read across the fruit juice and the seed extract. Those, as we go forward, would be okay.

DR. BELSITO: Okay. Seconded.

DR. BERGFELD: Seconded. Any other discussion regarding this ingredient? Seeing none, call the question, all those in favor please indicate by raising your hand. Unanimous, thank you.

DECEMBER 2019 PANEL MEETING – THIRD REVIW/DRAFT FINAL REPORT

Belsito's Team Minutes – December 9, 2019

DR. BELSITO: Okay, at the last meeting in September, we went insufficient. We asked for a NOEL for skin lightening for all ingredients and method of manufacture with regard to solvents for the extracts. And for a list of ingredients, that I won't read, we asked for composition and impurities, systemic toxicity data and dermal irritation and sensitization.

We got absolutely nothing except a comment from the SCC for PCPC, stating that why do you need skin lightening, you have dealt with this before. You have said that it should be formulated not to cause changes in skin pigmentation.

So I guess from my standpoint it's insufficient, but do we drop that insufficiency point about skin lightening and take the suggestion of the scientific committee?

MS. KOWCZ: Well, the reason we wrote that is because if it's a cosmetic, it shouldn't be skin lightening and so we really felt strongly about that piece. And that's why we don't think it should be part of this.

DR. EISENMANN: Well, and the studies that showed that were on materials that were concentrated. One would not have been called Pomegranate; one would have been called ellagic acid.

DR. BELSITO: Right, and it was in your letter.

DR. EISENMANN: And the other one was four percent, right.

DR. BELSITO: Yeah. I'm fine. I'm just passing this off to my colleagues. I think you stated it very well in your letter --

MS. KOWCZ: Thank you.

DR. BELSITO: -- the reasons why, and I do tend to agree with that. You know, we just point out that this has been reported, da-da-da-dah, and you know, it's not our purview, but a cosmetic should not lighten skin. But Paul, Dan, and Curt, what is your feeling?

DR. KLAASSEN: I agree with the change.

DR. SNYDER: I'm fine with that approach.

DR. BERGFELD: Are you agreeing to the discussion or to the conclusion?

DR. BELSITO: There is no conclusion; it's still insufficient. Were just dropping one insufficiency.

DR. BERGFELD: But are you going to put that in the discussion?

DR. BELSITO: I mean, we could, sure.

DR. BERGFELD: I think so.

DR. BELSITO: Yes.

DR. EISENMANN: But if you drop that insufficient -- then the seed powder, the fruit extract and the pericarp extract should be okay, because there is some information on solvents in there. And there is a published paper now on the composition of the --

DR. SNYDER: Fruit extract.

DR. EISENMANN: -- seed powder, that shows it has very low polyphenol concentration which would not result in skin -- which is the skin lightening material. I don't think it has been added to the report yet but --

DR. BELSITO: Okay, I guess I wasn't even thinking about that, looking -- ticking off the rest of the boxes.

DR. EISENMANN: The other ingredients with a lot of data needs, we agree, those are insufficient. But the three, I think you could go with.

DR. BELSITO: So, which three are you saying when we drop skin lightening we don't need to worry about the other endpoints that we asked for previously?

DR. EISENMANN: Seed powder, fruit extract, and pericarp extract.

DR. BELSITO: Okay, so for seed powder, we have a reported use and we have method of manufacture. And we didn't ask for composition and systemic tox or dermal irritation for the seed powder. Okay. The other one is?

DR. LIEBLER: Fruit extract.

DR. BELSITO: And what are we expecting to come back on the fruit extract? You said there was something that wasn't incorporated?

DR. EISENMANN: No, I said wasn't incorporated, there was a published paper that includes some composition on the seed powder.

DR. BELSITO: I see, okay. So, we have method of manufacturing, we have impurities. So, I presume we have solvent type if we, well it's not an extract so --

DR. LIEBLER: I think the fruit extract description on the method of manufacturing includes some information on solvents.

DR. BELSITO: Right.

DR. LIEBLER: This request is an old one. I didn't think it was really that necessary, but it turns out that the solvents used are typical of solvents used to extract fruits, alcoholic water mixtures, no surprise there. But I think that need has been met. And I think that the fruit extracts and the fruit really help us cover, with greater confidence, any of the seed ingredients like the seed powder.

DR. BELSITO: So, you're saying the fruit extract allows us to cover all of the fruit juice?

DR. LIEBLER: Yeah.

DR. BELSITO: So we're making significant changes to our -- based upon no new information. How did this change of mind come about in three months?

DR. LIEBLER: Well, the ones we said were insufficient, and we had a list of needs were the bark derived stuff, the callus culture, the flower, fruit, root, stem. I was okay with fruit, but not root and stem. Fruit sucrose ferment filtrate, leaf cell extract, peel extract and granatum seed cell culture lysate.

So, the cultured ingredients are derived from cells from the pomegranate, and then cultured to produce another material that is genetically similar but in other ways who knows. So, that is the callus and the cell culture.

The bark, root, stem, leaf, flower, those are all things that are not covered by the fruit in the first place; so we're not adding a whole lot of stuff here. Most of that insufficient list remains insufficient.

DR. BELSITO: But we're adding all of the seed and all of the fruit ingredients that don't include root, stem, leaves?

DR. LIEBLER: Correct. And if we go back up to the --

DR. BELSITO: So we're adding punica granatum extract as well? Because we just have a reported use. We don't know if that's the whole --

DR. LIEBLER: And that doesn't say what it really is.

DR. BELSITO: Right.

DR. LIEBLER: I mean, it's probably a fruit extract, but it doesn't specify. So, I don't think we can make a -- we could include it.

DR. BELSITO: Is there a definition --

DR. BERGFELD: Was that the whole plant, too? That's what my question was.

DR. LIEBLER: But that is a question and it is unanswered, so --

DR. BELSITO: It's not in the description? Because I'm just on the --

DR. EISENMANN: It has been removed from the dictionary. That was originally defined as the whole plant. But it hasn't made the process of getting out of the VCRP.

DR. BELSITO: I see.

DR. EISENMANN: So, when we went back to ask the suppliers what it was, it was either fruit or pericarp. So the trade names that were associated with that material have been moved to fruit or pericarp.

DR. BELSITO: Okay. So just to go through this, we would be saying the extract, no; the bark extract, no; the bark fruit extract, no; the callus culture extract, no; the flower extract, no. The fruit extract, yes; the fruit juice, yes; the fruit combined with root stem powder, no.

DR. LIEBLER: Fruit sucrose ferment filtrate, no.

DR. BELSITO: Okay.

DR. LIEBLER: And then fruit water.

DR. BELSITO: Fruit water, yes. Juice extract, yes. Is that correct?

DR. LIEBLER: Correct, yes.

DR. BELSITO: Okay, and all of the seed ones, yes. The seed cell culture lysate, seed cell extract, and then the seed powder?

DR. LIEBLER: Seed cell culture lysate, no.

DR. BELSITO: Okay.

DR. LIEBLER: But the other three of those last four ingredients, yes. Seed extract, seed powder.

DR. SNYDER: Don, it's probably easier if you go to page 45, where we have the insufficiency notice for the ones listed.

DR. LIEBLER: Yeah, the pericarp is still good.

MR. GREMILLION: Dr. Liebler, you mentioned some research that you said showed that fruit extract was similar to the juice extract. I wanted to make sure I was understanding your --

DR. LIEBLER: Yeah, this is more driven by the structure of the plant, of the pomegranate fruit. If you have ever had pomegranate, you know you get these little red, sort of translucent seeds that have a bunch of juice around them, and then they have a little seed piece in them. Those comprise, essentially, the fruit, and the seed pieces and the juice.

So, those are the parts that we eat. Those are the parts that we are very familiar with. And the other parts of the plant, obviously, leaf, stem, root, people don't eat those, at least. You know, we don't have any information on them that would support their safety.

MR. GREMILLION: So. I guess what -- you mentioned that, like, the way of extracting the fruit is similar to other fruit extraction processes.

DR. LIEBLER: Uh-huh.

MR. GREMILLION: So, this had an insufficient data conclusion for the fruit, but you're saying since there is no reason to think that this is a different extraction process than other fruit then the method of manufacturing --

DR. LIEBLER: So, it would include what comes out in the extraction. The request for information about the solvents used in the extraction, I thought, was unnecessary, originally, when it was made. And because I think that the methods to extract fruit-derived ingredients are essentially always alcohol-water mixtures, and it is -- it turns out to be the case. So, I wasn't really hung up on that.

But the fruit contains the seeds and the fruit juice, and all this. If you have evidence to say that the fruit is okay, then it logically follows that the components of the fruit are also okay.

DR. KLAASSEN: What is GRAS and what isn't GRAS, so therefore I contacted the FDA when I was reviewing this; and let me read what I got.

So, I wrote to them and I said, "I understand that soybeans is not officially GRAS, but for all practical purposes it is GRAS. Since you are the expert on this, can you explain to me?"

So then I got a response saying, "I am stating below, GRAS from a simple conceptual standpoint without using any regulatory language. Also I am focusing on the distinction between food additives, versus GRAS, to underscore what GRAS is.

Okay, so now, GRAS concept applies to food ingredients that are exempt from pre-market approval. So in plain language, the use of an ingredient as GRAS does not require pre-market approval by FDA, but the use of food additives requires pre-market approval and regulation writing by the FDA.

The most important thing to remember for GRAS, is that an ingredient is claimed GRAS for specific use. If the use is expanded or changed, then the additional or changed use is not automatically covered by the original GRAS claim.

Getting back to your specific question, soybeans is regarded as a food, not as a food ingredient. So, when we think of soybeans, we usually do not think of it as a GRAS ingredient. This is the simplest way of thinking about it. However, in a regulatory world, things can always get complicated because of new interpretation."

So then I said, "What does it mean by ingredient? Is an ingredient a pure chemical in regard to GRAS?"

And this is his last answer, "An ingredient could be many things. The regulatory definition is, any substance that is reasonably expected to become a component of food is a food additive that is subject to pre-market approval by FDA, unless the substance is generally required, generally regarded as safe, GRAS, among experts qualified by scientific training and experience to evaluate its safety under the conditions of its intended use.

So, a food ingredient can be a pure substance, such as lutein. Or it can be a mixture, such as P-protein, which is a mixture of different individual proteins. Then he says, you can click on this site to find the number of these GRAS substances.

So, I guess the bottom line to me is that, putting it in a simple person's language like myself, if it is a food that we have been eating kind of forever, it is called a food. But this whole GRAS didn't come about, actually, until I was a graduate student, so it has only been 50 years ago, and these are things that are added to foods. So you add an antioxidant to food, so it doesn't spoil or what have you.

So that's the word from someone at FDA. Do you agree with that?

MS. DEWAN: What response you got is actually correct for GRAS; because when the GRAS is for an ingredient and is for a specific use, that is actually qualified in regulations.

So, when its intended use is changed from one, then the sponsor has to resubmit the information to say, well, we would like to use even the same ingredient for a different GRAS intended use, so that is how it works. But people have been using it, thinking once it is GRAS you can use it forever; that is not how it is.

MR. GREMILLION: Yeah, and I would just like to add -- I mean, we have done a little bit of advocacy on it. And my understanding is that these GRAS determinations get made; I mean, there is a voluntary process where the companies can notify FDA.

But there are a lot of GRAS determinations out there that are effectively secret and something that, I guess -- I am not sure how this group is looking at where things are categorized as GRAS. But there's not a lot of requirements on how these determinations are made. I mean, the companies can hire their own people to make the determinations and then the transparency around it is not great.

MS. KOWCZ: Do you have any examples of that? That's an interesting concept that companies are --

MR. GREMILLION: I think trans-fat was a good one; where it was GRAS for a while and FDA finally revoked the GRAS status to trans-fat when the health impacts of that became better understood. But I don't have examples of secret GRAS determinations because they're secret.

There was kind of an understanding that these determinations had to be supported by a published journal article. And someone at EDF, Quinten (phonetic) and Pugh (phonetic) went and counted up the journal articles to kind of get a sense of how many of these determinations were being made, but since then the FDA has clarified that you don't need a peer review journal article.

MS. FIUME: I will say, for the purposes of our report, the only GRAS that we do -- GRAS status we include are those that are in the CFR that have actual citations.

DR. BELSITO: Are we okay if we, A) in the discussion, we introduce what the scientific committees suggested about skin lightening, pointing out the very high levels, yada-yada-yada. But despite all of that the cosmetics should not lighten the skin; so we are not looking at that effect and manufacturers should be certain that if they are producing a cosmetic product, it does not have that effect.

Having said that, we are then able to say that the fruit extract, fruit juice, fruit water, juice extract, seed, seed extract and seed powder are safe as used. And that we still want information on the granatum extract, even though it apparently has disappeared but has not disappeared from our list, the bark extract, bark fruit extract, callus culture extract, flower extract, fruit rose stem powder, fruit sucrose ferment filtrate, leaf cell extract, peel extract, pericarp extract and seed cell culture lysate. Is that correct?

DR. SNYDER: Are insufficient?

DR. BELSITO: Are insufficient.

DR. LIEBLER: Insufficient, correct.

DR. BELSITO: But going -- so I'm reading that off, just the list of ingredients on the front page. If you go to our insufficient announcement, there are 9 that I read but there are more than -- or 12 that I read, but for what we are asking for composition and impurities, systemic tox data and dermal irritation and sensitization, there are fewer.

So why are we -- I haven't had a chance yet to compare what I read versus the discussion here. Is it because we are lacking method of manufacture and solvent types for a couple of those? So let me go to the first page. Paul, if you want to tell me what I'm not reading off that appears on PDF 45 for our data needs.

DR. SNYDER: Uh-huh.

DR. BELSITO: Because there is some inconsistency there. So, we are saying the extract, and I don't think that is in that list, just punica granatum extract is not on the list.

DR. SNYDER: No. Correct.

DR. BELSITO: What do we need for that? Method of manufacture? Solvent type?

DR. LIEBLER: No. Let's get off the solvent type thing. But it's just method of manufacture and composition and impurities.

DR. BELSITO: Okay. So, for the granatum extract we need method of manufacture and composition and impurities. Okay, bark extract is on that list; right Paul?

DR. SNYDER: Correct.

DR. BELSITO: Okay, fruit -- bark fruit extract is on that list?

DR. SNYDER: Yes, correct.

DR. BELSITO: Callus culture extract?

DR. SNYDER: Correct.

DR. BELSITO: Flower extract?

DR. SNYDER: Yes.

DR. BELSITO: Fruit, root, stem powder.

DR. SNYDER: Correct.

DR. BELSITO: Fruit sucrose ferment filtrate?

DR. SNYDER: Is on there.

DR. BELSITO: Leaf cell extract?

DR. SNYDER: Is on there.

DR. BELSITO: Peel extract?

DR. SNYDER: Is on there.

DR. BELSITO: Pericarp extract?

DR. SNYDER: No.

DR. BELSITO: So, what do we need for the pericarp extract?

DR. LIEBLER: The pericarp is part of the structure of the fruit. Isn't that correct?

DR. BELSITO: Pericarp is that --

DR. LIEBLER: It's like the surrounding --

DR. BELSITO: It's inside the peel part.

DR. LIEBLER: Right.

DR. BELSITO: It's not quite fruit. It's like, I think, the white rind of a watermelon. Isn't it? And I know the pericarp can contain different chemicals, because with mango, if you are touching the pericarp, you are getting a good amount of pentadecacatechols, which is urushiol. And you get poison ivy if you are allergic to it.

And if you just don't handle the peel, and the inside of the peel, it doesn't happen because it's not in the fruit. So, I think the pericarp can be a little bit different than the fruit in terms of chemical composition.

MS. FIUME: According to Table 2, it is the fruit wall or the ripened wall of the plant or ovary of the fruit, consists of the peel, the fruit and the endocarp.

DR. BELSITO: Right, well maybe it's the endocarp that is the white part of the watermelon, but it can be different.

MS. FIUME: Yes.

MS. BURNETT: I think in the case of the pomegranate, it's the layer that surrounds the fruit.

DR. BELSITO: Yeah, it's very thin.

MS. BURNETT: It's very thin. It is kind of whitish.

DR. BELSITO: Yeah.

DR. LIEBLER: All right, in that case -- I mean, the question is, there is a little bit of uncertainty as to whether it is -- if it were part of what they use to make the fruit juice or fruit extract, or the fruit, then I think we have enough data from the fruit to save the pericarp.

But if we don't really know for sure whether fruit as processed into cosmetic ingredients includes the pericarp, then we can't save the pericarp.

MS. BURNETT: We do have a lot of data on the pericarp extract.

DR. KLAASSEN: That's what I was going to say.

DR. LIEBLER: Oh, well then we're good.

MS. BURNETT: Yeah, that's probably one of the main ingredients that we actually have --

DR. LIEBLER: So, pericarp should not be on that insufficient list.

MS. BURNETT: Pardon me?

DR. LIEBLER: Pericarp should not be on the insufficient list then.

MS. BURNETT: Right. Right.

DR. BELSITO: Well, let's see what data we got.

DR. LIEBLER: I'm looking at the data summary table on page 5, but if you look at the pericarp extract we've got reported use, we've got method of manufacture, composition and impurities. And then we've got acute oral, we've got genotox, dermal irritation, dermal sensitization, ocular irritation.

DR. BELSITO: Everything is checked off.

DR. LIEBLER: Yeah. Most everything, yeah.

DR. BELSITO: What is not?

DR. LIEBLER: DART. Then again, I don't think that we are lacking enough in DART and repeat dose to have concern.

DR. BELSITO: Yeah, okay.

DR. LIEBLER: And it's clean for genotox, so we don't need carcinogenesis. I don't really think that is supportable. And we've got -- the main thing I would be concerned about is sensitization. We've got an in vitro model, animal and human data.

DR. BELSITO: Okay, so then we are saying the pericarp is okay as well?

DR. LIEBLER: Yes. Correct. So if our insufficient list has the punica granatum extract, or the discontinued ingredient added to that list, and the pericarp is not on that list, then I think our numbers add up.

MS. FIUME: Ten is insufficient? I think the discussion is the list that is correct with the ingredients that have the additional insufficiencies. I believe what's missing from the transmittal is the fruit sucrose ferment filtrate, and the seed cell culture lysate, is not included in the list on the transmittal. That was an inadvertent mistake.

DR. LIEBLER: Oh, the transmittal memo.

MS. FIUME: Yes.

DR. LIEBLER: Yeah, okay.

MS. DEWAN: Can I ask a question?

DR. BELSITO: So, the list on page 45 should have as insufficient, granatum extract, bark extract, bark fruit extract, callus culture extract, flower extract, fruit, root, stem powder, fruit sucrose ferment filtrate, leaf cell extract, peel extract, and seed cell culture lysate.

DR. SNYDER: With the one caveat that punica granatum extract, it is up for it saying it's not --

DR. BELSITO: Manufacture, composition and impurities.

DR. SNYDER: Well, but it's whether we accept that it, it's been taken off.

DR. BELSITO: Well, do we mention that in the discussion?

DR. SNYDER: Yes, I think so.

DR. BELSITO: So, do we say it's not insufficient or it's simply no longer considered a cosmetic ingredient?

DR. SNYDER: Well, we can say in the discussion that if it's --

DR. BELSITO: That we were told that it's not a cosmetic ingredient.

DR. SNYDER: However, if it is --

DR. BELSITO: However, if it is used we would need --

DR. SNYDER: -- used, it's insufficient for the same --

DR. BELSITO: Right.

MS. FIUME: You're right, it's currently in the introduction but not the discussion, so it can be brought in there.

MS. DEWAN: So, one quick question. For fruit juice, the data will be taken from fruit extract? That's what I heard.

DR. BELSITO: Dan, for fruit juice, it's taken from fruit extract, correct?

MS. DEWAN: Correct, okay. So one of the studies in fruit juice that was done on humans, which says on cheeks of 25 subjects, this showed a significant decrease in skin melanin content. That's a structure function effect. Are you considering that study?

DR. BELSITO: We are discounting the skin lightening effect as a non-cosmetic effect that was caused at very high doses. And we are pointing out in the discussion that fact, that there were very high doses that wouldn't be achieved in cosmetics, number one; and number two, a cosmetic should not be formulated to cause skin lightening. If it is, it is misbranded, it's a drug.

MS. DEWAN: Okay, so four percent is considered at a very high concentration, okay. Thanks.

MR. GREMILLION: That's what you addressed in your letter, yeah.

DR. BELSITO: Sorry it's taking me a while. I'm not a quick typer and there's been a lot of changes here, so bear with me a second.

DR. SNYDER: So, how come we couldn't get more information from that study? It says details not provided -- no amount tested provided. There is very little detail on that study that she was referencing there, on the decreased melanin content in the human study. Reference 71.

DR. BERGFELD: While you're contemplating the discussion, are you going to add the usual botanic statement about impurities and metals?

DR. BELSITO: It's already in there. It's already in the current discussion along with the inhalation boilerplate. Page 45 PDF, first sentence -- first paragraph. And then the second is inhalation.

So to get back to Curt's point, though, in the discussion, in the third paragraph we say fruit extract to be sufficient and that, da-da-da-dah, and considered GRAS. So, this is not really considered GRAS; it's just a food.

DR. KLAASSEN: Yeah. It would be better to say food.

DR. SNYDER: I think we've been misusing GRAS.

DR. BELSITO: Yeah.

MS. FIUME: I think -- we use GRAS if it's a CFR citation that states it*s* GRAS as a food additive. That's when we use the GRAS status.

DR. BELSITO: Uh-huh.

MS. FIUME: If we don't have a CFR citation to say it's GRAS, we will state up front that it is a food, but we do not include the term GRAS in the report.

DR. BELSITO: So then this can also be used as a food additive?

MS. FIUME: It would be in the non-cosmetic use.

DR. BELSITO: Oh, okay.

MS. BURNETT: To answer Dr. Snyder's question about that study, so it was a study performed in Pakistan and they weren't very good at providing a whole ton of detail. So, the results, they just basically say it and then they give like a kind of a not too informative graph, that I wasn't able to interpret --

DR. SNYDER: Decipher anything else. Okay. I'm just not familiar with the methods they used to quantify the melanin content, so -- to know whether it was valid or not.

DR. BELSITO: Okay. I just want to make sure we are being consistent here. So, we have to change one of our data requests -- so the only extracts we're asking -- it said in our data request all the extracts; but we've now allowed fruit extract, juice extract, pericarp extract and seed extract. So, we have to -- so that was fruit, juice, pericarp and seed. So the extracts, there are four, six. It's probably easier to say except or should we say the ones we need it for? Okay.

And then, I didn't like the systemic toxicity data for -- where we say -- so, we're getting rid of the no observed effect level; we still want manufacture and sensitization. Don't we usually say 28-day dermal and if absorbed, other toxicity endpoints may be necessary?

DR. LIEBLER: We say dermal absorption and if absorbed.

DR. BELSITO: Right. So, I would like to change that data point to that. Well, the last one where it just says we want composition, impurity, systemic toxicity data. I would like absorption -- dermal absorption and, if absorbed, other toxicity endpoints may be necessary.

DR. LIEBLER: That's what we usually say.

MS. FIUME: Can I ask for a clarification then? Typically with botanicals, we state we don't have toxicokinetics or penetration data because we don't know what we are looking for, and these data are not expected.

DR. BELSITO: That's true.

MS. FIUME: So, how would you like the language changed to reflect that or to change in the toxicokinetic studies?

DR. BELSITO: Yeah, that's a good point. Because we don't know what we are looking for on the other side of the membrane, right?

DR. LIEBLER: Right. I mean, I think that practically speaking with these botanicals, with the parts of the plants that we are not sure about, what we really want to know is, is there any risk of systemic toxicity or carcinogenicity. And is there any irritation and sensitization to worry about with those things? So, I think our needs should be focused on that.

So, we could ask for a 28-day dermal and just not add "if absorbed," because that's not going to determine that. And then we can add the other endpoints if you wish.

DR. BELSITO: So, 28-day dermal.

DR. LIEBLER: Right.

DR. BELSITO: And if -- what are we looking for?

DR. LIEBLER: And, well 28-day dermal to clear systemic toxicity from dermal application. And then we can add, you know, genotox, and we can add the skin endpoints.

DR. BELSITO: Or we can just say 28-day dermal and, if effects are seen, further data may be necessary.

DR. LIEBLER: Yeah, I mean that's okay --

DR. SNYDER: But in this case, it actually could be also gleaned from oral toxicity data too. Because if there is no systemic toxicity from oral then -- what we are looking for is a little different. Like Monice said, we're actually looking to see if there is any evidence of systemic toxicity. So that could also be gleaned from an oral study. It wouldn't have to necessarily be a dermal study.

DR. BELSITO: So, then say evidence of --

DR. SNYDER: Absence of systemic toxicity.

DR. BELSITO: Evidence of the absence of systemic toxicity?

DR. SNYDER: Yeah.

DR. BELSITO: And then could be a 90-day oral or --

DR. SNYDER: It could be even an LD-50 if it's grams quantities and there's no systemic toxicity.

DR. BELSITO: Right.

DR. SNYDER: Then we would probably have more confidence of safety. So, we could just say systemic toxicity testing or something like that.

DR. BELSITO: Well, that's what we did, systemic toxicity data; so you're okay with that?

DR. SNYDER: Yes.

DR. BELSITO: Okay, fine. I just thought it was a little bit different but then wasn't thinking of, yes, the whole problem with absorption.

DR. SNYDER: So, I just did a search of this in light of what Curt has presented. I just did a search of this document and in two instances we mention GRAS in here.

And I think we need to be very clear as to what we are referring to as GRAS when we indicate so -- as a justification for safety. And I think, Monice, what you said regarding the CFA?

MS. FIUME: CFR, Code of Federal Regulations.

DR. SNYDER: Yeah, I think we need to specifically say that and cite that. And so -- well, it says, according to the U.S. FDA, but we don't say --

MS. FIUME: Page 39, PDF page 39, lists the actual CFR citation. And I know at the last meeting, and I haven't looked at the minutes to see if it was specifically this report, that for one of them the way it broke out what the necessary data were, were by interpreting which ingredients actually fell under the GRAS citation.

DR. SNYDER: Okay.

DR. BELSITO: Okay, anything more of this?

MS. KOWCZ: I just have a question. Would this be a tentative final or final?

DR. BELSITO: It's a tentative final. We've changed a lot.

MS. FIUME: This is, half the ingredients have changed conclusion, so I would imagine this will go out as a tentative report.

I do want to check; Christina, do you have the language that you need to address the skin lightening in the discussion?

MS. BURNETT: I believe so.

DR. BELSITO: It's pretty much what the SEC said.

MS. BURNETT: Right.

DR. BELSITO: You know, it point out the high concentrations; and the fact is that the CIR panel would assume that a cosmetic product that had a lightening effect was misbranded and should be removed from the market by the FDA.

MS. BURNETT: Okay. Just to -- before we move on, the discussion points are that. And the removal of the punica granatum extract, and if it is used, it is considered insufficient. And then the two -- and it would need method of manufacturing and composition and impurities. And then just reiterate the list of insufficiencies for the ingredients are insufficient. Anything else?

DR. BELSITO: Right. Yeah. So, the insufficiencies now are method of manufacture with regard to solvent type used for the extracts, except fruit extract, juice extract, pericarp extract, and seed extract.

MS. BURNETT: Right.

DR. BELSITO: And then that list that is the next part, we get -- essentially stays exactly as it is.

MS. BURNETT: Um hmm.

DR. BELSITO: And keep everything as it is, including systemic toxicity.

MS. BURNETT: Okay. Thank you.

DR. BELSITO: Okay.

DR. BERGFELD: I would like to ask a question. Do you think an additive might be a diagram of the plant with labeling of the parts?

DR. BELSITO: That's sort of hard to do.

DR. BERGFELD: Well, we do chemical structures.

DR. BELSITO: I understand, but would we be violating a copyright of someone --

MS. BURNETT: We'd have to make sure that we had permission --

DR. BELSITO: -- who drew it out?

MS. BURNETT: Yeah.

DR. BELSITO: Chemical structures are considered not patentable, they're there.

DR. SNYDER: I think in our description, we should be certain -- our understanding of what we are calling what. Because I think there's some --

DR. BERGFELD: Right.

DR. SNYDER: Because I'm still confused about some of the discussion about what the pericarp is. So maybe we should say for the context of this document, these following definitions are used.

MS. BURNETT: We do have Table 2 that is trying to describe that. In all honesty, I will say that when I do research a botanical, there isn't always a consensus on what's what. And so, I will look at five different pictures and none of them are the same. So it's --

MR. BELSITO: There's no Gray's Anatomy for fruit, huh?.

MS. BURNETT: No.

DR. SNYDER: But I think to Don's point, Don raises a really great point with the urushiol, because that is very specific to a very specific part and it has a very significant --

MR. BELSITO: Tox endpoint.

DR. SNYDER: Tox endpoint. And again, I think it's what Curt alluded to with the read-across thing, you know, it's the exceptions that we are really looking for. We are looking for the outliers, and so we can't -- we have to be cautious lumping things a little too much, so.

MR. BELSITO: Okay.

DR. BERGFELD: What's the final on that then? No diagram, but a definition of exactly where the part --

DR. BELSITO: Well, there is a definition.

DR. BERGFELD: I know, there is, but I was confused too.

DR. BELSITO: Yeah.

DR. BERGFELD: I was back and forth.

MS. BURNETT: I will see if I can tighten up the definitions a bit.

DR. BELSITO: Okay. Anything more? Does anyone wants a little break to get some pomegranate juice? No? Okay.

Marks' Team Minutes – December 9, 2019

DR. MARKS: Next is pomegranate, Punica granatum. So, we have a draft final safety on the pomegranate derived ingredients. At the September meeting, the panel concluded there is insufficient data to support the safety -- not the determination -- but support the safety of the 18 pomegranate-derived ingredients.

The needs were listed below in the memo. The NOEL for skin lightening -- and we'll be coming back to that point for sure with the CIR SSC comments.

DR. SHANK: Yes.

DR. MARKS: Method of manufacture. And then for a list of ingredients there, the bark extract, bark fruit extract, et cetera. We wanted composition and impurities data, systemic tox data and dermal irritation and sensitization.

And since September, we received method of manufacturing and specifics for the fruit extract. And then in Wave 2, we got comments about how to handle the skin lightening.

So, our team will be moving for a final report. I have different ways to approach it. Initially, it was the skin lightening before -- how to approach the skin lightening. I had safe for pericarp and food extracts, fruit juice, and seed extract. Okay if no skin lightening, which has been dealt with, I think, by the CIR, and insufficient for the rest. So we had a split conclusion.

But Ron, you're the master at sorting out botanicals and keeping us straight. Why don't we start with you, Ron?

First of all, do you want to comment about the NOEL for skin lightening? That was initially for all the ingredients, but the CIR recommends use the same approach for skin lightening as with licorice. And the one in the discussion, "is used in a manner that does not cause depigmentation."

DR. SHANK: Well, you know how I feel about these caveats on the formulation. I think the panel should press for actual concentrations, and formulations that are documented not to cause skin lightening. And if it can be shown that one or two components of pomegranate are the causative agents in skin lightening, then recommend limits on concentrations of those agents and not put in this caveat "when formulated not to cause skin."

This is getting out of hand. It used to be when formulated to be nonirritating. That's when we were dealing with acids that were buffer controllers. And when you tested the acid itself it's irritating, but in formula it's not.

Then when we add the botanicals with huge complex mixtures, we had to go to, when formulated to be nonsensitizing. Now we're adding when formulated to be non-skin lightening.

And every time we have a question, if we rely on this business of when formulated not, I think we're not doing our job. And I think we need to find out what concentrations can be used without depigmentation.

DR. MARKS: So, then you would have an insufficient conclusion?

DR. SHANK: Yes.

DR. MARKS: Needs below, especially the NOEL for skin lightening for all the ingredients.

DR. SHANK: Yes.

DR. MARKS: And the CIR's -- it's interesting. The does not cause depigmentation was in the discussion, not even in the conclusion for licorice. Somehow we got around that in licorice. Maybe you weren't at that meeting. Although, I read your notes, Ron. Does it --

DR. ANSELL: Well, we see this as a --

DR. MARKS: Yeah. I was going to ask, Jay.

DR. ANSELL: -- fundamentally different issue. I certainly agree the potential for overuse. But here, we're not talking about a tox endpoint; we're talking about transitioning from one regulatory status to another, since skin lightening products would be drugs -- they're not cosmetic anymore.

DR. SHANK: If they're used for that, they're drugs. But if it's a side effect, then it's an adverse effect.

DR. ANSELL: No, it's not actually the effect, it's the intent. And FDA allows itself to pierce the veil. So, even if it causes the effect, but it's not claimed, skin lightening is a drug effect and could be found as not a cosmetic or, more precisely, an illegal, unregistered new drug.

So, that's why we treat this a little differently and felt that the licorice was a better model since it's not clear that -- since it's really a, when does a drug become a cosmetic. If there were a toxic outcome, then it would be somewhat different. Certainly sensitization is something that would be more on the toxicity side then when it transitions from legal to illegal.

DR. SHANK: It would be a toxic effect if it was not intended to -- if it wasn't used to lighten the skin. Then it would be a toxic effect. It it's intended to be used to lighten skin, then it's a drug.

DR. ANSELL: Right.

DR. SHANK: So you can't win. Are any of these products used as skin lighteners? I didn't see that.

DR. ANSELL: Yeah. I don't -- no.

DR. LORETZ: No.

DR. SHANK: So if they do cause lightening --

DR. ANSELL: No, I mean it would be --

DR. PETERSON: I see it as an adverse effect.

DR. SHANK: Pardon?

DR. PETERSON: I view it as an adverse effect. Because if you use a product and you're not expecting your skin to lighten, and it lightens, I would be upset.

DR. SLAGA: That doesn't make it a drug.

DR. ANSELL: Right. It's not an illegal cosmetic. It's not a cosmetic effect; it's an illegal drug effect if it causes skin lightening.

DR. LORETZ: What CIR SSC is questioning, is the studies that showed skin lightening were not how these ingredients are formulated, because they were specific ingredients that were not representative of the pomegranate-derived ingredients that are actually used.

DR. MARKS: Yeah. From the memo, it says, "A potential hazard that is not relevant at the much lower levels of pomegranate-derived ingredients recently reported as used in cosmetics." To me, this is a more pertinent thing, not whether it's a drug or that.

For example, the in vitro study on P. granatum peel extract, containing 90 percent ellagic acid, is on a material that would be given an INCI name ellagic acid rather than pomegranate peel extract.

So, I guess another point that's being made that, if that's the depigmenting agent, the ellagic -- if that's how you say it -- acid, then the amount of that that's going to be found in a pomegranate cosmetic ingredient is going to be very low and should not be an issue. But Ron, it gets back to your point, how much is very low and non-depigmenting?

DR. SHANK: Right. If we can give a limit, I think we should.

DR. MARKS: So, I get the sense, Ron, you're not swayed by the CIR SSC memo of November 19th, arguing why it should be treated as licorice was.

DR. SHANK: That's from Council?

DR. MARKS: Yeah.

DR. SHANK: Yeah, no.

DR. MARKS: Okay. Tom? Insufficient conclusion?

DR. SLAGA: I think we have an insufficient.

DR. MARKS: Yep. Okay. Same needs as we have below.

DR. SLAGA: Yep.

DR. MARKS: That hasn't changed since we didn't get any new data. And obviously, the NOEL for skin lightening is going to be the key, at least at this point, or a better argument why we don't need it.

Lisa, did you have any comments? I know this is your first time, and you're jumping in at the end of this.

DR. PETERSON: No, I don't have any additional comments.

DR. MARKS: Okay. So, I'm going to move tomorrow insufficient conclusion. Needs are listed below in the memo, but especially the NOEL for skin lightening.

Okay. Any other comments? Any comments about the abstract, the conclusion, the discussion? Okay. So this would be a final report. Okay. Did I miss Christina?

DR. HELDRETH: No. She's still in process with the Belsito group.

MS. RAJ: They're on coconut right now.

DR. MARKS: Okay.

DR. SHANK: So, we should come back to this later.

DR. MARKS: I wish I had noticed that before. I was covering up.

DR. HELDRETH: That's all right, I'm taking notes for her.

DR. MARKS: Yeah. So, it's pretty straightforward from us. We had a long discussion, but we want to stick with the conclusion on the tentative report, or the draft final safety assessment. And I don't think, Christina, we didn't have any suggestions for editorial changes. Okay.

Full Team Meeting – December 10, 2019

DR. MARKS: So, at the September meeting the panel concluded that the data were insufficient to support the safety of 18 pomegranate-derived ingredients. The needs included NOAEL for skin lightening -- that's an important toxicological effect that we had quite a bit of discussion about -- method of manufacture, and then for a number of the ingredients, composition, impurities, systemic tox and dermal irritation and sensitization.

We did receive some data, but nothing concerning the lightening effects of pomegranate. So, our team makes a motion that a final report be issued with the insufficient conclusion; the needs are those that I mentioned.

DR. BERGFELD: The Belsito team, comment?

DR. BELSITO: Yeah, we accepted CIR SSC's rationale to discount the lightening effects as a non-cosmetic effect. And to make a very strong statement in the discussion that it would not be appropriate for a cosmetic to have this effect and that it would be misbranding. And based upon that, we thought that there were a number of ones that could be safe as used. And those would be the fruit, juice, seed, and pericarp products.

So that would be pomegranate fruit extract, the fruit juice, the fruit water, the juice extract, the pericarp extract, the seed, the seed extract, and the seed powder. We did not think the seed cell culture lysate could be included in that. So, those were the ones we thought safe as used.

The others were insufficient as originally stated, except we again got rid of the skin lightening requirement.

DR. MARKS: Yeah, we would agree on the ingredients. I guess, Ron Shank, do you want to talk about -- we also discussed the CIR SSC approach to dealing with the skin lightening as they suggested with licorice, what we had done in the past and handle it in the discussion. But, we had a little different conclusion from that, so Ron Shank?

DR. SHANK: How did you handle the skin lightening, you just dismissed it?

DR. BELSITO: No, we didn't dismiss it. We said that a product should not be formulated to result in skin lightening, that this would not be a cosmetic product; it would be an over-the-counter or prescription drug, and therefore it would be misbranded.

DR. SHANK: But if the product is prepared for --

DR. BELSITO: First of all, the levels that caused it were extremely high -- are not likely to be in a cosmetic product. The problem is that we don't have a NOAEL for it. But, we thought, again, we could handle it. We agreed with SSC that we could handle it, you know, as we did for licorice.

You know, point out A) that the effects were seen at very high concentrations; B) we don't have a NOAEL; and C) it would be inappropriate to formulate a cosmetic product that would have this effect, so manufacturers should assure that that doesn't exist.

DR. SHANK: That last part, C); it's not sold as a skin lightener, but it could be a side effect.

DR. BELSITO: It shouldn't have that side effect.

DR. SHANK: It should not have it.

DR. BELSITO: Right.

DR. SHANK: So, I think we should ask for a no effect level. We keep getting into this situation where, if we don't have data, we say formulated not to cause something. And, I think we should ask for actual concentrations in formulations that are effective in skin lightening; and set a limit rather than just saying when formulated not to lighten skin.

I don't think we're doing our job when we just sidestep the issue and say put the burden on the formulator.

DR. BERGFELD: Paul, comment?

DR. MARKS: Well, I want to clarify that. Would you have that in the conclusion, when formulated not to cause skin lightening? Or, I think what I heard is, if you handle it like licorice, it would be in the discussion. So, it wouldn't even be acknowledged in the conclusion.

DR. SNYDER: We did discuss the cheek study there on Page 42, the human with the punica granatum juice. That it was at four percent and the maximum leave-on concentration is 1.5 percent.

So, we're significantly clear of the maximum concentration of use. And so, we felt that we do have data that we could just address it in the discussion and say where that this is a potential. But at the current concentrations of used, it appears to be no.

DR. SHANK: You got concentration data where it is effective as a skin lightener, but you don't have a no effect concentration.

DR. BELSITO: At four percent it causes the decrease in melanin content.

DR. LIEBLER: Ron, you put your finger early on the thing that was a conundrum for me. And coming into the discussion yesterday, I felt that our problem is -- that's the problem study, the one that Paul just mentioned. And we don't have a NOAEL, but that's what we asked for.

But, you know, when I read the Council's memo, and we talked about it yesterday, I considered two things. One is that the difference between the maximum use concentrations got .1 percent in the table here for the fruit juice, versus the four percent of the juice. I realized the NOAEL is what proves it, you know, doesn't have an effect.

But, given that huge disparity, and what we know about the mode of action for skin lightening, which is that the polyphenols or phenolics in these juices are basically alternate substrates for tyrosinase, and essentially compete for melanin formation.

I felt that we can make an argument in the discussion, bringing the mode of action into the argument, that the panel did not feel that there was a risk of skin lightening at the concentrations of use, even though we don't have a NOAEL. So, I accepted that reasoning, but I can understand how you want the NOAEL to prove it. And I just felt I can go with the argument based on what we know of the mode of action. If we didn't know anything on the mode of action, then I'd be less comfortable with it, because I would really be blowing smoke. I might still be blowing smoke, but --

DR. SHANK: Okay, so you would add to the discussion?

DR. LIEBLER: Yeah.

DR. MARKS: It's going to be interesting, because I --

DR. SHANK: Okay, then I'll see what that is.

DR. MARKS: Yeah, I would compare this to the read across where, I think, Curt, you made the basis of all that is on scientific fact and experiments, and not interpretation.

And, of course, that's what we're dealing with here, is do we have enough reasoning to say we don't need a NOAEL. And I'll defer that on our team to Ron Shank. If he's convinced with that reasoning, then --

DR. SHANKS: We'd still like to have the data, though.

DR. MARKS: Yeah, do we want the data, or don't we want the data, that's what it comes down to.

DR. SHANK: Well, I understand the reasoning, and it's fine. I would prefer to have hard data to support it. But if the rest of the panel is happy with arguing on mechanism of action, that's fine.

DR. LIEBLER: I would even say in support of this sort of mechanism of action. I mean, it is a known mechanism of action for these polyphenols to inhibit tyrosinase. We've actually got the in vitro study on the same page with the melanocyte treated with a pomegranate fruit extract that is standardized to 20 percent panisa (phonetic) gallons, which is another phenolic -- a constituent in these. So, in other words, it takes a lot to inhibit the melanin formation.

You know, the study that we're concerned about is so poorly documented it's very hard to interpret. But, I think based on what we know about mode of action and how much it took in an in vitro model, and what our use concentration is, I think we can reason through the discussion.

DR. MARKS: And I might add one more thing as a clinician, and Don, you can concur with this if you want; is clinically we haven't seen an outbreak of skin lightening or concerns about that -- reports. So, from a clinical point of view it would reinforce what you're saying, Dan.

DR. BERGFELD: Well, at this point in time we have a motion but no second, and we have a second proposal by the Belsito team.

DR. MARKS: I'll withdraw my motion.

DR. BERGFELD: Okay.

DR. MARKS: And I agree with the safety of the ingredients you mentioned, Don; so I will second -- if you want to make that motion again and I'll second that.

DR. BELSITO: Okay. Let me go back, I was trying to figure out all the changes we made to coconut, but here we go.

DR. MARKS: Don, do you agree with me with the clinical reason also?

DR. BELSITO: Yeah.

DR. MARKS: We often use that when we talk about sensitization, and we certainly have not seen reports of skin lightening from pomegranate in cosmetics.

I think you talked about pericarp -- at least what I had as our alternative, was safe for pericarp and fruit extract, fruit juice and seed extracts. And I know that would cover.

DR. BERGFELD: Insufficient for cell culture.

DR. MARKS: Yeah.

DR. BELSITO: Okay, so, the safe as used were the fruit extract, fruit juice, fruit water, juice extract, pericarp extract, seed, seed extract and seed powder. The others remained insufficient for our original request.

We're also told that punica granatum extract is not used; it's no longer in the dictionary, or it's not being manufactured, I guess. But, if so, it would be insufficient for manufacture and composition and impurities.

MS. FIUME: There are uses.

DR. BELSITO: There are uses, okay. So, it also remains insufficient.

DR. BERGFELD: So, second?

DR. MARKS: I second that motion. And I'll make an editorial. This will have to be delayed -- we have to look at it again, I think, because it's significantly different from the conclusion in our tentative report which was issued.

DR. SNYDER: Agreed.

DR. BERGFELD: Bart, agreed?

DR. HELDRETH: Yes, agreed. This will need to go out for another comment period. And hopefully we'll find, and the panel returns, this significant change in the discussion language for the rational, the skin lightening for Christina package.

DR. BERGFELD: Okay. Any other comments regarding this ingredient, I'll call the question.

MS. BURNETT: Can I just verify the insufficiencies. So, we are removing the skin lightening insufficiency for all. And then it's for the non-fruit juice, seed, pericarp, it is composition and impurities data, systemic toxicity data, dermal irritation and sensitization data, and method of manufacturing?

DR. BELSITO: Yes.

MS. BURNETT: Okay.

DR. HELDRETH: And then, one final question; for those ingredients that are now deemed safe, are we including the non-sensitizing caveat?

DR. BELSITO: Again, I didn't see anything in them that would concern me.

DR. BERGFELD: So, we're not including the non-sensitizing caveat to the conclusion. All right, I'll call the question; all those in favor of this motion? Thank you, unanimous.

Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 18 *Punica granatum* (pomegranate)-derived ingredients. Most of these ingredients are reported to function as skin conditioning agents in cosmetic products. The Panel reviewed the available data to determine the safety of these ingredients. Industry should use good manufacturing practices to limit impurities. The Panel concluded that 8 *Punica granatum* (pomegranate) ingredients derived from the fruit, juice, pericarp, and seed are safe in cosmetics in the practices of use and concentration described in this safety assessment; however, the Panel also concluded that the data on the remaining 10 *Punica granatum* (pomegranate) ingredients are insufficient to make a determination of safety under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This assessment of the safety of the following 18 *Punica granatum*-derived ingredients is based on the data contained in this report.

Punica Granatum Extract‡
Punica Granatum Bark Extract
Punica Granatum Bark/Fruit Extract
Punica Granatum Callus Culture Extract
Punica Granatum Flower Extract
Punica Granatum Fruit Extract
Punica Granatum Fruit Juice
Punica Granatum Fruit/Root/Stem Powder
Punica Granatum Fruit/Sucrose Ferment Filtrate
Punica Granatum Fruit Water
Punica Granatum Juice Extract
Punica Granatum Leaf Cell Extract
Punica Granatum Peel Extract
Punica Granatum Pericarp Extract
Punica Granatum Seed
Punica Granatum Seed Cell Culture Lysate
Punica Granatum Seed Extract
Punica Granatum Seed Powder

‡ *Ingredient has been deleted from the Dictionary, but uses are currently reported.*

Most of the *Punica granatum*-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin conditioning agents, while some are reported to have other functions, such as abrasives and antioxidants, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*; see Table 1).[1]

It should be noted that Punica Granatum Extract, which was defined as an extract of the "whole plant," is no longer listed in the *Dictionary*; trade names that were associated with this ingredient are now included for the monographs associated with Punica Granatum Fruit Extract or Punica Granatum Pericarp Extract, as suppliers have indicated that extracts are not made from the "whole plant." However, Punica Granatum Extract is still included in the list of ingredients named in this report because it has the highest number of uses reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database, and because concentration of use data are still associated with this name.

Punica granatum, commonly referred to as pomegranate, has been used as a source of Unani and Chinese medicines.[2] Investigations into the antioxidant activity of various extracts derived from parts of *Punica granatum* are numerous; however, the Panel is not evaluating these claims as these are not related to the safety of the use of these ingredients in cosmetic products.[3-8]

In 2017, the Panel published a safety assessment of Punica Granatum Seed Oil and Hydrogenated Punica Granatum Seed Oil, and concluded that these ingredients are safe in the present practices of use and concentration.[9] The Panel also previously reviewed the safety of Punica Granatum Sterols, and concluded that this phytosterol ingredient is safe in the present practices of use and concentration.[10]

Essential oils, oleoresins (solvent free), and natural extracts (including distillates) derived from *Punica granatum* Linnaeus are generally recognized as safe (GRAS) for their intended use in foods for human and animal consumption according to the US FDA. Additionally, the pomegranate fruit, fruit juice, and seeds are consumed as food or beverages, and daily exposure from such consumption would result in much larger systemic exposures than those from use in cosmetic products. Accordingly, the focus of this safety assessment will be on data relevant to the use of *Punica granatum*-derived ingredients in cosmetics, with specific focus on topical exposure when available.

Botanicals, such as *Punica granatum*-derived ingredients, may contain hundreds of constituents. In this assessment, the Panel is reviewing the potential toxicity of each of the *Punica granatum*-derived ingredients as a whole, complex mixture. The Panel is not reviewing the potential toxicity of the individual constituents.

This safety assessment includes relevant published and unpublished data 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.

Note: In many of the published studies, it is not known how the substance being tested compares to the cosmetic ingredient. Therefore, if it is not known whether the substance being discussed is a cosmetic ingredient, the test substance will be identified as "pomegranate…" or "*Punica granatum* …" (e.g., "pomegranate seed extract" or "*Punica granatum* fruits"); if it is known that the substance is a cosmetic ingredient, the *Dictionary* nomenclature "Punica Granatum…" (e.g., "Punica Granatum Seed Extract" or "Punica Granatum Fruit Extract") will be used.

CHEMISTRY

Definition and Plant Identification

The definitions and functions of the *Punica granatum*-derived ingredients included in this report are provided in Table 1. The *Punica granatum*-derived ingredients, with the exception of Punica Granatum Fruit/Sucrose Ferment Filtrate and Punica Granatum Seed Cell Culture Lysate, are generically associated with the CAS number 84961-57-9; there are no CAS numbers associated with these exceptions.[1] The raw materials for the ingredients in this report are obtained from the deciduous shrub or small tree, *Punica granatum.*[11] These trees can grow to 6 to10 m (20 to 30 ft) tall. *Punica granatum* trees are native to Afghanistan, Iran, Iraq, Turkey, the Russian Federation, Tajikistan, Turkmenistan, and India.[12] In the US, the trees are cultivated in Arizona and California.[11]

Table 2 lists the generic definitions of the parts of plants that are most pertinent to the ingredients in this report.[1] The fruit produced by the tree are nearly round and are 2.5 to 5 inches wide with a non-edible, tough, leathery peel or rind, and are light to deep pink or red in color.[11] The fruit interior is separated into compartments by membranous walls and white spongy tissue. The compartments are filled with transparent sacs containing fleshy, tart pulp, known as arils, that are red, pink, or white in color. The seeds in the arils represent approximately half of the weight of the whole fruit.

Chemical Properties

Punica Granatum Fruit Extract

A supplier reported that Punica Granatum Fruit Extract prepared in water is a light to medium pink liquid with a characteristic odor.[13] At 25º C, the pH is 3.3 and the specific gravity is 0.99. This ingredient is soluble in any proportion in water.

Another supplier reported that a tradename mixture containing 20% Punica Granatum Fruit Extract was a clear to slightly hazy liquid with a specific gravity of 1.015 - 1.035 and a pH (direct) of 5.5 - 7.5.[14]

Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing glycerin, water, and 0.1% - 1% Punica Granatum Pericarp Extract was yellowish to red-brown with a density (at 20º C) of 1.176 - 1.232 g/ml.[15] Another supplier reported a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) was a light brown to brown liquid with a pH of 3.1 - 5.1 and a specific gravity of 1.0 - 1.1.[16]

Methods of Manufacturing

Punica Granatum Fruit Extract

A supplier reported that Punica Granatum Fruit Extract is produced through the mechanical processing (grinding/milling) of whole *Punica granatum* fruits followed by aqueous extraction at a specific pH, temperature, and duration.[17] The supplier incorporates this extract into a tradename mixture by dilution in butylene glycol, addition of phenoxyethanol and tetrasodium ethylenediaminetetraacetic acid (EDTA), filtration, and quality control. The final tradename mixture contains 20% Punica Granatum Fruit Extract.

Another supplier reported that Punica Granatum Fruit Extract is produced by extracting fresh or dried fruit with specified eluent(s) under appropriate temperature conditions to yield a concentrate.[13] Typical eluents include water, butylene glycol, carthamus tinctorius (safflower) seed oil, glycerin, and propylene glycol. The concentrate containing phytochemical constituents is then blended with the desired diluent(s) and preservation system to produce the final ingredient.

Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) is produced by extracting the dried raw material with a 50% ethanolic solution prior to filtering, concentrating, and incorporating 30% butylene glycolic solution.[16]

Another supplier reported that Punica Granatum Pericarp Extract (3.1%) in a tradename mixture is produced by water extraction and heating for 1 h at 110 ºC.[18] The same supplier reported that Punica Granatum

Pericarp Extract (2.5%) in a different tradename mixture is produced by hydroglycolic extraction of the dried pericarp and heating for 1 h at 110 ºC.[19]

Punica Granatum Seed Powder

A supplier reported that Punica Granatum Seed Powder is produced by grinding and sieving pomegranate seeds prior to decontaminating through heat or gamma-rays.[20]

Composition/Impurities

The main classes of phytochemicals identified from pomegranate (various plant parts) are as follows: ellagitannins, gallotannins, and derivatives; flavonoids; lignans; triterpenoids and phytosterols; fatty acids and lipids; organic acids and phenolic acids; alkaloids, including pelletierine (mainly found in bark); and other compounds, such as catechol and coumestrol.[21,22] Specifically, the triterpenes ursolic acid and oleanolic acid are reported to be constituents of pomegranate leaves, bud, fruits, flowers and seeds.[23] Gallic acid is reported to be a constituent of pomegranate peel, pomegranate juice, pomegranate fruit, and pomegranate flowers. The major constituents of pomegranate pericarp are reported to be hydrolysable ellagitannins (up to 28%) and other polyphenols.[24] The main biologically active constituents of pomegranate root and stem bark are alkaloids (0.5% to 0.9%) and tannins (up to 22% in bark).[24] Yields of constituents have been found to be dependent on solvent types, with polar solvents having a greater ability to extract antioxidants when compared to non-polar solvents.[4,5,25] Pomegranates grown in different conditions and locations may have varying composition levels in different plant parts.[6] Table 3 describes the total phytochemical contents of pomegranate extracts by plant part.[3,6,26-29]

Punica Granatum Flower Extract

The tannin content of a pomegranate flower extract used in a wound healing efficacy study was 48.7%.[30] The test material was extracted with ethanol. Analyses of methanol extracts of a flower extract characterized a total of 57 phenolic compounds.[31]

The gallic acid and ellagic acid contents of an ethyl acetate soluble fraction of a methanolic extract of pomegranate flower extract were 2.00 mg/g and 68.80 mg/g, respectively.[2] A methanolic extract, and the water-soluble fraction of the methanolic extract, quantified ellagic acid content as 18.85 mg/g and 10.88 mg/g, respectively.

Punica Granatum Fruit Extract

A food-grade pomegranate fruit extract that was produced from whole pomegranate fruit was standardized to contain 70% polyphenols total, including 30% punicalagins.[32] Other constituents of the extract included not more than 5% ellagic acid and 0.3% gallic acid. Analyses of methanol extracts of a patented pomegranate fruit extract characterized a total of 71 phenolic compounds, including 64 tannins.[31]

A supplier reported that a pomegranate extract contained 20% Punica Granatum Fruit Extract, ~40% butylene glycol, ~40% water, 1% phenoxyethanol, and 0.1% tetrasodium EDTA.[33] This supplier has certified that this product does not contain the 26 allergenic flavors or fragrances restricted by the European Union, nor does it contain pesticides exceeding US Environmental Protection Agency limits. Heavy metals, lead, arsenic, cadmium, microbial content, yeast and mold, and gram-negative bacteria were below detection limits.[14]

Another supplier reported that Punica Granatum Fruit Extract concentrate in an alcohol base had 0.013 mg/l cadmium.[13] Antimony, arsenic, chromium, iron, lead, mercury, and nickel were below levels of detection. No residual pesticides were detected. The 26 allergens defined by the European Union Cosmetic Directive were below threshold levels in a concentrate of Punica Granatum Fruit Extract concentrate in an alcohol base.

Punica Granatum Leaf Extract

A chromatogram of an acetyl acetate extract of pomegranate leaves identified the following constituents: punicalin, ellagic acid derivate, galloyl-hexahydroxydiphenyl-glucose, castalagin derivatives, granatin B, ellagic acid rhamnoside, kaempferol-3-*O*-glucoside, kaempferol-arabinoside, and a kaempferol derivative.[34]

Punica Granatum Peel Extract

The major constituents of aqueous pomegranate peel extract were reported as punicalagin, punicalin, ellagic acid, gallic acid, quercetin, luteolin, kaempferol, and naringenin. [35] Ellagic acid, punicalagin α, and punicalagin β contents of a methanolic pomegranate peel extract were 2.75 mg/g, 3.52 mg/g, and 5.04 mg/g, respectively.[2] A methanolic extract of pomegranate peel used in a wound healing efficacy study contained 34.03% gallic acid and 3.31% catcechin.[36]

Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) contains tannin and sugar.[16] The heavy metals content is not more than 20 ppm and the arsenic content is not more than 2 ppm.

Punica Granatum Seed Extract

The fatty acid composition of an ethanol extract of pomegranate seed is described in Table 4.[3]

An ethanolic extract of pomegranate seeds was found to contain triterpenoids, steroids, glycosides, saponins, tannins, alkaloids, and flavonoids.[37] No further details were provided.

Total phenolic content of pomegranate seed extracts was dependent on the solvent type used during extraction.[5] Methanol and water yielded the highest amount of phenolic compounds (27.93 and 22.61 mg/l seed extract, respectively), followed by acetone (3.41 mg/l), butanol (0.57 mg/l), ethyl acetate (0.37 mg/l), and hexane (0.29 mg/l).

Punica Granatum Seed Powder

The gross chemical components of pomegranate seed powder are protein (13.66%), fat (29.6%), ash (1.49%), fiber (39.36%), carbohydrate (13.12%), phenolics (0.25%), and moisture (5.82%).[38] Vitamin content includes thiamine (0.930 mg/100g), riboflavin (0.146 mg/100g), L-ascorbic acid (3.02 mg/100g), α-tocopherol (1.35 mg/100 g), and retinol (0.089 mg/100 g).

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the US FDA and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA VCRP database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

Although no longer listed in the *Dictionary*, 2020 VCRP survey data indicate that of the ingredients included in this report, Punica Granatum Extract has the most reported uses in cosmetic products, with a total of 334; the majority of the uses are in leave-on skin care products (Table 5).[39] Punica Granatum Fruit Extract has the second greatest number of reported uses in this safety assessment with 188 uses; the majority of these uses are also in leave-on skin care products. The results of the concentration of use survey conducted in 2017 by the Council indicated that Punica Granatum Seed Extract is used at up to 0.3% (in leave-on cuticle softeners).[40,41] Survey data from 2019 indicate that Punica Granatum Extract and Punica Granatum Fruit Extract are used at up to 0.13% (in moisturizing preparations) and 0.1% (in face and neck and night skin preparations), respectively. Punica Granatum Fruit Juice is used at up to 0.1% (in makeup preparations). Ingredients with no reported uses in the VCRP or by the Council are listed in Table 6.

Punica granatum-derived ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes; for example, Punica Granatum Seed Extract is reported to be used in lipstick at up to 0.11%.[40,41] Additionally, some ingredients have been reported to be used in products that may come into contact with the eyes; for example, Punica Granatum Fruit Extract is used at up to 0.018% in eye shadows. Moreover, some ingredients have been reported to be used in spray and powder products that could possibly be inhaled; for example, Punica Granatum Extract is used in a face and neck spray at 0.001% and Punica Granatum Fruit Juice is used in a face powder at 0.01%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump spray.[42-45] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[42,43] 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.[46-48]

The *Punica granatum*-derived ingredients described in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[49]

Non-Cosmetic

In the US, the essential oils, oleoresins (solvent-free) and natural extractives (including distillates) from *Punica granatum* L. (pomegranate) are GRAS for their use in food intended for human consumption and in animal

drugs, feeds, and related products according to 21CFR182.20 and 21CFR582.20, respectively. Minimum quantities of pomegranate juice have been established for use in juice, flavored beverages, and jellies (21CRF101.30 and 21CFR150.140).

Because of antioxidant and anti-inflammatory properties, the extracts of various parts of *Punica granatum* have been researched for use as alternative or therapeutic treatments (as herbal medicines or dietary supplements) for burn injuries and other dermal wounds, canker sores and oral hygiene, neurodegenerative conditions, convulsions, management of diabetes and weight, acute pancreatitis, acute lung injury, myocardial infarctions and other cardiovascular protection, and various cancers.[3,4,8,23,27,30,34,36,37,50-60] The juice and peel extracts have also been researched for use as antifungal and antibacterial treatments.[61-65]

TOXICOKINETICS STUDIES

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Punica Granatum Fruit Extract

In separate experiments performed by the same researchers, groups of 6 male and 6 female Wistar rats and Swiss albino mice received a single dose of pomegranate fruit extract (solvent not reported; the extract was standardized to contain 70% polyphenols, including 30% punicalagins) at 0, 50, 500, or 5000 mg/kg bw via gavage.[32] The oral LD_{50} was determined to be greater than 5000 mg/kg bw for both species. No adverse effects were observed during the 14-day observation period, and no gross pathological abnormalities were observed during necropsy in both the rats and mice.

Punica Granatum Pericarp Extract

A supplier reported that the oral LD_{50} for a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) was greater than 2000 mg/kg in mice.[16] No further details were provided.

Punica Granatum Seed Extract

An ethanolic extract of pomegranate seeds was administered orally to 5 groups of 6 fasted NMRI male mice.[37] Doses were 2000, 3000, or 5000 mg/kg. No mortalities were observed in any dose level. No further details were provided.

Short-Term Toxicity Studies

Oral

Punica Granatum Peel Extract

In a 15-day study, groups of 7 male Wistar rats received pomegranate peel extract by gavage at 250 mg/kg/d bw as a control and at up to 500 mg/kg/d bw in treatment groups induced with oral candidiasis.[63] At the end of the treatment period, macroscopic examination of the oral cavity and the tongue tissues and histopathological examinations of the tongue tissues were performed. No adverse effects from the test material were observed in the rats.

Intranasal

Punica Granatum Fruit Extract

The toxic effects of an ethanolic pomegranate fruit extract was studied in a 35 day intranasal study in groups of 10 male Wistar rats.[66] The rats received 0, 0.4, 1.2, or 7 mg/kg lyophilized extract in each nasal cavity with a microsyringe. The controls received saline solution. The rats were weighed and feed consumption was measured every 7 days. At the end of the treatment period, biochemical and histopathology samples were analyzed and organs were weighed. No statistically significant differences in mean animal weight or feed consumption were observed. There were no clinical signs of toxicity. The only biochemical effect noted was an increase in creatinine values in the highest dose group (7 mg/kg), but these values were still within the normal range and there was no

indication of kidney damage in the histopathology samples. No treatment-related effects were observed in any dose group.

Subchronic Toxicity Studies

Oral

Punica Granatum Fruit Extract

The toxicity of a pomegranate fruit extract was investigated in a 90-day oral toxicity study in Wistar rats in accordance with the Organization for Economic Co-operation and Development (OECD) test guideline (TG) 408.[32] Groups of 10 male and 10 female rats received 0, 60, 240, or 600 mg/kg bw/day pomegranate fruit extract (solvent not reported; the extract was standardized to contain 70% polyphenols, including 30% punicalagins) via gavage. Two additional groups of animals that received 0 and 600 mg/kg/day of the extract were recovery groups that were observed for 28 days after the initial 90-day treatment period. Clinical observations, body weight and feed consumption measurements, clinical pathology, and macroscopic and microscopic examinations of tissues from over 40 sites (including ovaries and uteri in females and testes and epididymides in males) were performed on all animals.

All animals survived until scheduled necropsies in both the 90-day study group and the recovery group. No adverse effects were observed during clinical observations. No treatment-related biologically significant effects were noted on body weight or body weight gain, feed consumption, in urinalysis parameters, in hematology parameters, in serum chemistry parameters, in absolute or relative organ weights, or in macroscopic or microscopic findings at any dose tested. No treatment-related effects were reported in the recovery groups. The no-observed-adverse-effect-level (NOAEL) for pomegranate fruit extract was determined to be 600 mg/kg/day.[32]

Chronic Toxicity Studies

No relevant chronic toxicity studies were found in the published literature, and unpublished data were not submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Punica Granatum Fruit Extract

Abnormal sperm were observed 5 weeks after male Balb/C mice were treated with a hydroalcoholic pomegranate fruit extract in a sperm-shape abnormality assay.[67] Route of exposure was not defined. The extract was tested at doses of 0, 7, 70, or 700 mg/kg bw in groups of 5 mice. There was a dose-dependent increase in sperm with amorphous and hookless head. The frequency of abnormal sperm was significant ($p < 0.05$) at doses $\geq$ 70 mg/kg bw.

Oral

Punica Granatum Fruit Juice Extract and Punica Granatum Seed Extract

The potential effects of pomegranate seed extract (described as husk extract) and pomegranate juice extract on chondrogenesis and osteogenesis in developing embryos was investigated in female Balb/c mice.[68] Both test materials were extracted in water. Groups of 10 pregnant mice received the seed extract (1.0 g/kg suspended in 0.2 ml distilled water), the juice extract (3.3 ml/kg suspended in 0.2 ml distilled water), a mixture of both extracts, or distilled water daily in an oral dietary supplement between days 8 and 18 of gestation. On day 19 of gestation, the embryos were weighed and the length of the femur, tibia, and the ossification zones were measured by stereomicroscopy. The bone calcium content of the femurs of the pregnant mice was also measured.

Body weight gains of the pregnant mice were not affected by the test material. The pregnant mice that received the pomegranate extracts had an increase in bone calcium content, with a statistically significant increase ($p < 0.05$) in the group that received pomegranate juice extract. The fetuses from the mixed extract group did have significantly reduced body weights and crown-rump lengths; these effects were not observed in the pomegranate seed extract only and pomegranate juice extract only treatment groups. Significantly increased femur lengths and osteogenesis indices were observed in all extract-exposed groups. No craniofacial abnormalities or limb defects were reported during gross observations, and no pathological changes, including necrosis, abnormal cells, or congestion in longitudinal section of fetuses were observed. The liver and kidneys of the fetuses and the dams were within normal parameters.[68]

Punica Granatum Fruit Juice

The effects of pomegranate juice on sperm quality, spermatogenic cell density, antioxidant activity, and testosterone levels were studied in male Wistar rats.[7] Groups of 7 rats received 0.25 ml pomegranate juice with 0.75 ml distilled water, 0.50 ml pomegranate juice with 0.50 ml distilled water, 1 ml pomegranate juice, or 1 ml distilled

water via gavage daily for 7 weeks. Body weights, reproductive organ weights, spermatogenic cell density, sperm characteristics, levels of antioxidant vitamins (A, C, and E), testosterone, lipid peroxidation, and antioxidant activities (glutathione, glutathione peroxidase, and catalase) were recorded. Analyses were done only once at the end of the study. There were no statistically significant effects on body weights in the treated groups when compared to the control group. Weights of testes, epididymides, seminal vesicles, prostate glands, and Cowper glands were higher in the treated groups when compared to the controls, but the differences were not statistically significant. A significant ($p < 0.05$) decrease in malondialdehyde level and marked increases in glutathione, glutathione peroxidase and catalase activities, and vitamin C levels were observed in rats treated with different doses of pomegranate juice. Increases in epididymal sperm concentration, sperm motility, spermatogenic cell density, diameter of seminiferous tubules, germinal cell layer thickness, and a decreased abnormal sperm rate were observed with pomegranate juice consumption when compared to the controls.

GENOTOXICITY

In Vitro

Punica Granatum Fruit Extract

The genotoxicity of a hydroalcoholic extract of pomegranate fruit (including peel) was assessed in an Ames study using *Salmonella typhimurium* strain TA100, with and without S9 metabolic activation.[67] The extract was tested at 0, 0.45, 1, 2, and 4 mg/plate. The higher doses of the extract induced significant increases of revertants (2 mg/plate, $p < 0.05$; 4 mg/plate, $p < 0.01$); the results of the lower doses tested were comparable with negative controls. The positive control yielded expected results.

The same pomegranate fruit extract (described above) was tested at concentrations up to 18 mg/ml in *Saccharomyces cerevisiae* strain D7..[67] The extract did not induce gene-conversion events, but an increased frequency of reverse mutations was observed in a dose-dependent manner, with and without metabolic activation. Statistical significance at the doses these effects occurred was not provided.

In mutagenic studies of a hydroalcoholic pomegranate fruit extract, Chinese hamster ovary (CHO) cells were tested with and without metabolic activation at concentrations of 0, 1, 50, 110, 230, 340, and 450 µg/ml in a sister chromatid exchange assay, and at concentrations of 0, 0.9, 45, 112, and 225 µg/ml in a chromosomal aberration assay.[67] A dose-dependent and statistically significant increase in sister chromatid exchanges per cell was observed; increases were observed with concentrations of $\geq$ 110 µg/ml ($p < 0.05$) in the absence of S9 metabolic activation. Significant increases in the percentage of chromosomal aberrations were also observed with $\geq$ 45 µg/ml ($p < 0.05$) without metabolic activation.

Punica Granatum Pericarp Extract

The mutagenic potential of a tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camellia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was studied in an Ames test using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2*uvr*A, with and without metabolic activation.[69] Cells were incubated with the test material at doses of 1.5 to 5000 µg/plate in sterile deionized water. No mutagenicity was observed at any dose level. Positive and negative controls yielded expected results.

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) was negative in an Ames test when tested at 5000 µg/plate.[16] No further details were provided.

In Vivo

Punica Granatum Fruit Extract

In a mouse bone marrow micronucleus assay studying the genotoxic effects of a hydroalcoholic extract of pomegranate fruit, the extract was administered intraperitoneally at doses of 7, 70, 184, 369, or 700 mg/kg bw to 5 Balb/C mice/sex/group at intervals of 24 h (further details on dosing not reported). [67] A dose-dependent increase in the number of polychromatic erythrocytes with micronuclei was observed. The genotoxicity index increase was statistically significant at doses $\geq$ 70 mg/kg bw in both sexes. The cytotoxicity index was significantly increased at doses of $\geq$ 70 and 184 mg/kg bw in males and females, respectively.

ANTI-GENOTOXICITY

Punica Granatum Leaf Extract

In a mouse bone marrow micronucleus assay studying anti-genotoxicity effects of an aqueous pomegranate leaf extract, groups of 6 male Swiss mice received 0, 400, 600, or 800 mg/kg bw of the extract in distilled water by gavage for 7 days before exposure to the genotoxicant cyclophosphamide (CPH).[29] Another two groups of 6 mice served as genotoxicant and test material (800 mg/kg extract) controls. Prior to the final treatment with the extract, the mice received 40 mg/kg CPH, and all mice were killed after 24 h. Anti-genotoxic effects were observed in a non-dose dependent manner at all 3 extract dose levels. The maximum reduction was observed in mice that received 800 mg/kg of the extract. There was no reduction in the percentage of polychromatic erythrocytes following treatment with the extract and CPH. No genotoxic effects were observed to the pomegranate leaf extract alone.

CARCINOGENICITY

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

OTHER RELEVANT STUDIES

Skin Lightening

In Vitro

Punica Granatum Fruit Extract

The potential for an ethanolic pomegranate fruit extract to inhibit melanin production has been studied in vitro using the Melan-a melanocyte cell culture model.[70] The Melan-a cells were treated with pomegranate fruit extract that was standardized to 20% punicalagins. The test material was produced from fruit (with peel) that was macerated and extracted with a 75% - 80% ethanol solution at a ratio of 1:4 (fruit:solvent) before filtration and vacuum processing. Melanin content was reduced by approximately 40% to 60% at test concentrations of 50 µg/ml and 100 µg/ml, respectively. Further testing with the purified punicalagins isolated from pomegranate fruit found that these constituents reduced melanin production by 60%, 70%, and 75% of control levels at test concentrations of 20 µg/ml, 60 µg/ml, and 100 µg/ml, respectively.

Punica Granatum Peel Extract

An aqueous pomegranate extract of rind containing 90% ellagic acid showed inhibitory activity against mushroom tyrosinase (IC_{50} 182.2 µg/ml) in vitro.[71] The inhibition effects were comparable to arbutin (IC_{50} 162.2 µg/ml), but was about ten times weaker than L-ascorbic acid (IC_{50} 18.4 µg/ml).

Animal

Punica Granatum Peel Extract

Mid-wavelength ultraviolet (UVB) light-induced skin pigmentation was inhibited in female brownish guinea pigs after the animals received aqueous pomegranate extract of rind orally for 35 days.[71] There were 6 animals per dose group that received either 100 mg/kg/day of the extract diluted in water at 100 mg/ml, 1000 mg/kg/day of the extract diluted in water at 100 mg/ml, water, or 600 mg/kg/day L-ascorbic acid diluted in water at 60 mg/ml. The animals were irradiated on days 7, 9, and 11. The number of L-3,4-dihydroxyphenylalanine (DOPA)-positive melanocytes in the epidermis of the UV-irradiated guinea pigs were reduced in the animals that received the pomegranate extract. The researchers of this in vivo study and the in vitro study above concluded that the skin-whitening effects were likely due to inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase in melanocytes.

Human

Punica Granatum Juice

In a study of a water/oil emulsion containing 4% concentrated pomegranate juice, the test material (amount not reported) was applied daily to the cheeks of 25 healthy volunteers for 60 days.[72] A Mexameter® was used to measure the melanin on the cheeks of the volunteers on the day prior to application and at weeks 1 - 4, 6, and 8. Significant decreases (details not provided) in skin melanin content were observed.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

In Vitro

Punica Granatum Pericarp Extract

An undiluted tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camellia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was predicted to be non-irritating in an EpiDerm™ reconstructed human epidermal model.[73] Negative and positive controls yielded expected results.

Human

Punica Granatum Juice

No dermal irritation was observed in a 60-day study of a water/oil emulsion containing 4% concentrated pomegranate juice in 25 healthy volunteers.[72] The test material (amount not reported) was applied daily to the cheeks, and the volunteers self-scored the patches on a scale of 0 to 3.0 for the presence of erythema.

Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) tested at 20% was negative in a human single patch test using 44 subjects.[16] No further details were provided.

Sensitization

In Vitro/In Chemico

Punica Granatum Pericarp Extract

A tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camellia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was not predicted to be a sensitizer in a direct peptide reactivity assay (DPRA) performed in accordance with OECD TG 442C.[74] The 100 mM product (in acetonitrile) was tested at 5 mM with the cysteine peptide and at 25 mM with the lysine peptide. The controls yielded expected results.

The same tradename mixture containing 10% Punica Granatum Pericarp Extract was not predicted to be a sensitizer in a KeratinoSens™ ARE-Nrf2 Luciferase test performed in accordance with OECD TG 422D.[75] The test material was prepared in dimethyl sulfoxide at 0.98 to 2000 µM. The controls yielded expected results.

Animal

Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) tested at 20% was negative in a guinea pig skin sensitization test using 5 animals.[16] No further details were provided.

Human

Punica Granatum Fruit Extract

In a human repeat insult patch test (HRIPT), the sensitization potential of a leave-on product containing 0.1% Punica Granatum Fruit Extract was tested in 100 subjects.[76] For both the induction and the challenge phases, 0.2 g of the test material was applied directly on the backs of the subjects and allowed to air dry: the test patches were not occluded. No adverse reactions were observed. The test material was determined to be non-irritating and non-sensitizing. No further details were provided.

Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids), when tested at 30%, was negative in a HRIPT using 52 subjects.[16] No further details were provided.

Photosensitization

Animal

Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) tested at 20% was negative in a photosensitization test using 5 guinea pigs.[16] No further details were provided.

OCULAR IRRITATION STUDIES

In Vitro

Punica Granatum Pericarp Extract

An undiluted tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camellia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was predicted to be non-irritating in an EpiOcular™ cornea epithelial model.[73] Negative and positive controls yielded expected results.

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) tested at 100% was predicted to be non-irritating in a human corneal epithelium eye irritation test.[16] No further details were provided.

SUMMARY

According to the *Dictionary*, most of the 18 *Punica granatum*-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin conditioning agents, while some are reported to have other functions, such as abrasives and antioxidants. It should be noted that Punica Granatum Extract, defined as an extract of the whole plant, is no longer listed in the *Dictionary*; trade names that were associated with this ingredient are now included for the monographs associated with Punica Granatum Fruit Extract or Punica Granatum Pericarp Extract. Punica Granatum Extract is still included in the list of ingredients named in this report, however, because it has the most uses in the US FDA Voluntary Cosmetic Registration Program VCRP database and because concentration of use data are also associated with this name.

Investigations into the antioxidant activity of various extracts derived from parts of *Punica granatum* are numerous; these studies are not detailed in this report. The available toxicity data that correspond to specific use of these ingredients in cosmetics are extremely limited. The focus of this safety assessment is on data relevant to the use of *Punica granatum*-derived ingredients in cosmetics, with specific focus on topical exposure when available.

According to 2020 VCRP survey data, Punica Granatum Extract has the most reported uses in cosmetic products, with a total of 334; the majority of the uses are in leave-on skin care products. Punica Granatum Fruit Extract has the second greatest number of reported uses in this safety assessment with 188 uses; the majority of these uses are also in leave-on skin care products. The results of the concentration of use survey conducted in 2017 by the Council indicated that Punica Granatum Seed Extract is used at up to 0.3% (in leave-on cuticle softeners). Punica Granatum Extract and Punica Granatum Fruit Extract are used at up to 0.13% (in moisturizing preparations) and 0.1% (in face and neck and night skin preparations), respectively.

In the US, the essential oils, solvent-free oleoresins, and natural extractives from *Punica granatum* L. (pomegranate) are GRAS for their use in food intended for human consumption and in animal drugs, feeds, and related products. Extensive research has been performed on the extracts of various parts of *Punica granatum* for use as alternative or therapeutic treatments for various conditions.

The oral LD_{50} in mice and rats for a pomegranate fruit extract was greater than 5000 mg/kg bw. No mortalities were observed in mice that received an ethanolic extract of pomegranate seeds at up to 5000 mg/kg. The oral LD_{50} for a tradename mixture containing Punica Granatum Pericarp Extract (0.5% solids) was greater than 2000 mg/kg in mice.

In repeated dose studies, no adverse effects were reported in a 15-day oral rat study of methanolic pomegranate peel extract at up to 500 mg/kg/day. In a 90-day study, the NOAEL for an oral study of a pomegranate fruit extract in rats was 600 mg/kg/day, the maximum dose tested. No adverse effects were noted in rats that received lyophilized ethanolic pomegranate fruit extract at up to 7 mg/kg intranasally for 35 days. The only biochemical effect observed was an increase in creatinine values in the high dose group, but there was no kidney damage noted histopathologically.

Abnormal sperm were observed in male mice treated with a hydroalcoholic pomegranate fruit extract at doses ≥ 70 mg/kg bw. Route of exposure was not defined. No adverse effects were observed in an oral DART study in female mice that received pomegranate seed extract (1.0 g/kg suspended in 0.2 ml distilled water) or pomegranate juice extract (3.3 ml/kg suspended in 0.2 ml distilled water) separately or as a mixture on gestation days 8 - 18, and there was no effect on the fetuses. In a 7-week rat sperm study, increases in epididymal sperm concentration, sperm motility, spermatogenic cell density, diameter of seminiferous tubules, germinal cell layer thickness, and a decreased abnormal sperm rate were observed with daily pomegranate juice consumption (0.25 ml or 0.5 ml in distilled water or 1.0 ml neat) via gavage when compared to the controls.

Positive genotoxic effects to a hydroalcoholic extract of pomegranate fruit were observed in an Ames test (at ≥ 2 mg/plate), a reverse mutation study in *S. cerevisiae*, and in CHO cell assays (at ≥ 45 µg/ml), with and without metabolic activation. The same extract was associated with a dose-dependent increase in the number of polychromatic erythrocytes in a mouse micronucleus assay, with statistical significance at ≥ 70 mg/kg bw. No genotoxic effects were observed to tradename mixtures containing Punica Granatum Pericarp Extract in Ames tests or to a pomegranate leaf extract in a mouse micronucleus assay.

In vitro and in vivo studies indicate that a pomegranate fruit extract, pomegranate juice, and a pomegranate peel extract may inhibit melanin production. Melanin content was reduced by approximately 40% to 60% at test concentrations of 50 µg/ml and 100 µg/ml pomegranate fruit extract, respectively, in an in vitro study; while in a 60-day human study, significant decreases in melanin content were observed to a water/oil emulsion containing 4% concentrated pomegranate juice.

In an in vitro human epidermal model, an undiluted tradename mixture containing 10% Punica Granatum Pericarp Extract was predicted to be non-irritating. In a 60-day self-scored study of an emulsion containing 4% concentrated pomegranate juice, no dermal irritation was observed following daily application to the cheeks of human volunteers. No irritation was observed in a human single patch test of a tradename mixture containing Punica Granatum Pericarp Extract (0.5% solids) tested at 20%. In in vitro and in chemico assays, a tradename mixture containing 10% Punica Granatum Pericarp Extract was not predicted to be a sensitizer. Results of a guinea pig sensitization test of Punica Granatum Pericarp Extract (0.5% solids), a photosensitization test in guinea pigs of Punica Granatum Pericarp Extract (0.5% solids), and sensitization tests in humans to a leave-on product containing Punica Granatum Fruit Extract (0.1%) and to a tradename mixture containing Punica Granatum Pericarp Extract (0.5% solids) were negative.

No ocular irritation was predicted in in vitro cornea epithelial models of tradename mixtures containing up to 10% Punica Granatum Pericarp Extract.

No relevant chronic toxicity or carcinogenicity studies on *Punica granatum*-derived ingredients were found in the published literature, and no unpublished data were provided. No relevant toxicokinetics studies were found in the published literature; however, in general, toxicokinetics data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

DISCUSSION

The Panel reviewed the botanical ingredients derived from the plant, *Punica granatum*. The Panel expressed concern about pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients, and stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

Data included in this report indicate that extracts of parts of *Punica granatum* may have a skin lightening effect. The Panel noted that skin lightening is considered to be a drug effect, and should not occur during the use of cosmetic products. Because of that caveat, and based on the low concentrations of use of these extracts in cosmetic products, the Panel's knowledge of the mechanism of action (i.e., inhibition of tyrosinase activity by polyphenols), the results of the in vitro study of pomegranate fruit extract, and clinical experience, concern for this effect in cosmetics was mitigated. Nevertheless, cosmetic formulators should only use *Punica granatum* extracts in products in a manner that does not cause depigmentation.

Some *Punica granatum*-derived ingredients were reported to be used in spray and powder products that could possibly be inhaled. For example, Punica Granatum Extract is used in a face and neck spray at 0.001% and Punica Granatum Fruit Juice is used in a face powder at 0.01%. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns (e.g., data on an ethanolic pomegranate fruit extract did not produce adverse effects in rats). Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, 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 product s is available at https://www.cir-safety.org/cir-findings.

Although the Panel found the data on the fruit, juice, pericarp, and seed ingredients to be sufficient, the Panel determined that the data are insufficient to make a determination of safety for the following ingredients: Punica Granatum Extract, Punica Granatum Bark Extract, Punica Granatum Bark/Fruit Extract, Punica Granatum Callus Culture Extract, Punica Granatum Flower Extract, Punica Granatum Fruit/Root/Stem Powder, Punica Granatum Fruit/Sucrose Ferment Filtrate, Punica Granatum Leaf Cell Extract, Punica Granatum Peel Extract, and Punica Granatum Seed Cell Culture Lysate. The additional data needed to determine safety for these cosmetic ingredients are:

- Method of manufacturing with regard to solvent-type used for the extracts
- Composition and impurities data
- Systemic toxicity data
- Dermal irritation and sensitization data

The Panel noted that Punica Granatum Extract is no longer listed in the *Dictionary*. However, this ingredient has the highest number of uses reported in the US FDA VCRP database, and concentration of use data are still associated with this name, indicating that this ingredient, as it was originally defined, may still be in use.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 8 *Punica granatum* (pomegranate)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Punica Granatum Fruit Extract
Punica Granatum Fruit Juice
Punica Granatum Fruit Water
Punica Granatum Juice Extract
Punica Granatum Pericarp Extract
Punica Granatum Seed
Punica Granatum Seed Extract
Punica Granatum Seed Powder

The Panel also concluded that the data were insufficient to make a determination of safety under the intended conditions of use for the following 10 *Punica granatum* (pomegranate)-derived ingredients:

Punica Granatum Extract‡
Punica Granatum Bark Extract
Punica Granatum Bark/Fruit Extract*
Punica Granatum Callus Culture Extract*
Punica Granatum Flower Extract
Punica Granatum Fruit/Root/Stem Powder*
Punica Granatum Fruit/Sucrose Ferment Filtrate*
Punica Granatum Leaf Cell Extract*
Punica Granatum Peel Extract*
Punica Granatum Seed Cell Culture Lysate*

‡ Ingredient has been deleted from the Dictionary, but uses are currently reported.
** Uses not reported.*

TABLES

Table 1. Definitions and functions of the ingredients in this safety assessment. [1]

Ingredient/CAS No.	Definition & Structure	Function
Punica Granatum Extract ‡ 84961-57-9 (generic)	Punica Granatum Extract is the extract of the whole plant, *Punica granatum*.	Fragrance Ingredient; Skin-Conditioning Agent – Misc.
Punica Granatum Bark Extract 84961-57-9 (generic)	Punica Granatum Bark Extract is the extract of the bark of *Punica granatum.*	Fragrance Ingredient; Skin-Conditioning Agent – Misc.
Punica Granatum Bark/Fruit Extract 84961-57-9 (generic)	Punica Granatum Bark/Fruit Extract is the extract of the bark and fruit of *Punica granatum*.	Antimicrobial Agent; Antioxidant; Cosmetic Astringent
Punica Granatum Callus Culture Extract 84961-57-9 (generic)	Punica Granatum Callus Culture Extract is the extract of a culture of the callus of *Punica granatum.*	Skin-Conditioning Agent – Misc.
Punica Granatum Flower Extract 84961-57-9 (generic)	Punica Granatum Flower Extract is the extract of the flowers of *Punica granatum.*	Skin-Conditioning Agent – Misc.
Punica Granatum Fruit Extract 84961-57-9 (generic)	Punica Granatum Fruit Extract is the extract of the fruit of *Punica granatum.*	Skin-Conditioning Agent – Misc.
Punica Granatum Fruit Juice 84961-57-9 (generic)	Punica Granatum Fruit Juice is the juice expressed from the fruit of the pomegranate, *Punica granatum.*	Flavoring Agent; Skin-Conditioning Agent – Misc.
Punica Granatum Fruit/Root/Stem Powder 84961-57-9 (generic)	Punica Granatum Fruit/Root/Stem Powder is the powder obtained from the finely ground fruit, roots, and stems of *Punica granatum.*	Antioxidants; Hair Conditioning Agent; Skin-Conditioning Agent – Misc.
Punica Granatum Fruit/Sucrose Ferment Filtrate	Punica Granatum Fruit/Sucrose Ferment Filtrate is a filtrate of the product obtained by the spontaneous fermentation of the fruit of *Punica granatum* and sucrose.	Antioxidants
Punica Granatum Fruit Water 84961-57-9 (generic)	Punica Granatum Fruit Water is an aqueous solution of the steam distillates obtained from the fruit of *Punica granatum*.	Flavoring Agent; Fragrance Ingredient; Skin-Conditioning Agent – Misc.
Punica Granatum Juice Extract 84961-57-9 (generic)	Punica Granatum Juice Extract is the extract of the juice of *Punica granatum*.	Skin-Conditioning Agent – Misc.
Punica Granatum Leaf Cell Extract 84961-57-9 (generic)	Punica Granatum Leaf Cell Extract is the extract of a culture of the leaf cells of *Punica granatum*.	Antioxidant; Skin Protectant
Punica Granatum Peel Extract 84961-57-9 (generic)	Punica Granatum Peel Extract is the extract of the peel of *Punica granatum*.	Antimicrobial Agent; Antioxidant; Cosmetic Astringent; Preservative; Skin-Conditioning Agent – Misc.
Punica Granatum Pericarp Extract 84961-57-9 (generic)	Punica Granatum Pericarp Extract is the extract of the pericarp of *Punica granatum*.	Skin-Conditioning Agent – Misc.
Punica Granatum Seed 84961-57-9 (generic)	Punica Granatum Seed is the seed of *Punica granatum*.	Abrasive; Bulking Agent; Skin-Conditioning Agent – Misc.
Punica Granatum Seed Cell Culture Lysate	Punica Granatum Seed Cell Culture Lysate is a lysate of a suspension of the cultured seed cells of *Punica granatum*.	Skin-Conditioning Agent – Misc.
Punica Granatum Seed Extract 84961-57-9 (generic)	Punica Granatum Seed Extract is the extract of the seeds of *Punica granatum*.	Skin-Conditioning Agent – Misc.
Punica Granatum Seed Powder 84961-57-9 (generic)	Punica Granatum Seed Powder is the powder obtained from the dried, ground seeds of *Punica granatum*.	Abrasive

‡ Ingredient has been deleted from the *Dictionary*, but uses are currently reported.

Table 2. Generic plant part definitions as they apply to pomegranate-derived ingredients.[1]

Plant Part	Definition
Bark	Tough protective covering of the woody stems and roots of trees and other woody perennial plants, consisting of cells produced by a cork cambium.
Callus Culture	An undifferentiated mass of cells produced through tissue culture
Flower	The reproductive shoot in flowering plants, usually with sepals, petals, stamens and pistil(s).
Fruit	Mature, ripened ovary of flowering plant, containing seeds
Juice	The liquid contained in the vegetative parts or fruits
Leaf	Flattened photosynthetic organs, attached to stems.
Pericarp	Fruit wall; ripened walls of a plant ovary/fruit, consists of exocarp (peel), mesocarp ("fruit") and endocarp (surrounds seed)
Root	Organ of a plant that absorbs and transports water and nutrients, lacks leaves and nodes, usually underground.
Seed	A propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm, or seed coat.
Stem	A slender or elongated structure that supports a plant or a plant part or plant organ.

Table 3. Phytochemical constituents of pomegranate extracts (mg/g of dry extract) [3,6,26-29]

	Flower Extract	Peel Extract	Seed Extract	Juice Extract	Leaf Extract	Stem Extract
Total phenolic content	336.51 (M)	276-413 (E) 190.27-298 (M) 185 (A)	2.57-73 (E) 0.65 (M)	12.4-23.8 (E) 0.094 (A) 0.057 (B)	87.81 (M) 70.00 (A)	52.92 (M)
Total flavonoid content	213.54 (M)	36-54 (E) 49.8-80.10 (M) 23.05 (A)	7.55-38.0 (E) 0.33 (M)	1.8-8.7 (E) 0.46 (A) 0.22 (B)	63.89 (M) 50.43 (A)	41.36 (M)
Total flavonol content		25-45 (E) 0.39-0.44 (A)	3.4-22 (E)	1.5-2.0 (E)		
Total proanthocyanidin content	1.46 (M)	2.48-14.09 (M) 9.09 (A)	0.13 (M)		0.21 (M)	0.32 (M)

Solvents: M = methanol, E = ethanol, A = water/aqueous, B = *n*-butanol

Table 4. Fatty acid composition (%) for pomegranate seed extract (ethanolic)[3]

Palmitic Acid	4.7
Stearic Acid	2.2
Oleic Acid	5.3
Vaccenic Acid	0.8
α-Linoleic Acid	8.8
α-Linolenic Acid	0.5
Gondoic Acid	0.5
Punicic Acid	73.7
α-Eleostearic Acid	1.6
Catalpic Acid	1.2

Table 5. Frequency (2020) and concentration of use (2017 and 2019) according to duration and type of exposure for *Punica granatum*-derived ingredients.[39-41]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Punica Granatum Extract*		**Punica Granatum Bark Extract**		**Punica Granatum Flower Extract**		**Punica Granatum Fruit Extract**	
Totals†	**334**	**0.00001-0.13**	**15**	**NR**	**5**	**0.0001**	**188**	**0.0000002-0.1**
Duration of Use								
Leave-On	235	0.00001-0.13	14	NR	4	NR	127	0.0000002-0.1
Rinse Off	98	0.0001-0.00085	1	NR	1	0.0001	59	0.000005-0.1
Diluted for (Bath) Use	1	NR	NR	NR	NR	NR	2	0.0005
Exposure Type								
Eye Area	18	0.001	1	NR	NR	NR	20	0.000005-0.018
Incidental Ingestion	13	NR	NR	NR	NR	NR	2	0.0005-0.02
Incidental Inhalation-Spray	2; 79[a]; 69[b]	0.00001-0.001; 0.00001-0.003[a]	3[a]; 9[b]	NR	2[b]	NR	38[a]; 52[b]	0.00002-0.0005; 0.00002-0.02[a]
Incidental Inhalation-Powder	7; 69[b]	0.02-0.1[c]	9[b]	NR	2[b]	NR	52[b]	0.005; 0.0002-0.1[c]
Dermal Contact	256	0.001-0.13	12	NR	4	NR	162	0.0000002-0.1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.0005
Hair - Non-Coloring	55	0.00001-0.1	2	NR	1	0.0001	20	0.00002-0.1
Hair-Coloring	8	NR	NR	NR	NR	NR	NR	NR
Nail	2	NR	NR	NR	NR	NR	NR	0.00001-0.001
Mucous Membrane	26	NR	NR	NR	NR	NR	17	0.0005-0.02
Baby Products	2	NR	1	NR	NR	NR	NR	0.000005
	Punica Granatum Fruit Juice		**Punica Granatum Fruit Water**		**Punica Granatum Juice Extract**		**Punica Granatum Pericarp Extract**	
Totals†	**86**	**0.0001-0.1**	**15**	**NR**	**6**	**0.005**	**5**	**0.0000002-0.1**
Duration of Use								
Leave-On	68	0.01-0.1	9	NR	3	NR	4	0.0000002-0.005
Rinse Off	18	0.0001	6	NR	2	0.005	1	0.01-0.1
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR	NR	NR
Exposure Type								
Eye Area	9	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	3	NR	NR	NR	NR	NR	3	NR
Incidental Inhalation-Spray	27[a]; 23[b]	NR	9[a]	NR	1[a]; 1[b]	NR	1[b]	0.00002; 0.00002-0.005[a]
Incidental Inhalation-Powder	23[b]	0.01	NR	NR	1[b]	NR	1[b]	NR
Dermal Contact	75	0.01-0.1	15	NR	5	0.005	2	0.0000002-0.01
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	8	0.0001	NR	NR	NR	NR	NR	0.00002-0.1
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	8	NR	NR	NR	2	NR	3	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

Table 5. Frequency (2020) and concentration of use (2017 and 2019) according to duration and type of exposure for *Punica granatum*-derived ingredients.[39-41]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Punica Granatum Seed		**Punica Granatum Seed Extract**		**Punica Granatum Seed Powder**			
Totals†	**5**	**NR**	**2**	**0.01-0.3**	**6**	**0.01**		
Duration of Use								
Leave-On	3	NR	2	0.01-0.3	4	NR		
Rinse Off	2	NR	NR	NR	1	0.01		
Diluted for (Bath) Use	NR	NR	NR	NR	1	0.01		
Exposure Type								
Eye Area	NR	NR	1	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	0.11	NR	NR		
Incidental Inhalation-Spray	3[a]	NR	1[a]	NR	1[a]; 2[b]	NR		
Incidental Inhalation-Powder	NR	NR	NR	NR	2[b]	NR		
Dermal Contact	5	NR	2	0.01	6	0.01		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR		
Hair-Coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	0.3	NR	NR		
Mucous Membrane	2	NR	NR	0.11	1	0.01		
Baby Products	NR	NR	NR	NR	NR	NR		

NR = Not reported.

***** Uses are reported in the VCRP and concentration of use survey under this non-INCI name

† 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.

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

[b.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

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

Table 6. Ingredients not reported in use.[39-41]

Punica Granatum Bark/Fruit Extract
Punica Granatum Callus Culture Extract
Punica Granatum Fruit/Root/Stem Powder
Punica Granatum Fruit/Sucrose Ferment Filtrate
Punica Granatum Leaf Cell Extract
Punica Granatum Peel Extract
Punica Granatum Seed Cell Culture Lysate

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2020 FDA VCRP Raw Data

PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	01A	Baby Shampoos	1
PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	03F	Mascara	1
PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	05I	Other Hair Preparations	1
PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	12C	Face and Neck (exc shave)	8
PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	12D	Body and Hand (exc shave)	1
PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	12F	Moisturizing	2
PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	12G	Night	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	01A	Baby Shampoos	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	01C	Other Baby Products	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	02D	Other Bath Preparations	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	03C	Eye Shadow	2
PUNICA GRANATUM (POMEGRANATE) EXTRACT	03D	Eye Lotion	9
PUNICA GRANATUM (POMEGRANATE) EXTRACT	03G	Other Eye Makeup Preparations	7
PUNICA GRANATUM (POMEGRANATE) EXTRACT	04A	Cologne and Toilet waters	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	04E	Other Fragrance Preparation	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	05A	Hair Conditioner	20
PUNICA GRANATUM (POMEGRANATE) EXTRACT	05E	Rinses (non-coloring)	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	05F	Shampoos (non-coloring)	20
PUNICA GRANATUM (POMEGRANATE) EXTRACT	05G	Tonics, Dressings, and Other Hair Grooming Aids	8
PUNICA GRANATUM (POMEGRANATE) EXTRACT	05I	Other Hair Preparations	5
PUNICA GRANATUM (POMEGRANATE) EXTRACT	06A	Hair Dyes and Colors (all types requiring caution statements and patch tests)	3
PUNICA GRANATUM (POMEGRANATE) EXTRACT	06C	Hair Rinses (coloring)	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	06D	Hair Shampoos (coloring)	4
PUNICA GRANATUM (POMEGRANATE) EXTRACT	07A	Blushers (all types)	3
PUNICA GRANATUM (POMEGRANATE) EXTRACT	07B	Face Powders	7

PUNICA GRANATUM (POMEGRANATE) EXTRACT	07C	Foundations	3
PUNICA GRANATUM (POMEGRANATE) EXTRACT	07E	Lipstick	11
PUNICA GRANATUM (POMEGRANATE) EXTRACT	07I	Other Makeup Preparations	3
PUNICA GRANATUM (POMEGRANATE) EXTRACT	08A	Basecoats and Undercoats	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	08G	Other Manicuring Preparations	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	09C	Other Oral Hygiene Products	2
PUNICA GRANATUM (POMEGRANATE) EXTRACT	10A	Bath Soaps and Detergents	6
PUNICA GRANATUM (POMEGRANATE) EXTRACT	10E	Other Personal Cleanliness Products	6
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12A	Cleansing	22
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12C	Face and Neck (exc shave)	48
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12D	Body and Hand (exc shave)	21
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12F	Moisturizing	38
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12G	Night	9
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12H	Paste Masks (mud packs)	12
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12I	Skin Fresheners	5
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12J	Other Skin Care Preps	32
PUNICA GRANATUM (POMEGRANATE) EXTRACT	13A	Suntan Gels, Creams, and Liquids	1
PUNICA GRANATUM (POMEGRANATE) EXTRACT	13B	Indoor Tanning Preparations	18
PUNICA GRANATUM (POMEGRANATE) FLOWER EXTRACT	05A	Hair Conditioner	1
PUNICA GRANATUM (POMEGRANATE) FLOWER EXTRACT	12C	Face and Neck (exc shave)	2
PUNICA GRANATUM (POMEGRANATE) FLOWER EXTRACT	12J	Other Skin Care Preps	2
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	02B	Bubble Baths	2
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	03A	Eyebrow Pencil	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	03C	Eye Shadow	6
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	03D	Eye Lotion	4
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	03F	Mascara	2

PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	03G	Other Eye Makeup Preparations	7
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	05A	Hair Conditioner	9
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	05F	Shampoos (non-coloring)	8
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	05G	Tonics, Dressings, and Other Hair Grooming Aids	2
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	05I	Other Hair Preparations	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	07C	Foundations	2
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	07E	Lipstick	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	07I	Other Makeup Preparations	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	09C	Other Oral Hygiene Products	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	10A	Bath Soaps and Detergents	7
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	10C	Douches	2
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	10E	Other Personal Cleanliness Products	4
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	11G	Other Shaving Preparation Products	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12A	Cleansing	14
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12C	Face and Neck (exc shave)	42
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12D	Body and Hand (exc shave)	10
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12F	Moisturizing	28
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12G	Night	4
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12H	Paste Masks (mud packs)	13
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12I	Skin Fresheners	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12J	Other Skin Care Preps	12
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	13B	Indoor Tanning Preparations	3
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	03D	Eye Lotion	7
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	03G	Other Eye Makeup Preparations	2
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	05A	Hair Conditioner	3
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	05E	Rinses (non-coloring)	1

PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	05F	Shampoos (non-coloring)	1
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	05G	Tonics, Dressings, and Other Hair Grooming Aids	2
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	05I	Other Hair Preparations	1
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	07C	Foundations	1
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	07E	Lipstick	1
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	07F	Makeup Bases	1
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	09A	Dentifrices	1
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	09B	Mouthwashes and Breath Fresheners	1
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	10A	Bath Soaps and Detergents	5
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	12A	Cleansing	4
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	12C	Face and Neck (exc shave)	14
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	12D	Body and Hand (exc shave)	9
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	12F	Moisturizing	14
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	12G	Night	7
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	12H	Paste Masks (mud packs)	2
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	12J	Other Skin Care Preps	6
PUNICA GRANATUM (POMEGRANATE) FRUIT JUICE	13B	Indoor Tanning Preparations	3
PUNICA GRANATUM (POMEGRANATE) FRUIT WATER	12A	Cleansing	6
PUNICA GRANATUM (POMEGRANATE) FRUIT WATER	12F	Moisturizing	9
PUNICA GRANATUM (POMEGRANATE) JUICE EXTRACT	01B	Baby Lotions, Oils, Powders, and Creams	1
PUNICA GRANATUM (POMEGRANATE) JUICE EXTRACT	02D	Other Bath Preparations	1
PUNICA GRANATUM (POMEGRANATE) JUICE EXTRACT	10C	Douches	1
PUNICA GRANATUM (POMEGRANATE) JUICE EXTRACT	12A	Cleansing	1
PUNICA GRANATUM (POMEGRANATE) JUICE EXTRACT	12C	Face and Neck (exc shave)	1
PUNICA GRANATUM (POMEGRANATE) JUICE EXTRACT	12J	Other Skin Care Preps	1

PUNICA GRANATUM (POMEGRANATE) PERICARP EXTRACT	07E	Lipstick	3
PUNICA GRANATUM (POMEGRANATE) PERICARP EXTRACT	12A	Cleansing	1
PUNICA GRANATUM (POMEGRANATE) PERICARP EXTRACT	12C	Face and Neck (exc shave)	1
PUNICA GRANATUM (POMEGRANATE) SEED	10A	Bath Soaps and Detergents	2
PUNICA GRANATUM (POMEGRANATE) SEED	12J	Other Skin Care Preps	3
PUNICA GRANATUM (POMEGRANATE) SEED EXTRACT	03G	Other Eye Makeup Preparations	1
PUNICA GRANATUM (POMEGRANATE) SEED EXTRACT	12F	Moisturizing	1
PUNICA GRANATUM (POMEGRANATE) SEED POWDER	02D	Other Bath Preparations	1
PUNICA GRANATUM (POMEGRANATE) SEED POWDER	12A	Cleansing	1
PUNICA GRANATUM (POMEGRANATE) SEED POWDER	12C	Face and Neck (exc shave)	2
PUNICA GRANATUM (POMEGRANATE) SEED POWDER	12F	Moisturizing	1
PUNICA GRANATUM (POMEGRANATE) SEED POWDER	12J	Other Skin Care Preps	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: December 3, 2019

SUBJECT: Draft Final Report: Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics (draft prepared for the December 2019 CIR Expert Panel meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics.

Key Issue

It is not clear why a NOEL for skin lightening effects is needed for Punica Granatum Seed Powder (for which abrasives is the only function listed). A published paper[1] not yet cited in the CIR report indicates that a pomegranate seed powder contains (mean of triplicate determinations) 5.82% moisture, 13.66% protein, 29.6% fat, 1.49% ash, 39.36% fiber, 13.12% carbohydrate and 0.25% phenolics.

Additional Considerations

Genotoxicity, In Vitro - For the chromosomal aberration study in CHO cells, it would be helpful to also state the highest concentrations at which no chromosomal aberrations were observed.

Skin Lightening, Human - It should also be noted that the formulation containing 4% concentrated pomegranate juice decreased skin erythema.

Summary - In the Summary, please state that the Punica Granatum Extract "defined as an extract of the whole plant" was removed from the Dictionary.

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[1]Rowayshed G, Salama A, Abul-Fadl M, et al. 2013. Nutritional and chemical evaluation for pomegranate (*Punica granatum* L.) fruit peel and seeds powders by products. *Middle East Journal of Applied Sciences*, 3(4): 169-179.

It would be helpful if the description of the rat sperm study in the Summary included the route of exposure, dose and duration. It should be made clear that improvements in sperm endpoints were observed in this study.

It would be helpful to include the doses/concentrations of pomegranate ingredients associated with effects on melanin production.

Discussion - For a complex mixture such as extracts from plants, the meaning of "chemical and biological properties" is not clear. Perhaps the CIR Expert Panel should consider if they have concerns for potential inhalation exposure based on composition of the pomegranate-derived ingredients.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 14, 2020

SUBJECT: Revised Tentative Report: Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics (release date: December 16, 2019)

The Personal Care Products Council respectfully submits the following comments on the revised tentative report, Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics.

Key Issues

The Discussion indicates that the mechanism of action for skin lightening is known, but this mechanism (inhibition of tyrosinase activity by polyphenols) is not mentioned in the CIR report.

It would be helpful if the paragraph in the Discussion on potential respiratory exposure was customized to the information in the report. For example, the Discussion currently includes a sentence to indicate that there is no concern from "droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract" based only on "the chemical and biological properties of these ingredients." This report includes a 35-day intranasal study of an ethanolic pomegranate fruit extract in rats (reference 66) that did not report any treatment-related effects. This study should be mentioned as supporting the safety of the fruit-derived ingredients in the nasopharyngeal region. As these ingredients are complex mixtures, the meaning of "chemical and biological properties" for these ingredients is not clear. Perhaps the determination of safety should be related to the composition of these ingredients.

Additional Considerations

Composition/Impurities, Punica Granatum Seed Powder - Please correct "13012%" (likely 13.12%)

Cosmetic Use; Summary; Table 5 - It should be made clear that the PCPC concentration of use survey was completed in 2017. In 2019, companies reporting use of the Punica Granatum Extract were asked to identify the plant part being used and corrections were made for

those companies that responded. The Cosmetic Use section and Table 5 indicate that the survey was completed in 2019, while the Summary states it was completed in 2018.

DART, Punica Granatum Fruit Juice - In the description of the study in male rats (reference 7), glutathione should not be included as an "antioxidant enzyme" as it is not an enzyme.

Genotoxicity, In Vitro, Punica Granatum Pericarp Extract - Please correct the strain "A100" to "TA100"; please correct "stu died" to "studied"

Discussion - Historically, ingredients from plants were named with common names only, e.g., Pomegranate Extract. Then Latin names and various plant parts were added to the name. The date of the Dictionary in which Punica Granatum Extract was defined as an extract of the whole plant should be stated. It is likely that the "original" definition of Pomegranate Extract was an extract of the fruit. Rather than suggesting that Punica Granatum Extract may be just an extract of the whole plant, the Discussion should also state that it may also represent extracts of specific plant parts such as the fruit or pericarp but the supplier is still using an older naming convention that did not include plant parts.