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

Status: Draft Tentative Report for Panel Review
Release Date: August 22, 2019
Panel Meeting Date: September 16-17, 2019

The 2019 Cosmetic Ingredient Review Expert Panel 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.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.



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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: August 22, 2019
Subject: Draft Tentative Safety Assessment on *Punica granatum*-Derived Ingredients

Enclosed is the Draft Tentative Report of the Safety Assessment of *Punica granatum*-Derived Ingredients as Used in Cosmetics. (It is identified as *pomegr092019rep* in the pdf document).

In 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.

Since the April Panel meeting, CIR has received the following data, which have been incorporated into the report and have been designated with highlighting (*pomegr092019data1* and *pomegr092019data2*).

- Method of manufacturing with solvent type for Punica Granatum Pericarp Extract
- Summary of an HRIPT on a leave-on product containing 0.1% Punica Granatum Fruit Extract

Additional composition data from the published literature have also been incorporated in the report and designated appropriately.

Comments provided by the Council prior to the April meeting on the draft report have been addressed (*pomegr092019pcpc*). Other supporting documents for this report package include a flow chart (*pomegr092019flow*), report history (*pomegr092019hist*), transcripts from the previous meeting (*pomegr092019min*), a search strategy (*pomegr092019strat*), and a data profile (*pomegr092019prof*).

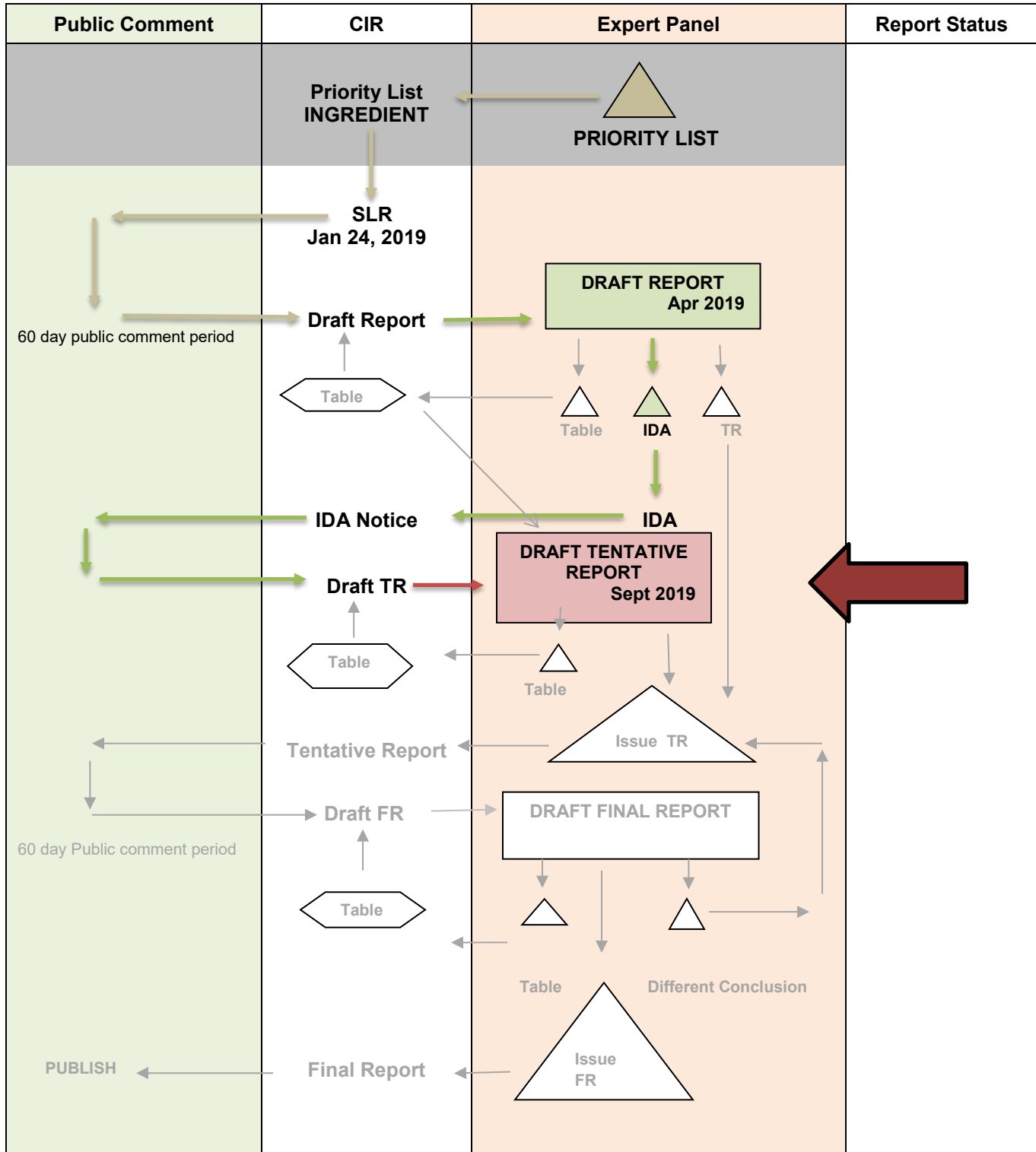
Based on the proceedings and comments from the April meeting, a draft Discussion with some points for the Panel to consider, including the outstanding data needs, has been included.

The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Punica granatum -Derived Ingredients

MEETING September 2019



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:

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Punica granatum-Derived Ingredients, September 2019 – 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

[illegible]

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 July 2019 – 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/fcnavigation.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/HPVISlogin>
- 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/>

Punica granatum-Derived Ingredients

April 8-9, 2019

Belsito's Team Meeting

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. LIEBLER: 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.

Dr. Marks' Team

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

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 mashed 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.

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

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The 2019 Cosmetic Ingredient Review Expert Panel 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.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

DRAFT ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (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. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Industry should continue to use good manufacturing practices to limit impurities that could be present in botanical ingredients. The Panel concluded that ...[to be determined].

INTRODUCTION

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

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

It should be noted that Punica Granatum Extract 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. 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 yet 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, CIR is not evaluating these claims as these are not related to the safety of the use of these ingredients in cosmetic products.³⁻⁸ There are no publicly available toxicity data that correspond to any one of these cosmetic ingredients, specifically. The Panel has previously reviewed the safety 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

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. Additionally, 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. 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, some of which may have the potential to cause toxic effects. In this assessment, CIR is reviewing the potential toxicity of each of the *Punica granatum*-derived ingredients as a whole, complex mixture. CIR 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 CIR typically evaluates, is provided on the 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 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 to 10 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 tough, leathery skin 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.

Physical Properties

Punica Granatum Fruit Extract

A 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 - 7.5.¹³

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 20° C) of 1.176 - 1.232 g/ml.¹⁴ 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 - 1.1.¹⁵

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.¹⁶ 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.

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.¹⁵

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 °C.¹⁷ 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 °C.¹⁸

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.¹⁹

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.^{20,21} Specifically, the triterpenes ursolic acid and oleanolic acid are reported to be constituents of pomegranate leaves, bud, fruits, flowers and seeds.²² 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.²³ 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).²³ 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.^{4,5,24} 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.^{3,6,25-28}

Punica Granatum Flower Extract

The tannin content of a pomegranate flower extract used in a wound healing efficacy study was 48.7%.²⁹ The test material was extracted with ethanol. Analyses of methanol extracts of a flower extract characterized a total of 57 phenolic compounds.³⁰

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.³¹ 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.³⁰

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.³² 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.¹³

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.³³

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.³⁴ 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.³⁵

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.¹⁵ 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.³⁶ 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).

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*, 2019 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 312; the majority of the uses are in leave-on skin care products (Table 5).³⁷ Punica Granatum Fruit Extract has the second greatest number of reported uses in this safety assessment with 172 uses; the majority of these uses are also in leave-on skin care products. The results of the concentration of use survey conducted in 2019 by the Council indicated that Punica Granatum Seed Extract is used at up to 0.3% (in leave-on cuticle softeners).³⁸ Punica Granatum Extract and Punica Granatum Fruit Extract are used at up to 0.13% (in a moisturizing preparation) 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%.³⁹ 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.⁴⁰⁻⁴³ 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.^{40,41} 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.⁴⁴⁻⁴⁶

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.⁴⁷

Non-Cosmetic

In the US, according to 21CFR182.20 and 21CFR582.20, 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.

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.^{3,4,8,22,26,29,33,35,36,48-58} The juice and peel extracts have also been researched for use as antifungal and antibacterial treatments.⁵⁹⁻⁶³

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.³¹ The oral LD₅₀ 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 LD₅₀ for a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) was greater than 2000 mg/kg in mice.¹⁵ 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.³⁶ Doses were 2, 3, or 5 g/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.⁶¹ 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.⁶⁴ 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) 408.³¹ 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.³¹

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.⁶⁵ 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 ≥ 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.⁶⁶ 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.⁶⁶

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 enzyme 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.⁶⁵ The extract was tested at 0, 0.45, 1, 2, and 4 mg/plate. 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) did not induce gene-conversion events in *Saccharomyces cerevisiae* strain D7, but an increased frequency of reverse mutations was observed, with and without metabolic activation.⁶⁵ The yeast cells were treated with the extract at concentrations up to 18 mg/ml.

In Chinese hamster ovary (CHO) cell tested with and without metabolic activation at concentrations up to 450 µg/ml of a hydroalcoholic pomegranate fruit extract, a dose-dependent and statistically significant increase in sister chromatid exchanges per cell was observed; increases were observed with concentrations of ≥ 110 µg/ml ($p < 0.05$) in the absence of S9 metabolic activation.⁶⁵ Significant increases in the percentage of chromosomal aberrations were also observed with ≥ 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 sinesis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was studied in an Ames test using *S. typhimurium* strains TA98, A100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA, with and without metabolic activation.⁶⁷ 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.¹⁵ 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, a dose-dependent increase in the number of polychromatic erythrocytes with micronuclei was observed.⁶⁵ 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). The genotoxicity index increase was statistically significant at doses ≥ 70 mg/kg bw in both sexes. The cytotoxicity index was significantly increased at doses of ≥ 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 genotoxin cyclophosphamide (CPH).²⁸ Another two groups of 6 mice served as genotoxin 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.⁶⁸ 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 μ g/ml and 100 μ g/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 μ g/ml, 60 μ g/ml, and 100 μ g/ml, respectively.

Punica Granatum Peel Extract

An aqueous pomegranate extract of rind containing 90% ellagic acid showed inhibitory activity against mushroom tyrosinase (IC₅₀ 182.2 μ g/ml) in vitro.⁶⁹ The inhibition effects were comparable to arbutin (IC₅₀ 162.2 μ g/ml), but was about ten times weaker than L-ascorbic acid (IC₅₀ 18.4 μ g/ml).

Animal

Punica Granatum Peel Extract

Ultraviolet-B (UV-B) light-induced skin pigmentation was inhibited in female brownish guinea pigs after the animals received aqueous pomegranate extract orally for 35 days.⁶⁹ 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 vitro study and the in vivo 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

Significant decreases (details not provided) in skin melanin content were observed in a study of a water/oil emulsion containing 4% concentrated pomegranate juice.⁷⁰ The test material (amount not reported) was applied daily to the cheeks of 25 healthy volunteers for 60 days. A Mexameter® was used to measure the melanin on the cheeks of the volunteers on the day prior to application and on weeks 1 - 4, 6, and 8.

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% *Camillia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was predicted to be non-irritating in an EpiDerm™ reconstructed human epidermal model.⁷¹ 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.⁷⁰ The test material (amount not reported) was applied daily to the cheeks.

Sensitization

In Vitro/In Chemico

Punica Granatum Pericarp Extract

A tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camillia 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.⁷² 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.⁷³ 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.¹⁵ 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.⁷⁴ 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.

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 patch test using 44 subjects.¹⁵ No further details were provided.

The same supplier reported that the above tradename mixture, when tested at 30%, was also negative in a HRIPT using 52 subjects.¹⁵ 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.¹⁵ 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% *Camillia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was predicted to be non-irritating in an EpiOcular™ cornea epithelial model.⁷¹ 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.¹⁵ 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 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. There are no publicly available toxicity data that corresponds to any one of these cosmetic ingredients, specifically. 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.

According to 2019 VCRP survey data, Punica Granatum Extract has the most reported uses in cosmetic products, with a total of 312; 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 172 uses; the majority of these uses are also in leave-on skin care products. The results of the concentration of use survey conducted in 2018 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 a moisturizing preparation) 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 LD₅₀ 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 LD₅₀ 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 \geq 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 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 pomegranate juice consumption 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 μ g/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.

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 study of an emulsion containing 4% concentrated pomegranate juice, no dermal irritation was observed following daily application to the cheeks. Sensitization was not predicted in in vitro and in chemico assays of a tradename mixture containing 10% Punica Granatum Pericarp Extract. 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.

DRAFT DISCUSSION

This discussion below is in draft form and may be modified.

The botanical ingredients in this report are each a mixture of constituents derived from the plant, *Punica granatum*. Because final product formulations may contain multiple botanical ingredients, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. When formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

The Panel also expressed concern about pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

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%. There were no inhalation toxicity data available. 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 based on the chemical and biological properties of these ingredients. 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 products is available at <https://www.cir-safety.org/cir-findings>.

The additional data needed for these cosmetic ingredients are:

- 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.

CONCLUSION

To be determined.

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, <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Flower Extract 84961-57-9 (generic)	Punica Granatum Flower Extract is the extract of the flowers of <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Fruit Extract 84961-57-9 (generic)	Punica Granatum Fruit Extract is the extract of the fruit of <i>Punica granatum</i> .	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, <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	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 <i>Punica granatum</i> 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 <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	Antioxidant; Skin Protectant
Punica Granatum Peel Extract 84961-57-9 (generic)	Punica Granatum Peel Extract is the extract of the peel of <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Seed 84961-57-9 (generic)	Punica Granatum Seed is the seed of <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Seed Extract 84961-57-9 (generic)	Punica Granatum Seed Extract is the extract of the seeds of <i>Punica granatum</i> .	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 <i>Punica granatum</i> .	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)^{3,6,25-28}

	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. 2019 frequency and concentration of use according to duration and type of exposure for <i>Punica granatum</i>-derived ingredients. ^{37,38}						
	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>
	Punica Granatum Extract*		Punica Granatum Bark Extract		Punica Granatum Flower Extract	Punica Granatum Fruit Extract
Totals†	312	0.00001-0.13	13	NR	5	0.0001
Duration of Use						
Leave-On	219	0.00001-0.13	12	NR	4	NR
Rinse Off	92	0.0001-0.00085	1	NR	1	0.0001
Diluted for (Bath) Use	1	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	20	0.001	1	NR	NR	NR
Incidental Ingestion	13	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2; 73 ^a ; 62 ^b	0.00001-0.001; 0.00001-0.003 ^a	2 ^a ; 8 ^b	NR	2 ^b	NR
Incidental Inhalation-Powder	7; 62 ^b	0.02-0.1 ^c	8 ^b	NR	2 ^b	NR
Dermal Contact	238	0.001-0.13	10	NR	4	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	53	0.00001-0.1	2	NR	1	0.0001
Hair-Coloring	8	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	24	NR	NR	NR	NR	NR
Baby Products	2	NR	1	NR	NR	NR
	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
Duration of Use						
Leave-On	68	0.01-0.1	9	NR	3	NR
Rinse Off	18	0.0001	6	NR	2	0.005
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR
Exposure Type						
Eye Area	9	NR	NR	NR	NR	NR
Incidental Ingestion	3	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	27 ^a ; 23 ^b	NR	9 ^a	NR	1 ^a ; 1 ^b	NR
Incidental Inhalation-Powder	23 ^b	0.01	NR	NR	1 ^b	NR
Dermal Contact	75	0.01-0.1	15	NR	5	0.005
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	8	0.0001	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	8	NR	NR	NR	2	NR
Baby Products	NR	NR	NR	NR	1	NR

Table 5. 2019 frequency and concentration of use according to duration and type of exposure for <i>Punica granatum</i>-derived ingredients. ^{37,38}						
	<i># of Uses</i> <i>Max Conc of Use (%)</i>		<i># of Uses</i> <i>Max Conc of Use (%)</i>		<i># of Uses</i> <i>Max Conc of Use (%)</i>	
	Punica Granatum Seed		Punica Granatum Seed Extract		Punica Granatum Seed Powder	
Totals[†]	3	NR	1	0.01-0.3	6	0.01
<i>Duration of Use</i>						
Leave-On	3	NR	1	0.01-0.3	4	NR
Rinse Off	NR	NR	NR	NR	1	0.01
Diluted for (Bath) Use	NR	NR	NR	NR	1	0.01
<i>Exposure Type</i>						
Eye Area	NR	NR	1	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.11	NR	NR
Incidental Inhalation-Spray	3 ^a	NR	NR	NR	2 ^a ; 2 ^b	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	2 ^b	NR
Dermal Contact	3	NR	1	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	NR	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.**^{37,38}

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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2019 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)	7
PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	12D - Body and Hand (exc shave)	1
PUNICA GRANATUM (POMEGRANATE) BARK EXTRACT	12F - Moisturizing	1
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	4
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)	19
PUNICA GRANATUM (POMEGRANATE) EXTRACT	05G - Tonics, Dressings, and Other Hair Grooming Aids	7
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	09C - Other Oral Hygiene Products	2
PUNICA GRANATUM (POMEGRANATE) EXTRACT	10A - Bath Soaps and Detergents	4
PUNICA GRANATUM (POMEGRANATE) EXTRACT	10E - Other Personal Cleanliness Products	6
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12A - Cleansing	21
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12C - Face and Neck (exc shave)	41
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12D - Body and Hand (exc shave)	21
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12F - Moisturizing	34
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12G - Night	9
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12H - Paste Masks (mud packs)	10
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12I - Skin Fresheners	4
PUNICA GRANATUM (POMEGRANATE) EXTRACT	12J - Other Skin Care Preps	29
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	5
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	03F - Mascara	2
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	03G - Other Eye Makeup Preparations	6
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	05A - Hair Conditioner	6
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	05F - Shampoos (non-coloring)	7
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
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	07F - Makeup Bases	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	07I - Other Makeup Preparations	2
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	13
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12C - Face and Neck (exc shave)	39
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12D - Body and Hand (exc shave)	9
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12F - Moisturizing	24

PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12G - Night	4
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12H - Paste Masks (mud packs)	11
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12I - Skin Fresheners	1
PUNICA GRANATUM (POMEGRANATE) FRUIT EXTRACT	12J - Other Skin Care Preps	10
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	12J - Other Skin Care Preps	3
PUNICA GRANATUM (POMEGRANATE) SEED EXTRACT	03G - Other Eye Makeup Preparations	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
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Memorandum

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

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

DATE: April 18, 2019

SUBJECT: Punica Granatum Pericarp Extract

CEP - Solabia Group. 2012. Ingredient breakdown Pomegranate Milk 1.5PS (Water, Punica Granatum Pericarp Extract, Propylene Glycol Dicaprylate/Dicaprate, Phenoxyethanol, Xanthan Gum, Potassium Sorbate).

CEP - Solabia Group. 2012. Ingredient breakdown Glycolysat BG of Pomegranate UP (Butylene Glycol, Water, Punica Granatum Pericarp Extract).

Pomegranate Milk 1.5PS
Lait de Grenade 1,5PS

Ref. FL542

Water.....	91.90 %
Punica granatum pericarp extract.....	3.10 %
<i>3g under halogen, 1 hour at 110°C</i> <i>(water is the extraction solvent)</i>	
Propylene glycol dicaprylate / dicaprinate.....	2.90 %
Phenoxyethanol.....	1.50 %
Xanthan gum	0.30 %
Potassium sorbate.....	0.30 %

Notes - Remarques :

- Because of the natural origin of the raw material, the centesimal composition is susceptible to slight variations.

En raison de l'origine naturelle des matières premières, la composition centésimale est susceptible de subir une légère variation.

Glycolysat[®] BG of Pomegranate UP
Glycolysat[®] BG de Grenade UP

Ref. FG309

Butylene glycol 68.50 %

Water 29.00 %

Punica granatum pericarp extract 2.50 %
3g under halogen, 1 hour at 110°C.

(hydroglycolic extract from the dry pericarp)
(propylene glycol and water are used as the extraction solvents)

Notes - Remarques :

- Because of the natural origin of the raw material, the centesimal composition is susceptible to slight variations.

En raison de l'origine naturelle des matières premières, la composition centésimale est susceptible de subir une légère variation.



Memorandum

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

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

DATE: April 24, 2019

SUBJECT: Punica Granatum Fruit Extract

Anonymous. 2019. Summary of an HRIPT of a leave-on product containing 0.1% Punica Granatum Fruit Extract.

April 2019

Summary of an HRIPT of a Leave-on Product Containing 0.1% Punica Granatum Fruit Extract

- Completed in 2012
- 100 subjects completed the study
- Open patch conditions and 0.2 gram of test material was applied directly to the subject's back and allowed to air dry
- Induction phase consisted of a series of 9 x 24-hour applications over three consecutive weeks (Monday, Wednesday and Friday of each week); 2 weeks rest period; challenged dose of 0.2g of test material on naïve site under open patch conditions with scorings made at 24 and 48 hour post challenged dose
- No adverse reactions scored during the process. Test material considered as non-primary irritant and non-primary sensitizer.



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: March 27, 2019

SUBJECT: Draft Report: Safety Assessment of *Punica granatum*-Derived Ingredients as Used in Cosmetics (draft prepared for the April 8-9, 2019 CIR Expert Panel meeting)

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

Key Issues

The CIR report should state that Punica Granatum Extract defined as an extract of the “whole plant” has been deleted as an INCI name. Trade names included under this name have been moved to the INCI names Punica Granatum Fruit Extract or Punica Granatum Pericarp Extract.

Although reference 15 (information on Punica Granatum Pericarp Extract submitted by the Council on March 4, 2019) did not state the amount of Punica Granatum Pericarp Extract in the trade name mixture, it did state that the mixture contained 0.5% solids. When describing information from this reference (multiple place in the report including the Summary), rather than stating “concentration not stated”, it should state “0.5% solids”.

Additional Considerations

Introduction - Although the fruit is used as food, is there any evidence that pomegranate flowers, bark and roots are used as food? Rather than stating that “The pomegranate ingredients in this assessment are found in foods...”, perhaps it would be better to be more specific and state that the fruit is used as food.

Introduction - As there are no individual constituents under review in this report, is the following sentence needed in the Introduction? “CIR is not reviewing the potential toxicity of the individual constituents, except wherein such constituents are also ingredients under review.”

Acute Toxicity; Subchronic - Although the extraction solvent is not stated in reference 24, it does state that the fruit extract was standardized to contain 70% polyphenols including 30% punicalagins. This composition, rather than “solvent not reported” should be stated.

Genotoxicity, In Vitro, Punica Granatum Fruit Extract; Summary - Concentrations/doses that did not result in a genotoxic effect should be clearly stated.

Summary - The doses/concentrations that did not cause abnormal sperm or genotoxic effects should also be stated. The gestation days of treatment in the mouse study should be stated in the Summary.

Table I - A reference should be associated with this table.

Reference 58 - Please correct “while” to “whole”