Safety Assessment of Soy-Derived Ingredients as Used in Cosmetics

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

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

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Priya Cherian, Scientific Analyst/Writer, CIR

Date: May 15, 2020

Subject: Draft Final Report on Soy-Derived ingredients

Enclosed is the Draft Final Report on 28 soy-derived ingredients (identified by *soy062020rep* in the pdf document). At the December 2019 meeting, the Expert Panel for Cosmetic Ingredient Safety (Panel) issued a Tentative Report with the conclusion that 24 of the 28 soy-derived ingredients are safe in the present practices of use and concentration described in the safety assessment. However, the Panel determined that there were insufficient data to determine the safety of the remaining 4 ingredients. The insufficiencies include a lack of composition, impurities, method of manufacture, 28-day dermal toxicity, and sensitization/irritation data.

Comments on the Draft Tentative and Tentative Report were submitted by Council, and have been addressed (*soy062020pcpc_1* and *soy062020pcpc_2*, respectively). Other documents in this packet include report history (*soy062020hist*), flow chart (*soy062020flow*), search strategy (*soy062020strat*), minutes from previous meetings (*soy062020min*), and data profile (*soy062020prof*). Updated 2020 FDA VCRP data have also been provided. According to these data, Glycine Soja (Soybean) Sprout Extract (listed as Glycine Max (Soybean) Sprout Extract), is now reported to be in use.

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

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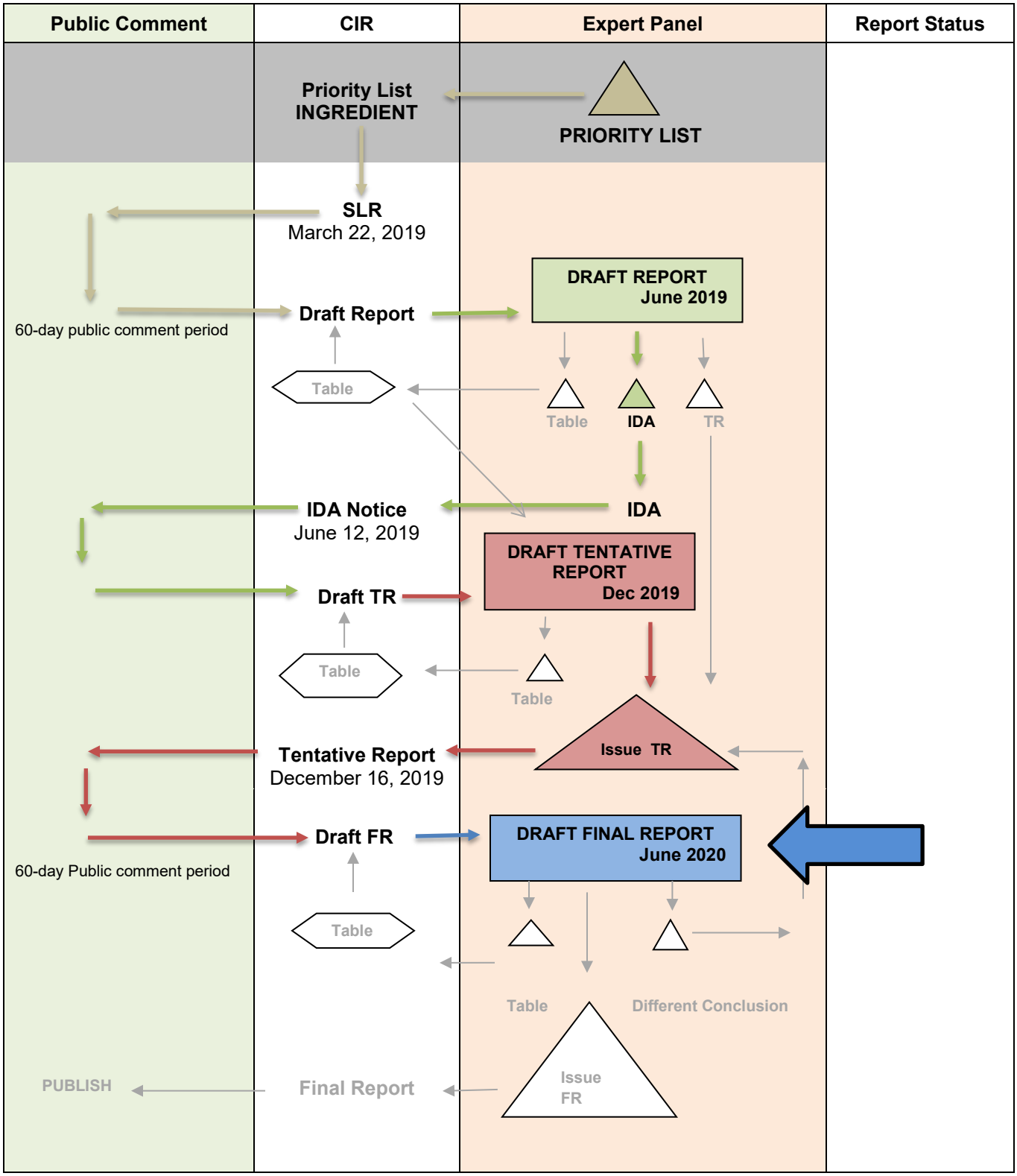
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Soy-Derived Ingredients

MEETING June 2020



CIR History of:

Soy-Derived Ingredients

February 2019

A Scientific Literature Review (SLR) on the Soy-derived ingredients was issued on February 14, 2019. Unpublished data were received from the Council after announcement of the SLR.

March 2019

The following unpublished data were received from council:

-specifications of a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract
-list of limitations on possible allergens of a trade name mixture containing Glycine (Soja) Phytoplacenta Extract
-method of manufacturing information on a trade name mixture containing Glycine (Soja) Phytoplacenta Extract
-cell viability assay on a trade name mixture containing Glycine (Soja) Phytoplacenta Extract

April 2019

-unpublished data was received from Council regarding an HRIPT on a leave-on product containing 0.3% Glycine Soja (Soybean) Germ Extract

-unpublished data received from Council regarding a 48-hour patch test and an in vitro ocular irritation assay on a mixture consisting of water and Glycine Soja (Soybean) Seedcake Extract (13%)

-Draft report was revised to include the unpublished data from Council

June 2019

-Expert Panel reviews the Draft Report
-An Insufficient Data Announcement (IDA) was issued, the following are the insufficiencies:
-sensitization data on either Glycine Max or Glycine Soja (Soybean) Seed Extract at the current maximum use concentration of 2%
-composition, method of manufacture, or general characteristics of the callus ingredients
-Unpublished data received from Council regarding an HRIPT on a skin care product containing 0.198% Glycine Soja (Soybean) Seed Extract

August 2019

-Unpublished data received from Council regarding an HRIPT on a leave-on product containing 3% Glycine Soja (Soybean) Seed Extract

December 2019

-Expert Panel reviews Draft Tentative Report
-Expert Panel issues a Tentative Report for public comment

January 2020

-2020 FDA VCRP data received
-comments on Tentative Report received from Council

June 2020

-Expert Panel reviews Draft Final Report

Soy-Derived Ingredients Data Profile* – June 2020 – Priya Cherian

						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
Glycine Max (Soybean) Callus Culture																													
Glycine Max (Soybean) Callus Culture Extract																													
Glycine Max (Soybean) Callus Extract																													
Glycine Max (Soybean) Fiber																													
Glycine Max (Soybean) Flower/Leaf/Stem Juice																													
Glycine Max (Soybean) Leaf Cell Extract			**X**																										
Glycine Max (Soybean) Phytoplacenta Conditioned Media																													
Glycine Max (Soybean) Phytoplacenta Extract	**X**				X																								
Glycine Max (Soybean) Pulp			**X**	X																									
Glycine Max (Soybean) Seed Extract	**X**																												
Glycine Max (Soybean) Seedcake Extract																						x					x		
Glycine Max (Soybean) Seedcoat Extract			**X**	X					X			X																	
Glycine Max (Soybean) Seed Powder																													
Glycine Max (Soybean) Sprout Extract			**X**																			X					X		
Glycine Soja (Soybean) Extract	**X**		**X**	X			X					X										X							X
Glycine Soja (Soybean) Fiber																													
Glycine Soja (Soybean) Flour	**X**		**X**									X																	
Glycine Soja (Soybean) Germ Extract	**X**			X																				X					
Glycine Soja (Soybean) Hull																													
Glycine Soja (Soybean) Lipids	**X**																												
Glycine Soja (Soybean) Phytoplacenta Extract			**X**																										
Glycine Soja (Soybean) Seed	**X**																												
Glycine Soja (Soybean) Seedcake Extract																													
Glycine Soja (Soybean) Seed Extract	**X**																							X					
Glycine Soja (Soybean) Seed Powder																													

Glycine Soja (Soybean) Seed Water																															
Gylcine Soja (Soybean) Sprout Extract																															

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

[Soy-Derived Ingredients]

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Glycine Max (Soybean) Callus Culture		X	X				X													
Glycine Max (Soybean) Callus Culture Extract		X					x													
Glycine Max (Soybean) Callus Extract		X	X				x													
Glycine Max (Soybean) Fiber		X	X	X			x													
Glycine Max (Soybean) Flower/Leaf/Stem juice		X					x													
Glycine Max (Soybean) Leaf Cell Extract		X					x													
Glycine Max (Soybean) Leaf Extract		X		X			x													
Glycine Max (Soybean) Phytoplacenta Conditioned Media		X					x													
Glycine Max (Soybean) Phytoplacenta Extract		X					x													
Glycine Max (Soybean) Pulp		X	X				x													
Glycine Max (Soybean) Seedcake Extract		X					x													
Glycine Max (Soybean) Seedcoat Extract		X		X			x													
Glycine Max (Soybean) Seed Powder		X					x													
Glycine Max (Soybean) Sprout Extract		X	X	X			x													

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Glycine Soja (Soybean) Extract		X		X			x													
Glycine Soja (Soybean) Fiber		X					x													
Glycine Soja (Soybean) Flour	68513-95-1	X		X			x													
Glycine Soja (Soybean) Germ Extract		X					x													
Glycine Soja (Soybean) Hull		X					x													
Glycine Soja (Soybean) Lipids		X					x													
Glycine Soja (Soybean) Phytoplacenta Extract		X					x													
Glycine Soja (Soybean) Seed		X					x													
Glycine Soja (Soybean) Seedcake Extract		X					x													
Glycine Soja (Soybean) Seed Extract		X					x													
Glycine Soja (Soybean) Seed Powder		X					x													
Glycine Soja (Soybean) Seed Water		X					x													
Glycine Soja (Soybean) Sprout Extract		X					x													

X = useful hits were found

Typical Search Terms

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

Key Words: dermal, irritation, sensitization, inhalation, metabolism, toxicity

LINKS

Search Engines

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

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org

- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

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

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

JUNE 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Marks Team – June 6, 2019

DR. MARKS: The next is the soy derived ingredients. This is the first review. As I understand it, Glycine max and Glycine soja -- that's how you pronounce it, depending on --

DR. SLAGA: Which one are we on?

DR. BERGFELD: Soy.

DR. SLAGA: Oh, yeah. Oh, I'm sorry.

DR. MARKS: That's okay. I'll hold off, Tom.

DR. SLAGA: Okay. Sorry.

DR. MARKS: No, that's okay.

DR. SLAGA: I dropped down to EHC. I went too far.

DR. MARKS: I'm going to somewhat set the stage. So I think as far as the different names, which on the list of ingredients look like they're different species -- my understanding is, actually, it's the same. That's how you say it. I would say it Glycine max and then Glycine soja are the same, so we don't to worry about is there a difference among species because they're the same.

So in a minute, Ron and Tom, I'm going to ask you --

DR. SLAGA: Well, that can be changed, then, can't it?

DR. MARKS: I don't know how, other than it states that these are the same species.

DR. BERGFELD: It's in the document both ways.

MS. CHERIAN: So we stated that one -- so Glycine soja is the wild soybean, and Glycine max is the cultivated soybean. So we were saying that, in cosmetics, we don't assume that there would be a difference when used that way.

DR. MARKS: Thank you for clarifying that. So presumably, are they still the same species, or do you refer to the wild versus the cultivated as cultivars? And cultivars, botanically -- and I'm not a botanist -- are different forms of the same species, so to speak.

But any rate, we have a number of ingredients here: callus, leaf cell, fiber, juice, seed extract, the extract itself, flower. I can't wait until Ron Shank sorts these out for me because he always, with clarity, decides how to subdivided them.

So I'm depending on you. Of these, only eight are being used, if I read the table. So the question I would have, Ron and Tom, are these ingredients okay? And then what needs do we have for them?

There are some specific questions I have like tumor promotion, estrogenic effect, et cetera. And then, can the previous safe conclusions for the soy oil, spirals, peptide, polypeptides, and protein be used for these soy ingredients as a read across?

And can we read across from the extract to the callus, the fiber, flower, leaf stem, sprout, phytoplacenta germ pulp? That's a lot of reading across, but can we use the extract to do that?

There was only one sensitization data for the germ extract at 0.3 percent. I kind of wanted to see sensitization data on the seed -- or that's germ extract at 0.3 percent. Sensitization data was okay. I wanted to see sensitization data on the seed extract and the extract alone. What's the concentration? So lots of issues.

Tom and Ron, do you want to weigh in? With me, for sensitization, I'd probably issue an insufficient data announcement and give me sensitization data on the seed extract at 1 percent and the extract at whatever concentration it's being used. But that depends on whether we can use the germ extract, the seed extract, and the extract itself as a read across for things like the fiber, the flower, the leaf, the stem, the hull, et cetera. We could have a lot of insufficient data needs if we do each one of these individual ingredients.

DR. SLAGA: Separately, yeah. I mean, most of them --

DR. BERGFELD: Aren't these GRAS?

DR. SLAGA: -- there's no data at all.

DR. MARKS: Well, GRAS would be the -- obviously, we get into what is GRAS again, and does that substitute for all the needs, since, if they're GRAS, you would expect significant systemic toxicity.

But who wants to go first, Ron or Tom?

DR. SHANK: I'll go first. I agree -- well, for systemic toxicology, geotox DART studies -- I don't think those are necessary because the soybean is a food. And preparations from that would be unlikely to have greater toxicity -- systemic toxicity than the food itself. But the sensitization is weak, so I think you need skin sensitization on seed extracts. And the highest concentration for G. max is 1 percent. G. soja is 2 percent.

So do we do both of them separately, or do 2 percent G. soja? And then, apparently, there's quite a difference in the extracts, depending on what solvent you use. And that confuses everything. Do you have to do a sensitization study on every different solvent preparation? So we probably should discuss that.

It's interesting that the sprout extract inhibits tyrosinase, so you might want to do a study on depigmentation of guinea pig skin just as a consideration. I guess I'll stop there for now.

Dr. Hill feels read across is very difficult without a lot more information. Basically, he feels the ingredients are okay -- reasonable. He sees needs as constituent characterization for all of the ingredients that are not derived from the bean, description of production processes representative of each ingredient type, dermal sensitization up to concentration for all ingredients except germ extract, and information enabling assessment of risk for individuals with allergies to soy products. That's going to be a tough one.

DR. BERGFELD: One of them bound to protein, which would be --

DR. MARKS: So I'm going to ask you to summarize that back again because I have just a few sensitization data, but that was based on can we read across to the other ones. And we always get into this discussion about different plant parts. It would be nice if we had a component list and see how closely the different plant parts -- we know they have the same ingredients. It's just how much they're -- so at this point, I think we can say the germ extract is safe. But after that, it becomes difficult because we don't have the sensitization data.

The reason I picked 1 percent seed extract -- because, of the ones that are used, the max seed extract -- we know the highest use leave-on concentrations are 1 percent. Again, it gets into -- if this is the same, the soja seed extract -- I assume is the same since, again, one's wild, one's the cultivated. So I just put 1 percent. I think we said higher concentration on -- to me, 1 percent in the seed sensitization date on the seed extract would be okay. And I assume it's a non-sensitizer. We don't have a clinical alert on these. But at the same time, we don't have any sensitization data either.

So which ones -- and I guess I want to go back. Does the previous safe conclusion for these other soy oils, steroids, peptides -- other than noting it in the discussion, does this have any bearing on this report?

DR. SHANK: Well, it would be supportive of --

DR. MARKS: The overall.

DR. SHANK: -- overall.

DR. MARKS: But we can't use that --

DR. SHANK: You can't use that as --

DR. MARKS: A substitute for sensitization. Yeah. I agree.

DR. SHANK: Now, the sensitization I have for germ extract was at 0.3 percent.

DR. MARKS: Correct.

DR. SHANK: And the maximum use is 0.45 percent in leave-ons. But then we have the seed extracts at 1 and 2 percent.

DR. MARKS: So seed extract -- I didn't have the 2 percent. I have just 1 percent is the leave-on. That's the Glycine max. Lots of uses. That has the most uses, 395. But I have 1 percent. Maybe I read that incorrectly. And there's nothing on the soja because that's, supposedly -- at least, before you look at it, there's no data on that.

DR. SHANK: Okay. I have to find that table.

DR. MARKS: But at least we agree we need sensitization at the leave-on use concentration. How about -- and then, I put the extract itself. There are only 11 uses. But I kind of use -- when I look at the extract, I kind of look at that as all the ingredients of the soja bean. I assume the extract means everything. And that would be the best proxy to read across. That's my reasoning, but I don't know if that's correct when we come to a botanical.

DR. SHANK: Okay. On Table 5, Page 29, it has Glycine soja seed extract at 2 percent in leave-ons. That's where I got it.

DR. MARKS: Glycine soja extract?

DR. SHANK: Yes. Twice as much as the Glycine max.

DR. MARKS: Oh, yeah. Hmm. Okay.

DR. SHANK: The problem is the extract's different than some of the --

DR. MARKS: Thank you. I missed that.

DR. SHANK: -- between solvents.

DR. MARKS: Have we brought that up before in terms of -- Ron, have we dealt with that issue before?

DR. SLAGA: You said something was 2 something?

DR. SHANK: Oh, 2 percent.

DR. MARKS: 2 percent. It's the last -- it's that last one.

DR. SHANK: On Page 29.

DR. MARKS: Yeah. It's the last ingredient there listed. Glycine soja seed extract, 2 percent. Yeah. I don't know why I didn't have that. Hmm.

So we would want the -- let me go back to the beginning. So we want sensitization on that. The seed extract at 2 percent, whether it's max or soja, we had at 2 percent. I had the extract itself, but I didn't know what concentration to do it. And the reason -- and there aren't that many uses of the extract, but my reasoning was the extract, perhaps, is the whole gemisch.

What else did you have in your needs for sensitization, Ron?

DR. SHANK: Just 1 percent for G. max and 2 percent for G. soja. But that doesn't solve the problem of what solvent extract should be tested, because they differ. I guess base it on use. Either you have to test them all or, if one is 90 percent of the extracts and one kind of a solvent, do that.

I had the question about the sprout extract could be a potential depigmentation problem. There are lots of bioactive compounds in soybeans -- lots of them.

DR. BERGFELD: Could I ask a question about bean and seed?

DR. SHANK: Yeah. My understanding is they're the same.

DR. BERGFELD: Does a bean have a seed in it, or are they the same? I thought they might be the same.

DR. SHANK: I took it as they're the same.

DR. SLAGA: The same.

DR. SHANK: Well, go back to the beginning.

DR. SLAGA: You plant the bean.

DR. BERGFELD: They have the hull, and then they have the outer shell. They're talking about parts of the seed and parts of the bean. Are they the same? Different?

DR. SHANK: It comes in a pod, like a pea.

DR. BERGFELD: The bean is in the pod and it has a hull. And then they talk about the shell or something on the seed.

DR. SHANK: True.

DR. BERGFELD: What is that? Is that the hull, also?

DR. SHANK: Yes, I think so.

DR. BERGFELD: It might be interesting to know.

DR. SHANK: Be sure.

DR. MARKS: Do you think if -- we have the sensitization for the germ extract. If we get the seed extract, do you think we'll have enough to read across? My sense is it's going to be negative, that it's not going to be a sensitizer since we haven't had significant clinical alerts. But I want to see some either animal or human data to support that it's not a significant sensitizer or is a non-sensitizer at the use concentration. And I'll just pick 2 percent.

And I'm not going to differentiate. I'm just going to say 2 percent of the seed extract. To me, I don't care whether it's max or soja. Just give me 2 percent. And I'm going to probably put "in the most frequently used solvent." Because of the 395 uses for the max seed extract, whatever the most common solvent is because I don't --

DR. BERGFELD: Is that the hexane?

DR. SHANK: I suspect it would be the hexane.

DR. BERGFELD: Can I ask a question? Isoflavones -- these are antioxidants, and this is what's in these parts. Is it just by concentration that there's a difference? Because there's such overlap with the isoflavones in here.

DR. SLAGA: The concentration -- I don't -- if you get into an estrogenic effect in other tissues from the skin are extremely small. Now, if you put a large amount internally, sure, you get effect.

DR. MARKS: So I think that will need to be -- you already anticipated. I was going to ask Ron that, Tom, but you've already answered it, the question of estrogenic effect. In the discussion, we would just say the amount of skin exposure, dermal exposure, is going to be extremely small.

DR. SLAGA: Compared to what you would take internally.

DR. MARKS: Right.

DR. BERGFELD: Interesting enough, an estrogen placed on the skin gives hyperpigmentation, and the sprout give depigmentation. So it would be -- isoflavone would be the depigmenter.

DR. SLAGA: That's doing the depigmentation?

DR. BERGFELD: I believe so.

DR. SHANK: Well, I haven't seen depigmentation data.

DR. SLAGA: I haven't either.

DR. SHANK: I'm predicting that could be a problem.

DR. BERGFELD: Yeah.

DR. SLAGA: Well, we don't know what it would be --

DR. BERGFELD: But if it had an estrogenic effect clinically, that would be seen by hyperpigmentation, because we get melasma from that. Women apply estrogen to their skin.

DR. MARKS: So other needs? So I think we're going to move forward. I can't imagine I won't be seconding a motion, an insufficient data announcement. The question is going to be what do we need. So far, for our team, I have the sensitization data on the seed extract at 2 percent, perhaps in the most frequently used solvent. We'll see what we get.

It's hard to ask for data on the extract because we don't even know what concentration it's being used in. But we could ask for the extract itself. That presumably will give -- do you think the seed can be read across for the other sensitization concerns? To me, I think it would, but we've dealt with this in the past. We have a lot of plant parts here, as Wilma's brought out.

DR. SLAGA: The seed gives rise to all of them.

DR. MARKS: Yeah. So I think -- to me, the seed, if we get that, that should take care of the needs for sensitization. Because the sprout extract causes depigmentation, we need more data on that.

DR. BERGFELD: Don't we eat all forms of this plant?

DR. SLAGA: Between humans and animals we do.

DR. BERGFELD: Yeah. And we don't have any alerts from that.

DR. MARKS: Well, Ron brought that up right in the beginning. The systemic tox data is not an issue since we eat soybean as a food.

DR. BERGFELD: How about the isoflavones in patch testing? Do you do that?

DR. MARKS: No.

DR. BERGFELD: So it isn't even in your arena of sensitizers?

DR. MARKS: No, but usually you'll get a clinical alert. Somebody will start reacting to a particular product, which is put on the skin. And then, when they separate out the ingredients -- usually, as you well know in the clinical reports, we usually will get one or two reports -- case reports, and then there may be a case series. And that's what, in some of the other ingredients -- we use both to ask for more data.

Or the other is, as I just mentioned, with the rereview, that there were no clinical alerts, even though the initial sensitization data was lower than the use concentration.

Anything else? So the needs -- sensitization on the seed extract at 2 percent, perhaps in the most frequently used solvent. The sprout extract causes depigmentation, so we need more data on that. And I would say those were the needs for the insufficient data announcement. Anything else? And the ingredients, we're all fine with.

DR. SHANK: Dr. Hill wanted constituent characterization for all the ingredients not derived from the bean. So that would be sprouts, whatever.

DR. MARKS: Well, I think that's kind of interesting because who was that made the comment all these come from the bean? When you grow it, they all come from the bean.

DR. BERGFELD: I'd like to ask you about the occupational exposure with an associated, elevated IG4 and specific IGE against the hull at a rate of 39 percent and IG4 at 27.

DR. MARKS: That was page?

DR. BERGFELD: I don't have the page; I just have the printout. That's at the end, before the summary -- two paragraphs before the summary.

DR. MARKS: Let me see.

MS. FIUME: PDF page 23.

DR. MARKS: I noted that, but I didn't --

DR. BERGFELD: I'd just suggest it's possible if it's inhaled.

DR. SHANK: The G. soja is used at 2 percent in inhalable products. That's page 29.

DR. MARKS: I guess when I read that, Wilma, I didn't think the occupational exposure -- again, it's sort of what Jay has brought up earlier. It's not only just the amount but the time. And these workers -- they're working at a processing plant, and they all, in this questionnaire, had respiratory symptoms. Not surprising, depending on how this was processed. But none of them had anaphylactic symptoms, that sort of thing.

So to me, as long as I didn't have an anaphylactic alert, I didn't feel this was really relevant to the cosmetic use. Although, I think noting it in the report is fine.

DR. BERGFELD: How about in the discussion?

DR. MARKS: Could be. I'm neutral on that.

Ron, Tom, what's your feeling on it?

DR. SLAGA: Neutral on it, too. I don't know if it's needed for discussion.

DR. MARKS: We could see what the Belsito team feels tomorrow.

Ron, what was your feeling? Do we need to highlight that in the discussion?

DR. SHANK: I don't think so.

DR. MARKS: Okay. Thanks, Wilma. Thank you for pointing that out.

Any other comments?

MS. FIUME: Jim, I came in late. So I'm sorry if I'm asking questions that were already answered.

DR. MARKS: Oh, yeah. We already took care of that. We covered the entire waterfront. No, go ahead.

MS. FIUME: I thought you might. So I actually have two. So first, for the sprout extract, you said more data? Is it specific information that you would like?

DR. MARKS: Depigmentation. Relevant to depigmentation.

DR. SLAGA: I think that's all we need.

MS. FIUME: And then, you may have covered this, but the extracts of the cultures -- like the callus culture and the phytoplacenta ingredients -- those are covered, as well, under the rest of the information?

DR. MARKS: Yeah. We felt the systemic toxicity is not an issue because they're eaten as a food, and we can use that as our prototype for saying all of these from a systemic point of view are fine.

Then, in terms -- the real need was actually cutaneous: One, the depigmentation, which you already brought up, with the sprout extract. And the other was the sensitization data on the seed extract at 2 percent. We felt that could be, again -- if there's no alert there, we would feel comfortable with the other ingredients. We felt all the ingredients were fine. We didn't want to delete any of the ingredients.

Did I capture that correctly, Ron and Tom?

DR. SLAGA: Yes.

DR. SHANK: Dr. Hill felt you could not read across.

DR. MARKS: Yeah. I think we brought up in the minutes. I didn't get a sense here that we had a problem, and we'll see what comes up tomorrow. Do you want me to mention that Dr. Hill said I couldn't read across tomorrow? It's captured in the minutes here. I don't know what the other team --

DR. SLAGA: Let's see what the other team says.

DR. SHANK: If it's important, I'll bring it up.

DR. MARKS: Good. Thank you, Ron. Yeah.

MS. FIUME: And then, I actually had a third question.

DR. MARKS: Come on, now. You started out with one.

MS. FIUME: I know. I warned you up front there were two. I just added one. Was clarification needed between the Glycine max and the Glycine soja, what's what?

DR. MARKS: Yeah. We actually talked about that right in the beginning. One's cultivated --

MS. FIUME: That's what I figured I missed.

DR. MARKS: -- and one's wild. Same species. And as I said -- and I don't know what the answer is, but do you refer to these two different, even though they have different names -- what botanically, I believe -- is anybody a botanist in here? -- is cultivars. So you have the same species but different cultivars.

MS. FIUME: Okay. So that's not something that we need to go into the IDA. Just the clarification in the report should be fine?

DR. MARKS: Yeah. That's what -- yes, that's correct.

MS. FIUME: Okay. Thank you.

DR. MARKS: Yeah. We didn't include that in the insufficient data announcement.

DR. BERGFELD: IDA?

MS. FIUME: IDA, insufficient data announcement.

DR. MARKS: Okay. So we'll see if we have any soy for lunch or dinner.

DR. BERGFELD: Well, it makes you lose weight and shrinks your testicles.

DR. MARKS: Next -- that woke us up there, if we were sleeping.

Belsito Team – June 6, 2019

DR. BELSITO: Okay, soy. We're dealing with -- first of all, we're told Glycine max and Glycine soya or soja -- is it "soya" or "soja?"

MS. CHERIAN: I'm not sure.

DR. BELSITO: Hmm. I'll say "soya." We'll make it Spanish. How's that?

MS. CHERIAN: Yeah, that's okay.

DR. BELSITO: So, we're told that they're actually the same, but then there seem to be differences in the color. But does that mean there are differences in the composition? There must be. Otherwise, they wouldn't have different color differences. There's black soy and white soy and yellow soy.

MS. EISENMANN: What I know, based on history of the name, when they first started naming plants by genus species, there was an agreement with Europe to use one specific book. And this book didn't have a choice of multiple names for a species. It didn't have Glycine max as a choice, so that's why they had to go with Glycine soja.

But that's why, for the context of the INCI name, they're the same. But whether or not they're truly same in the plant world, it sounds like one is the wild versus what's grown. But for the context of INCI names, I would consider them, I think, the same, even though there are varieties -- or I don't know exactly of soybeans with different colors.

DR. BELSITO: Right. Which, to me, means they're different compositions.

DR. LIEBLER: Well, we just don't have data to assess that. I just took a look again at the measurements of constituents. And first of all, they don't distinguish between -- some of them are just soybean without indicating Glycine soja or Glycine max. And then the one table we have, Table 4, that has concentrations is just for Glycine soja, not Glycine max.

So, we just don't have the information to distinguish them. But I don't think we've invoked this. For example, apple, where we've got golden, green, reds, McIntoshes, all kinds. I think you can have a color difference based on only a couple pigments in their relative abundances.

DR. KLAASSEN: Yes.

DR. LIEBLER: I think it doesn't necessarily indicate that there is a substantial difference between any other constituents, but I have no data. But that didn't occur to me as an issue. We'll put it that way. I thought we actually had pretty good method of manufacturer and characterization on these with the exception of the callus ingredients.

DR. BELSITO: Do we know what parts of the plants are GRAS?

MS. CHERIAN: None of these parts are GRAS.

DR. BELSITO: Okay. So, the only thing that's GRAS is soybean?

MS. CHERIAN: Hydrogenated soybean oil, which isn't an ingredient on this list. Soybeans technically aren't GRAS either.

DR. BELSITO: We eat them all the time.

DR. HELDRETH: So, remember, with foods, if it's been present and in use in the U.S. for more than 50 years or something like that, it may be also what's considered GRAS. But there's not going to be some CFR representation saying that this new genus and species is GRAS.

So, it's in use without observed adverse events, or something to that effect. But official referenceable cite that's going to say that it's GRAS, that's not something that can always be found for foods.

DR. LIEBLER: But I'm comfortable relying on the fact that these are widely consumed in foods. And of the ingredients that are on our list, it would be -- leave aside the callus, but the soybean fiber, the pulp, all the seed stuff, all the sprout stuff, extract, fiber, flour, germ, hull seeds, seedcake; those all, I think, I'm comfortable with for systemic exposure endpoints.

DR. BELSITO: Okay. Not to raise a sore point after parabens, short-term oral toxicity, page 17, lowering of relative epididymis weights were found in all extract-dosed males. Anyone concerned about that?

DR. SNYDER: I wasn't. I pulled a bunch of papers on the reproductive toxicity of soybeans and it's all attributed to the isoflavone and the phytoestrogen contents. So, I think we need to probably put that in the context of what else is known in the literature regarding the reproductive effects of the isoflavones. I've got some articles that --

DR. BELSITO: So, that needs to go into a discussion?

DR. SNYDER: Yeah.

DR. BELSITO: Okay. And Paul, you can help Priya craft that?

DR. SNYDER: Yes. Um-hm.

DR. BELSITO: Okay.

DR. KLAASSEN: Yeah. This was a pretty well-known phenomenon.

DR. BELSITO: Yeah. I mean, we dealt with it with yam many years ago. The tumor-promotion studies -- that's page 19 of the PDF. The effect is probably from azaserine. And I don't see this as a component of soy. So, am I missing something as to why this is here? This is soy flour. They were fed soy flour, but they were fed it with azaserine.

DR. LIEBLER: Azaserine being the carcinogen.

DR. BELSITO: Right. Or the tumor promoter in this case. So, I think that should just be deleted.

MS. CHERIAN: It was added because the amount of pancreatic nodules increased as the amount of soy flour increased. But without these azaserine injections, the incidence of nodule was low. So, I understand why we could take it out.

DR. LIEBLER: Did the authors of the study suggest that dietary soy is a tumor promotor for azaserine pancreatic carcinogenesis? Did they say that, or did you interpret this as tumor-promotion?

MS. CHERIAN: I interpreted it.

DR. LIEBLER: Okay. I'd actually like to hear what Tom thinks about this.

DR. BELSITO: Okay.

DR. LIEBLER: Because this is a little different than the classic tumor promotors where it's all topical, skin tumor promotion; although there are systemic tumor promotion studies in literature that look like this.

So, I don't disagree with your interpretation. I was wondering if the authors actually came out and made this point for this conclusion in their paper. But reference 44 -- but I'd like to hear what Tom thinks.

DR. BELSITO: Same thing for the anti-tumorigenic studies.

DR. LIEBLER: Yeah. Drug Nutrient Interactions, that's the journal.

DR. SNYDER: In reference 44?

DR. LIEBLER: Yeah. Boy, I don't even know if I could find that.

DR. SNYDER: Me neither.

DR. BELSITO: We have no genotoxicity data. You're okay with that lack of data?

DR. SNYDER: Yeah. I mean, that and Carci are the same thing. I don't think there's anything to alert us that we have any concern with.

DR. BELSITO: Okay. But that would need to go into the discussion as to long-term use of soy as a food have not been reported?

DR. KLAASSEN: Um-hm.

DR. SNYDER: Yeah.

DR. BELSITO: Okay.

DR. LIEBLER: Priya, if you have a copy of reference 44 -- I just looked; I can't get on Vanderbilt. They have pretty good coverage, but they don't even have this listed. If you could send me a PDF, I'd take a peek at it tonight.

MS. CHERIAN: Okay.

DR. BELSITO: Okay. And then, on page 20 of the PDF, it says, "An aqueous extract of black soybean sprouts was examined for whitening capacity. Whitening capacity was measured by tyrosinase-inhibition." And tyrosinase inhibition --

DR. SNYDER: Tyrosinase.

DR. BELSITO: Tyrosinase. And it was seen at 40 mgs per mL, reaching 98 percent. Now, obviously, that's a huge dose.

DR. LIEBLER: Right.

DR. BELSITO: Do we need to put it into the discussion?

DR. LIEBLER: Yeah. I noted that too, Don. I just said the in vitro effect may not be relevant.

DR. BELSITO: But in the discussion?

DR. LIEBLER: Sure.

DR. BELSITO: Okay. So we need the respiratory boilerplate, the plant boilerplate, dismiss the pigment inhibition, a little bit about the endocrine effects and the phytoestrogens.

We have no information on GRAS, but maybe sort of like a little summary of what Bart says. They're not GRAS, but they're sort of exempt because of their long-term use as foods.

I will point out that we have no sensitization data at the highest concentrations of use. That doesn't really bother me.

DR. SNYDER: What's the highest -- we have it at 6.3. What's the highest use concentration?

DR. BELSITO: Oh, we do have 6.3?

DR. SNYDER: Yeah, for the Glycine soja germ extract.

DR. LIEBLER: For what? Sensitization?

DR. SNYDER: Um-hm.

DR. BELSITO: Go back to my comments. We also need to do the IgE-mediated allergy in the discussion.

DR. SNYDER: 108 subjects, Don, at the top of page 23.

DR. BELSITO: Pardon?

DR. SNYDER: Top of page 22. 108 subjects, HRIPT. 0.3. I'm sorry.

DR. BELSITO: Zero point three. Yeah.

DR. SNYDER: I'm sorry. 0.3. My zero looked like a six.

DR. BELSITO: Yeah. And it's used up to 2, I think. Had that some place. Right? It's 2 percent as the highest leave-on? Yeah.

MS. CHERIAN: With seed extract?

DR. BELSITO: Yeah.

DR. SNYDER: Okay. Sorry.

DR. BELSITO: But I'm not concerned. But that would need to go in the discussion that we have data at 0.3. We noted that it was used up to 2 percent but given the relative lack of case reports of a delayed type hypersensitivity, we did not feel we needed data to support the 2 percent use.

So, Dan, you're comfortable with everything except for the callus?

DR. LIEBLER: Right. I think method of manufacture and impurities is fine. This is a pretty well documented group actually. But the callus is completely undocumented. And again, we've seen callus stuff before, but I don't know what it is in this case. There's no description.

DR. BELSITO: So it's a simple lack of description? Because we know how callus is formed. We had that lecture.

DR. LIEBLER: I vaguely remember it. If somebody wants to remind me that, oh, it's the same as -- callus is --

MS. FIUME: It's simply a cell extract.

DR. BELSITO: Yeah.

MR. GREMILLION: It's cultured cells.

MS. FIUME: Yeah, it's cultured cell extract.

DR. BELSITO: Cultured cells.

DR. LIEBLER: Cultured cells from -- so, we have gone through this before, and they are different?

MS. FIUME: Because the one thing I do remember when we received our lecture on it that the information that was in the report was not sufficient. That's the one thing I do remember. But I don't remember what they are cultured from. And I will look and see if I can find it.

DR. LIEBLER: So, if we could provide any information as to how the callus ingredients are derived, I'd probably be willing to fold on that one. But right now, we got nothing. Excuse me.

DR. BELSITO: Okay. So, our conclusion right now is that they're safe as used except for the callus?

DR. LIEBLER: So, Priya, I just looked at this paper on the tumor-promotion. It's interesting. They don't use that term anywhere in the paper. But it looks like a tumor-promotion paper. So, if Tom feels it's okay to label it as such, I'm completely in agreement. So, let's check with him.

DR. BELSITO: And regarding the soy IgE-mediated allergy, how have we dealt with that in other reports? I know hydrolyzed, we restricted the -- I also know that manufacturers at least of some topical drugs that have peanut oil have a strong label on them saying "warning" about people with peanut allergy. Do cosmetics do that?

MS. EISENMANN: Well, I think that's one of the reasons why there's a name in parentheses in this one, so that somebody could see -- the ingredients should be on the label so they can see soy listed.

DR. BELSITO: But how prominent is that labeling?

MS. EISENMANN: It's going to be part of the ingredient label.

DR. BELSITO: Okay. Again, there have not really been significant reports of anaphylactic reactions from use of topical products with soy. I'm just curious because probably pharmaceuticals are much more conservative. There are usually big, black, bold warnings on them.

Okay. So, we're basically just going insufficient for composition and manufacture of the callus? Or an explanation of what callus is, right?

DR. LIEBLER: Yes.

DR. BELSITO: Okay. So what I have for the discussion is the respiratory boilerplate, the plant boilerplate, the pigment defect that we're discounting because of the high doses. We're not concerned about the lack of carcinogenicity data and genotox data because of the long-term food use of this. The repro data, Paul's going to write something up about phytoestrogens. Sensitization and irritation, we have 0.3, but given the lack of case reports, we're okay with 2 percent as the highest leave-on. And then IgE.

And that's it. That's what I have. Safe as used except for callus, method of manufacture, impurities, or a definition that callus is essentially the same as what we've looked at. Okay. Quick bio break since we're not done?

DR. LIEBLER: Sure.

DR. SNYDER: Yep.

DR. BELSITO: It's 3:03. Back here at 3:15.

DR. LIEBLER: Sounds good.

Full Panel – June 7, 2019

DR. BELSITO: So this is the first time we're looking at this ingredient. And it is not GRAS because it's been used for multiple years as a food source. So it's sort of grandfathered out of that type of conclusion. And we felt that there were insufficiencies for composition and manufacture of the callus, or further explanation of the callus. Otherwise we were happy with the report. There was no sensitization or irritation at the highest use concentration, which is two percent, but there is a complete lack of case reports.

The reproductive and endocrine effects were seen, because these are phytoestrogen so that is to be expected. And the genotox was absent, but again, because these are GRAS. So we're just really looking for composition and manufacture of the callus.

DR. BERGFELD: And that is a motion.

DR. MARKS: Second. We also felt an insufficient data announcement, although, we felt that perhaps the sensitization data on the seed extract at two percent would be necessary. We only have one sensitization data point that was okay for the Germ extract at 0.3 percent, so significantly higher concentration for the seed extract.

And then, Ron Shank brought up an interesting point is, we would want it in the most frequently used solvent. So, the solvents might affect the sensitization studies. So he brought that up.

And then Ron also brought up the issue of depigmentation that the sprout extract caused and wanted to see more data relevant to the depigmentation. So, you're shaking your head, Paul, but I'll -- that's what our team felt. And, Ron Shank, if you want to make any more comments, please do.

DR. SHANK: The report states that the sprout extract inhibits tyrosinase.

DR. BELSITO: Yeah, we discussed that. Paul, I forget what you said about that.

DR. SHANK: And if it does?

DR. SNYDER: It was an in vitro effect and we determine that that probably wasn't biologically relevant. So, it was just an in vitro effect.

DR. BELSITO: At very high levels.

DR. SNYDER: At very high levels.

DR. LIEBLER: It appeared to be tyrosinase enzymes in solution, exposed to 40mgs/ml of the extract which I thought was pretty high. And, I mean it -- many flavones or phenols can inhibit tyrosinase, by acting as alternate substrates for tyrosine oxidation, because it's basically a red-hot oxidant for phenols.

And, so I thought of this as most likely a nonspecific effect of, you know, it could happen with any flavonoid, phenols rich mixture. But under these conditions, I just didn't think it was compelling enough to be, you know, relevant to an in vivo effect on skin pigmentation.

DR. BERGFELD: Ron, response?

DR. SHANK: Well, I think it's an alert. But if I'm -- it is just an in vitro test, I agree.

DR. LIEBLER: Yeah, I mean, if it was an animal test with painted on soy extract, and then there was an in vivo effect of some sort, even if it was a high concentration that would be a bigger red flag for me. I think this could be handled in the discussion.

So, anyway, that was how I interpreted these results.

DR. SHANK: Okay.

DR. BERGFELD: May I just add as a female sitting here. And there are soy ingredients in cosmetics that are used for discoloration and evening out skin tones.

DR. LIEBLER: What's our top concentration of use in leave-ons?

DR. MARKS: Two percent in the seed extract, I believe.

DR. SHANK: The in vitro study here on Page 20 was on sprout extract.

DR. LIEBLER: Yeah. So 2mg/ml produced 40 percent inhibition of the tyrosinase activity in solution. You know, it's a high concentration relative to the amount that would be in a cosmetic ingredient. Much of that stuff won't even get through the stratum corneum either. So, you know, the effective dose at the level of melanocytes would be considerably smaller than was used in this in vitro experiment model.

DR. SLAGA: I agree with Dan. I think this can be handled in the discussion.

DR. BERGFELD: All right, what do you think, Ron, discussion or request?

DR. SHANK: Okay, I would still like the pigmentation study, but I'll go along with everybody else and handle it in the discussion.

DR. BERGFELD: All right, so we --

DR. LIEBLER: Is there like an OECD test for depigmentation?

DR. BELSITO: No.

DR. BERGFELD: No, the quinones have been used.

DR. LIEBLER: I just wonder what it would be, you know, what data could be brought forward to satisfy and in vivo endpoint on that.

DR. SHANK: Skin painting on a guinea pig for depigmentation. That's old-fashion toxicology, but it works.

DR. BERGFELD: All right, would you restate your motion, Don?

DR. MARKS: I'll restate it's not old fashion, it's gold standard.

DR. BERGFELD: Good for you. Please restate your motion.

DR. BELSITO: Before we do that, we had a question for Tom on the tumor promotion studies and anti-tumorigenic studies on Page 19. Whether these should be in the report at all?

DR. SLAGA: I think that it can be handled in the discussion. They're not really relevant. I mean, it's a tumor promotion effect, which is in itself is not cancer, okay? You know, you have to have a series of things to occur before tumor promotion before you get cancer. And I think it's best to handle it in a discussion.

DR. BELSITO: Okay. So we leave it in and handle it in the discussion.

DR. MARKS: So, Tom, just to clarify for me. Don, thank you for bringing up this point. So if I had somebody who has severely sun-damaged skin, high propensity to develop skin cancers. And now I put on a tumor promoter, would that be a concern as a consumer? Because I think that's the issue in the discussion that would have to be addressed.

DR. SLAGA: Well, I mean, in reality your skin, being exposed to ultraviolet light for many, many years, you have a lot of what I would say initiated cells in there. And, sure, you could at a high dose for long-term use of something, which tumor promotion is not a one treatment. It's a multiple long-term to bring those initiated cells into a condition where they lead to a tumor. So, it's really, if you want to use it every day, many times a day for years and years, there could be potentially a problem.

DR. BERGFELD: Thank you. Don?

DR. BELSITO: So then, we would need to discuss that?

DR. SLAGA: In the discussion, yeah.

DR. BELSITO: So, the insufficiencies were composition and manufacture of the callus, or explanation of the callus. Again, we really weren't certain on that. And, while we had none other, I hear from the Marks team that they want sensitization at two percent.

DR. MARKS: That's correct, on the seed extract.

DR. BELSITO: On the seed extract.

DR. MARKS: That has the highest usage.

DR. BELSITO: Right.

DR. MARKS: Close to 400, and the highest concentration at two percent.

DR. BELSITO: And then everything else would go in the discussion, the respiratory boilerplate, the plant boilerplate, the pigmentation effect, the phytoestrogen effects and the tumor promoting effects.

DR. BERGFELD: All Right, any other discussion before we call the question? The conclusion has been seconded by Dr. Marks, so called the question, all those in favor of the conclusion? Thank you. So we have an insufficient for the callus and those needs have been expressed.

So, in moving on to the last ingredient in this particular group, the Caprylhydroxamic Acid, Dr. Marks.

DECEMBER 2019 MEETING – SECOND REVIEW/DRAFT TENTATIVE REVIEW

Belsito Team – December 9, 2019

DR. BELSITO: Okay, so at the June meeting we issued an IDA. We wanted the sensitization data either on glycine max or glycine soja seed extract at maximum of two percent concentration data, identifying composition, method of manufacture, general characteristics of the callus-derived ingredients.

So we got what we asked for soja. We didn't get what we asked for the callus. So, all safe as used except callus for which we need a method of manufacture, impurities, use concentration, 28-day dermal and if the composition is different, other endpoints.

MS. FIUME: So the abbreviated HRIPTs are acceptable?

DR. BELSITO: Yeah, I thought so. But then it's before we had this discussion, so now I guess I have to look at them.

MS. FIUME: Sorry.

DR. BELSITO: But I can't imagine they saw any irritation with this. If they did, then there's an issue. What page is the PDF?

MS. FIUME: 172.

DR. BELSITO: Okay. This was three percent glycine soybean seed, soja seed extract, semi-inclusive, 59. That was negative for irritation.

No low-level reactions, and no reactions at all. I think that it's fine. I think it's when you start seeing these low-level reactions that you really want to be able to evaluate it. I don't know, what do you think team members?

DR. SNYDER: I was fine with it.

DR. BELSITO: Yeah. So, just the callus is insufficient.

DR. BERGFELD: There was no read-across?

DR. BELSITO: Not to the callus. Not unless we have composition.

DR. LIEBLER: Nope.

DR. BELSITO: And method of manufacturer and impurities.

DR. LIEBLER: Right. I mean, the callus really have to be sort of taken from the ground up because, again, it's a secondary cell culture product that genetically may be related to the precursor plant. But other than that, all bets are off.

I do have a couple comments on the discussion. Top of Page 42, first paragraph and last sentence of that it says; however, the panel noted that those with a high propensity to develop skin cancer should take caution during long-term use of cosmetics containing these ingredients. I looked through --

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

DR. LIEBLER: Page 42, PDF 42, first paragraph, last sentence. And when I was looking through the meeting minutes, I saw the discussion of this. And I think it came up in the context of Paul asking Tom, at the full panel meeting, well -- because we were talking about genotox data.

And he was -- I think you were asking Tom, well, could there be a possible issue of skin cancer risk in people that are at high risk of skin cancer or sun-damaged skin and so forth. And my comment is, I recall this as a hypothetical point in our meeting minutes, but that we don't have any data to support a concern about that.

So, normally we have a cautionary statement like this when there are some data, but we don't have anything. So, I think it was, you know, mentioned in the minutes, but I think this sentence could be deleted. Because we really don't have any data that suggests that this is an issue.

MS. FIUME: So, can I ask for clarification? Because this is a botanical, is it safe as used when formulated to be non-sensitizing, being that it's a botanical?

DR. BELSITO: I didn't see any ingredients of concern.

MS. FIUME: And I didn't know. I didn't know if there were, so that's why I just wanted to confirm.

DR. BELSITO: Let me look again but, I mean, soy has no terpenoids, right? No terpenes.

MS. EISENMANN: We were wondering if the discussion might bring in some of the information from the soy protein report on the size limitations that were in there. I mean, it's certainly oral and it's IgE.

It's not contact dermatitis, but if you read through the report, there's really not a whole lot to bring up that issue. But since you've already done it, you might just put a little bit more in the discussion.

DR. BELSITO: It doesn't have any fragrance per se; and, you know, it's a food so I wouldn't be concerned about any toxic substance.

So, I'm sorry, Carol. I was just checking for fragrances. What was your point again?

MS. EISENMANN: That you've done a report on soy proteins and hydrolyzed soy proteins, that there might be a little bit in the discussion -- because some of these could contain protein -- about what you had a discussion for that. So it's the food IgE response. But I don't think there's anything in the discussion at this point to address that.

DR. BELSITO: No, there's not, but we also didn't bring in anything anywhere from that report. So, your point is that some of these, well, I guess the soja extract could have protein in it.

MS. EISENMANN: And the flour, F-L-O-U-R.

DR. BELSITO: Right. Yeah, then I think we should. No, but then should we summarize the protein points from the hydrolyzed protein?

MS. EISENMANN: I thought maybe -- there's a nice section in the discussion of that that deals with --

DR. BELSITO: Just in the discussion, not in the data?

MS. EISENMANN: Right. Right.

DR. BELSITO: Is it appropriate to enter -- well, I guess, yeah -- something in the discussion that you haven't brought in as data?

MS. KOWCZ: No, the discussion in the report. The discussion from the report of 2015 --

MS. EISENMANN: Well, I think you also mentioned it earlier a little bit, in the report, that there's an IgE. And so, then you would just say in the 2005 report --

MS. KOWCZ: 2015.

MS. EISENMANN: -- 2015 report. So, I can read what you have in that report if you want.

MS. KOWCZ: Would you like us to read it? It's in 2015, in the discussion. Would that be helpful?

MS. EISENMANN: Or maybe you want to put it in the introduction, but I thought something a little bit more --

DR. BERGFELD: Meaty.

DR. BELSITO: Yeah, so we do have some. We have immunotoxicity. And it says, percutaneous exposure of the soybean extract causes systemic secretion of soybean specific to IgEs. And then we have the clinical case reports of IgE. So yeah, it probably would be worth bringing that into the discussion. Could you read it please?

MS. EISENMANN: "The panel noted that soy proteins are known food allergens that can elicit Type 1 immediate hypersensitivity reactions when ingested by sensitized individuals. However, the panel is not concerned that such

reactions would be induced by dermal exposure, because these ingredients are water soluble, would not penetrate the skin, and have molecular weights that are well-below that which would cause IgE cross-linking.

The panel reviewed studies showing no relevant ocular irritation in animals, no dermal irritation" -- I'm not sure you need all of that. "And no dermal irritation or sensitization in animals and humans subjects. And no reported cases of Type 1 immediate hypersensitivity reactions from cosmetic use, which support the conclusion for these ingredients.

MS. CHERIAN: There is a paragraph in the discussion right now from that report. Do you want me to just expand on that paragraph? It's the third to the last paragraph in the discussion.

It starts with, "the panel noted the immunotoxicity study regarding IgE mediated allergy to ingested soy proteins. However, the panel is not concerned that such reactions would be induced by cosmetic exposure because these ingredients are water soluble, would not penetrate the skin, and have molecular weights that are well below that which would cause IgE cross-linking."

DR. BELSITO: So that's actually what you wanted.

MS. KOWCZ: Same thing.

MS. EISENMANN: Right. But you could say that it's from the original -- you could say that it's from the 2015.

MS. CHERIAN: Okay.

MS. KOWCZ: 2015 CIR report.

DR. BELSITO: Yes.

MS. DEWAN: Okay. One of the ingredients out of 28 ingredients is glycine max soybean phytoplacenta conditioned media. Just for my own understanding, is it the media that they're using as an ingredient?

DR. LIEBLER: It's defined as the growth media removed from cultures of the phytoplacenta after several days of growth. So this is actually -- I put this in the same category as the callus, where we have a secondary bioproduct generated by cell cultures. It's not the cells, but it's the medium and it is of questionable compositional relationship.

MS. DEWAN: That's the reason I asked.

DR. LIEBLER: And particularly condition medium because it's not even genomically similar. It's not genomic.

DR. BELSITO: So, is that insufficient, Dan?

DR. LIEBLER: Yeah. We should add that to our insufficient list. That just slipped by. Thank you.

DR. BELSITO: So, we have the callus extract that's insufficient and we have those needs which we said were method of manufacture, composition and impurities. So, you saying the same thing for the conditioned media?

DR. LIEBLER: Yeah. And actually, the phytoplacenta extract is the same issue, same problem. So this slipped by me. Phytoplacenta extract is the -- I'm kind of reading from the definition on Page PDF 44 top. "Is the extract of the phytoplacenta cells directly isolated from the plant or grown in culture."

So it's that "or" that's a problem. Isolated from the plant, glycine soja, I would be okay with that; it's just a cell population directly isolated from the plant. But then the ones grown in culture, who knows what happens when you do that.

But it's got an "or" so it could be either, and -- one that I would find acceptable and one that I would find questionable. I agree with the conditioned media being thrown out. I think we can keep the phytoplacenta extract. So, okay.

DR. BELSITO: So, we can keep that?

DR. LIEBLER: Yeah, right. So, we got four exclusions now, right? Three callus and then the condition medium.

MS. FIUME: There's two of those ingredients, isn't there?

DR. BELSITO: Three callus.

MS. FIUME: No, the phytoplacenta?

DR. LIEBLER: Yeah, but only the conditioned medium.

DR. BELSITO: The conditioned medium.

MS. FIUME: Oh, okay. Only the one. Okay.

DR. LIEBLER: Only that -- only one is excluded. Because the one that's phytoplacenta is described as directly isolated from the plant or grown in culture. I think -- the directly isolated from the plant is probably fine.

MS. DEWAN: Okay. One of the functions mentioned for phytoplacenta extract is antimicrobial agents. And if it's an antimicrobial agent, it falls in the area of OTC. So, just wanted to bring it to your attention.

DR. KLAASSEN: On Page 42, in the third paragraph that starts with, "In addition." But in the middle of that paragraph, it says "Tyrosine inhibition." I think that should be tyrosinase inhibition.

DR. LIEBLER: I corrected it in my copy too.

DR. KLAASSEN: Good.

DR. LIEBLER: Thanks.

DR. BELSITO: Okay. So, all are safe as used except the three callus and the phytoplacenta conditioned medium.

DR. LIEBLER: Correct.

DR. BELSITO: And for those we need method of manufacture, impurities, composition, use concentration, 28-day dermal, and if composition is different, other tox endpoints.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay. Palm. Where's Wilbur?

MR. JOHNSON: Here I am.

DR. BELSITO: Oh, where are you hiding there, Wilbur? You're behind me. It's a sneak attack, huh?

Marks Team – December 9, 2019

DR. MARKS: Okay. Next is soy. So, there are 28 soy-derived ingredients. At the June meeting this year, the panel issued an insufficient data announcement. And the needs are in Priya's November 15 memo there: HRIPT, summary of HRIPT. That's for the 3 percent glycine soja seed extract. That was okay.

And requested sensitization data. In addition, data identify- -- and the composition, method of manufacture, or general characteristics of the callus derived ingredients. And we did get some HRIPT data as I mentioned.

So, we're at the point where we should be issuing a tentative report. We got nothing on the callus. Sensitization for the 3 percent seed extract was okay.

Ron, Tom, questions and comments, and where should we go in the tentative report? I was wondering whether or not we go safe for all except the callus ingredients. Ron, you're very good at sorting through all these darn botanicals.

DR. SHANK: I have safe as used. I would like to see a better definition of callus. This keeps coming up all of a sudden. We keep coming up with callus. I think it's cultured, parenchymal cells of the plant. But I'd like a cosmetic dictionary definition of what do you mean by a callus. We just assumed it's a cell culture.

But if we could get a better definition of what callus is. If it is just squashed plant, and then you isolate cells and grow them on a petri dish, then I would say that all forms are safe.

DR. MARKS: Yeah. Okay.

DR. SHANK: But I'm not really sure what a --

DR. MARKS: So should we go through with the tentative report safe for all except the three callus ingredients? And the insufficiencies, which were pointed out in the previous meeting, was composition, method of manufacture, or explanation of callus. And that's where you are, explanation of callus.

DR. SLAGA: Yeah. Right.

DR. MARKS: So, I think we could leave that stand at this point, can't we? Until -- and then hopefully it'll be clarified for the next time we look at these ingredients. But you would like to move forward, just safe for all, and then get that information before we see the draft final report?

DR. SHANK: Well, I hate to hold it up just for a definition.

DR. SLAGA: Right.

DR. MARKS: No, that's my thought.

DR. SHANK: We should be complete. And we did ask for it and haven't gotten it yet.

DR. MARKS: Yep. Tom?

DR. SLAGA: Well, we still could go insufficient for the callus.

DR. MARKS: Yeah. Insufficient for the callus, safe for everything else.

DR. SLAGA: Everything else.

DR. MARKS: So that's 25 out of the --

DR. SLAGA: If we get it soon, then everything's fine -- the definition.

DR. ANSELL: I will note there are no uses.

DR. SLAGA: Yeah. No one uses it.

DR. PETERSON: That was my question. I mean, there's no uses for it, but you're using some of the data derived from it for the non-reactivity, right? That was my understanding; that there was -- it was not used in cosmetic, but there's sensitization data using it.

So if you're making a judgement about the lack of sensitization, and using that extract, then you kind of need to know what's in it. You need to understand what it is that you're testing and how equivalent it is to the other things that test weren't done on.

DR. HELDRETH: I can write to the nomenclature committee and ask them for an explanation of what callus is. I know that Minnie Goldstein, on the INCI committee, probably understands what a callus is better than anybody. I'm sure she can give a solid explanation of what it is, and what it typically results in, in a cosmetic.

Maybe not, specifically, details about the honey callus extract. Because I don't know if she has specific experience with that ingredient. But she can certainly give us a better explanation of what a callus is in general.

DR. MARKS: Yeah. Like you said, it's a culture of the cell, it isn't just cells? And where are the cells derived from? Now, if we issue a --

DR. ANSELL: An extract of a culture of the callus of --

DR. SHANK: The callus isn't part of the plant.

DR. SLAGA: That's right.

DR. PETERSON: There are people that, when they eat soy, are very sensitive to it. I guess I was wondering, if you're making a judgement on something, based on the sensitization of something that's not used in cosmetics, then there might be a concern that people would react when it was a whole plant. That would be my concern. Again, but I'm not sure how -- I'm not an expert on the sensitization.

DR. MARKS: You're absolutely right. There was in vitro dermal at 18 percent with the callus culture, and that was negative for sensitization. I'm not sure what in vitro they -- but the others that we have responses for were okay.

DR. ANSELL: To the first question --

DR. MARKS: Yeah. Sure.

DR. ANSELL: So, I mean, that really is the heart of what read across is all about. It's quite possible to take a data point from a material and carry it over to the subject molecule, without having complete data on what you're starting with.

So, in one case the data is reliable for interpretation of another material. It doesn't mean that the first material is complete. So, you could have a material go insufficient in and of itself.

And that's often one of the problems is that -- is the data of the entire family reliable for supporting the safety of the entire family? And we often -- the industry liaison often argue that the families are too large. That there are data

points which are reliable, but you can't put a material in a family and then say most of the family's okay, and some of the family isn't, because then they're not a family.

So it's one of the problems that we, as the industry representatives, often cite in the formation of the families. But the read across would certainly allow that.

DR. PETERSON: I would think this is where the read across gets problematic for the botanicals because you're making assumptions that -- because certainly, the compositions of the different key ingredients are going to change depending on what part of the plant you get the --

DR. ANSELL: Oh, certainly by part. But I would argue that key ingredients don't change within a part. So, all the leaves, depending on which side of the hill they grow on, may have small differences, but the major components stay the same. But certainly going from leaves to roots to fruit could have major changes.

DR. SLAGA: Right.

DR. PETERSON: The thing that's driving me even about the leaves on the different side of the hill, is that I know with, like, Brussel sprouts, the key ingredient can vary by quite a large amount depending on the cultivar, how it's grown, that sort of thing. So, that's just my perspective.

DR. MARKS: Yeah. We struggle with that.

DR. PETERSON: It's really hard with botanicals.

DR. MARKS: Yes. So, the good thing about it is we're just going to a tentative report, so that means we can still ask for this. It's not like we're going to have to change the conclusion, and we'll expect to get the data.

So, I think tomorrow I would move that a tentative report be issued, safe for all the ingredients except the three callus ingredients. And we're still with composition, method of manufacture or explanation of what callus is. And if we get that, then we could go safe for all.

Priya, I wanted to mention your discussion. In the last meeting, there was quite a bit of comments about different issues with these ingredients. And I thought you did a really nice job in the discussion with obviously adding the respiratory and the plant boilerplate.

But the pigmentation effect you explained. The phytoestrogen effect, and the tumor promoting effects, to me, in the discussion looked good. Tom, Ron, Lisa, any comments on Priya's discussion going out this time?

DR. SHANK: It was good.

MS. LORETZ: Can I bring up a point?

DR. MARKS: Sure. Absolutely.

MS. LORETZ: And that is on the tumor promotion. There's a study with soy flower where oral exposure followed by azaserine, and it resulted in some pancreatic nodules. In the discussion, that translates to there's not a concern -- there's a mention of tumor promotion.

And then it says, "The panel noted that those with the high propensity to develop skin cancer should take caution during long-term use of cosmetics containing these ingredients." Does that result really warrant a warning? It just seems like there's so much about that study that's not at all like cosmetic exposure to soy ingredients.

DR. SLAGA: Well, the tumor promotion, which I've done a lot of work there over the years, you have to have a primary carcinogen at a low dose to initiate some process. With the skin, you have the problem that UV can do that. So there's possibly initiated cells.

The only thing that limits tumor promotion is that it has to be -- the promoter has to be given for a long time, in most cases at a relatively high dose, to bring about the process. And if you don't have any alerts towards extreme irritation from any ingredient, or something that's going to stimulate self-proliferation, which irritation can, then it really is not a concern.

DR. MARKS: So I guess --

DR. ANSELL: The study was subcutaneous.

DR. SLAGA: Huh?

DR. ANSELL: This was an SQ study.

DR. SLAGA: Yeah.

MS. LORETZ: No, it was an oral study.

DR. MARKS: So, any rate, on page 42, while you sort that out, Tom, what are you thinking? Lisa, since you've done a lot with cancer biology, I see what you bring up there because it's a problematic sentence.

"However, the panel noted that those with high propensity to develop skin cancer should take caution during long-term use of cosmetics containing these ingredients." That's Page 42, the end of the first paragraph that's highlighted in yellow. So the paragraph begins on page -- it's actually, what --

DR. SHANK: The first paragraph of the discussion.

DR. MARKS: The paragraph under the draft discussion. I can see how you're concern when you read that. You say, hmm, is the CIR Expert Panel saying hmm, well, if you have soja and you have a propensity to develop skin cancer, should you avoid these cosmetics?

Do you think that sentence should be deleted? Because I can see -- thanks for pointing that out.

MS. LORETZ: Yeah. It just seems --

DR. PETERSON: I don't have a comment, but I didn't understand what the whole thing meant. Although, as we've been talking about it, I think there is some value in a statement for the people who are sensitive to worry about it.

I think there is something about the sentence before that, that may need to be edited. But I'm not going to be able to respond to that in the moment, I need to think about it. But I'm not sure that I would eliminate it because there are individuals --

DR. SLAGA: Yeah. There would be alerts for some people.

MS. LORETZ: -- that need to think about it. So I think --

DR. MARKS: All right. Boy, I'll tell you it's tough because then you get into, if I were a Caucasian senior citizen in Texas, or Florida, or Southern California and grew up there, or lived most of my life there, I'd be concerned because I've already had lots of UV. So, now do I avoid anything that contains soja in it?

DR. PETERSON: It might be worth thinking about. I certainly would -- as a person, would want to have a sense of that.

DR. SLAGA: To me, once again, it would take a large exposure from the soy ingredients to bring this about. The thing with tumor promotion, too, is that, if you interrupt it, it wipes out the past history. And you have to restart it. It has to be a continuous exposure to soy and the ingredients to have a potential. And the concentration has to be pretty high.

Can that occur with some people? Possibly, but not -- in general, it would not occur. And once you get old, almost everybody has some actinic keratosis and gets skin cancer at some point. I think by the time you're 80, it's almost like everybody has had a skin cancer, if they're off a certain -- yeah, depending on one to five skin sensitivity.

DR. MARKS: So these --

DR. SLAGA: If you're Irish, freckled, then, you know, you have to be very -- because you're going to start getting skin cancer at 40 or 50.

DR. MARKS: Yeah. Ron, what's your sense? Is this last sentence helpful for the public and the cosmetic industry? "However, the panel noted that those with high propensity to develop skin cancer should take caution during long-term use of cosmetics containing these ingredients." Hmm. Linda, do you have alternative wording. Because we have this dynamic tension here between, yes, it's possible.

DR. SHANK: I felt it was overconservative to put it in.

DR. MARKS: Overconservative. Yeah. That's why I said should we delete that sentence?

DR. SLAGA: Maybe to modify it a little bit.

MS. CHERIAN: Okay. To say continuous exposure at high concentrations?

DR. PETERSON: Yes.

MS. LORETZ: Yeah, I guess I -- I thought it was more unnecessary.

DR. PETERSON: I think to qualify it by, "continuous exposures at high concentrations, there might be a concern."

DR. MARKS: There you go.

DR. SLAGA: Yeah.

DR. PETERSON: That's sort of a compromised language that expresses the concern without --

DR. HELDRETH: So, the max use concentration is 2 percent. Is that so low that it couldn't have this effect, even if you used the product every day?

DR. SHANK: I would think too low.

DR. HELDRETH: You'd have to exceed intended cosmetic use.

DR. PETERSON: So, does it -- the tumor promotion, does it require irritation? And would somebody that's being irritated by a product, wouldn't continue to use it?

DR. SLAGA: Yeah. There's usually signs. I mean, if you do experimental animals, you actually see signs of the irritation on the skin in that there's things happening. And it has to be around all the time, or otherwise, if interrupt it for several weeks, it's like you have to restart everything over again. It wipes out the memory of it.

DR. PETERSON: So perhaps, then, another way to -- a person that would experience irritation -- there's always going to be somebody that might be sensitive. Could you modify even more by saying, "If irritation, discontinue," -- putting something in there? Because if you're not seeing irritation, you wouldn't see the tumor promoting activity, correct?

DR. SLAGA: Yeah. The irritation self-proliferation is an absolute requirement.

DR. PETERSON: Yeah. That's why sometimes we say, when formulated to be non-irritating.

DR. ANSELL: Our concern is about the --

DR. SLAGA: To eliminate that.

DR. PETERSON: Right. Right. Right. Oh, I understand that now. Okay. Because I saw that a lot, and I was wondering -- okay.

DR. ANSELL: Our concern is about the relevance of that study to cosmetics.

DR SLAGA: Yeah. It's more for internal.

DR. ANSELL: Not like whether these types of studies can show something in the continuous -- and the requirement for proliferation. So, we just don't think this study justifies that warning.

DR. SLAGA: Yeah. Okay.

DR. MARKS: So, I think we're at qualify the sentence or delete the sentence.

DR. SLAGA: Either qualify it or delete it, could be either/or.

DR. MARKS: So delete. Ron? Let's start with Lisa. Delete or qualify?

DR. PETERSON: Well, perhaps instead of deleting that sentence, you could rewrite it so that -- including the language about formulating it so it's non-irritating, to remove any concern about this. Does that make sense? It's not a complete deletion, but it's a --

DR. SLAGA: We only put formulated to be non-irritating when there's a study or two to show that it has some slight -- some irritation. But if there's nothing, we don't want to put that in because it raises an alert that you don't want.

DR. ANSELL: Right. I mean, some materials --

DR. PETERSON: Right. So if there's no indication of irritation, then you should delete it.

DR. SLAGA: Yeah.

DR. ANSELL: We just don't think this study supports that statement.

DR. SLAGA: Right. Okay.

DR. ANSELL: It's not a concentration issue, it's not an interpretation issue. It's that this study doesn't suggest that people with a high propensity should avoid these cosmetics. That's just our suggestion.

DR. SHANK: I think in that first paragraphs of the discussion, you can eliminate the last two sentences, "The possible tumor promoting effects." And, "However, the panel." I certainly wouldn't start with that.

DR. SLAGA: Yeah.

DR. MARKS: So you would delete the last two sentences in that paragraph? "The patient noted a lack of genotoxicity data but considered those data to be unnecessary to the long-term ingestion of foods. Possible tumor promoting effects of soy was evaluated and not considered to be of concern."

So you would delete the sentence saying the possible tumor promotion effect of soy, et cetera, and then the last sentence, "However, the panel." Yeah. I kind of like that.

DR. SLAGA: Yeah. That would be good.

DR. MARKS: Tom?

DR. SLAGA: Yup.

DR. MARKS: Makes it easier for you, Priya. You don't have to wordsmith, just delete. So Lisa, is that okay with you?

DR. PETERSON: Can you just --?

DR. MARKS: So we're on page 42. And instead of just deleting the last sentence where we're talking about individuals with high propensity to develop skin cancer, we're also going to delete the sentence before "The possible tumor promoting effect was evaluated."

And that's where we talk about the persistent activation. That's what you were saying, Tom, with continuous -- I like that, Ron. I'm sure that addresses your concerns, Linda, because we eliminate it.

MS. LORETZ: Yes.

DR. MARKS: And, Jay, yours since --

DR. ANSELL: I'm just --

DR. MARKS: -- you make the point -- no, you make the point that the studies are not relevant, those studies that it bypasses. Okay.

DR. SHANK: That's too much emphasis on that oral study that really is not --

DR. MARKS: Okay. I'll mention that tomorrow.

DR. SHANK: -- pertinent.

DR. MARKS: If for some reason -- let me go back up here in the beginning. Where am I? Because I think that's an important -- that I will mention tomorrow when Wilma asks for editorial comments.

So tomorrow, I'm going to move that a tentative report be issued, safe for all except callus ingredients. There are three of them. We talked about the insufficiencies, either the composition, manufacture, or explanation of what the callus is, define it.

And then we recommend deleting the last two sentences. Oh, man. Let me see here. Let's go back up here. Delete last two sentences in the discussion under the tumorigenesis.

DR. PETERSON: So, if we have editorial comments -- I mean, this is one where in the non-cosmetic food I was just -- basically, it says that people consume the dyes without adverse effects. But there are people that are sensitive. Is it worth noting that? That's my comment in here. I don't know if it's worth discussion.

And then I found the -- on Page 35, the use of just 5 percent, I found very conf- -- 2 percent, 5 percent, without a little modifier, like the 5 percent extract group, would make it clearer. I struggled reading that part.

DR. MARKS: Any comments -- other comments? Okay. If not, let me save this and we'll move on to the next ingredient or ingredients.

Full Panel – December 10, 2019

DR. MARKS: At the June meeting this year the panel issued an insufficient data announcement. The panel requested sensitization data on either glycine max or glycine soja seed extract, at the current maximum use concentration of 2 percent. In addition, the panel requested data identifying the composition, method of manufacture, a general characteristic of the callus-derived ingredients.

We did get HRIPT data on three percent glycine soja seed extract, and so our team moves a tentative report be issued safe for all the ingredients except the callus ingredients and the same needs as previously. We want the composition, method of manufacture of the callus or an explanation of what the callus is. And then we had some discussion, but that's the motion, tentative report safe for all except callus.

DR. BERGFELD: Dr. Belsito?

DR. BELSITO: Well, we were insufficient for callus, but we're also insufficient for phytoplacenta conditioned medium, because it's apparently the medium that's being used and not the phytoplacenta.

And we thought for both of those we needed method of manufacture, impurities, composition, use concentration, 28-day dermal, if the composition was significantly different from the others.

DR. MARKS: I'll withdraw my motion; you can add that second ingredient, that's fine.

DR. BERGFELD: So we have a motion that's been seconded, any further discussion?

DR. MARKS: Now, does this go out as a tentative report? Because, again, we've sort of changed the -- I think, the data needs. We didn't ask for this second ingredient data needs that we're now saying.

DR. HELDRETH: I believe this can proceed as a tentative report.

DR. MARKS: Okay.

DR. HELDRETH: Because this will be the first time we put out a conclusion for it, formally.

DR. MARKS: Okay.

DR. LIEBLER: I wanted to mention one thing in the discussion, when I was looking through the minutes for the last discussion, and at some point we're talking about the tumor promotion, anti-promotion biology potentially involved here.

And I think in discussion with Tom and Paul, Paul asked if it's possible that people with a susceptibility to skin cancer might be at higher risk here. That's actually captured at the top of PDF 42, at the last sentence, the first paragraph.

But it seems to me that that was more of a hypothetical, that we didn't really have any data to suggest that. So, I suggested deleting that sentence, even though it's hypothetically possible. We just don't have any data to point to it.

DR. MARKS: Yeah, that was a discussion point I was going to bring up, Dan, we concur.

DR. LIEBLER: Okay.

DR. MARKS: No, we concur but we felt we could delete the last two sentences, not just the last one.

DR. LIEBLER: Okay, yup.

DR. BERGFELD: So there'll be modification of the discussion?

DR. MARKS: Yeah, and I think that's an important point because we spent a fair amount of time yesterday discussing if you're predispose obviously with severe -- or with chronic ultraviolet light damage, then adding this, that sentence just didn't seem appropriate.

DR. BERGFELD: All right, any other discussion regarding soy? All right, I'll call the question, all those in favor, please indicate by raising your hand. Unanimous.

Then moving on to Polysilicone-11, Dr. Belsito.

Safety Assessment of Soy-Derived Ingredients as Used in Cosmetics

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

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ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 28 soy-derived ingredients in cosmetic products. These ingredients are reported to primarily function as antioxidants, skin protectants, skin-conditioning agents, and hair-conditioning agents. The Panel considered the available data relating to the safety of these ingredients in cosmetic formulations, and concluded that 24 of the 28 soy-derived ingredients are safe in the present practices of use and concentration described in this safety assessment. However, the data on the remaining 4 soy-derived ingredients are insufficient to make a determination of safety under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This is a safety assessment of the following 28 soy-derived ingredients as used in cosmetic formulations:

Glycine Max (Soybean) Callus Culture
Glycine Max (Soybean) Callus Culture Extract
Glycine Max (Soybean) Callus Extract
Glycine Max (Soybean) Fiber
Glycine Max (Soybean) Flower/Leaf/Stem Juice
Glycine Max (Soybean) Leaf Cell Extract
Glycine Max (Soybean) Leaf Extract
Glycine Max (Soybean) Phytoplacenta Conditioned Media
Glycine Max (Soybean) Phytoplacenta Extract
Glycine Max (Soybean) Pulp
Glycine Max (Soybean) Seed Extract
Glycine Max (Soybean) Seedcake Extract
Glycine Max (Soybean) Seedcoat Extract
Glycine Max (Soybean) Seed Powder
Glycine Max (Soybean) Sprout Extract
Glycine Soja (Soybean) Extract
Glycine Soja (Soybean) Fiber
Glycine Soja (Soybean) Flour
Glycine Soja (Soybean) Germ Extract
Glycine Soja (Soybean) Hull
Glycine Soja (Soybean) Lipids
Glycine Soja (Soybean) Phytoplacenta Extract
Glycine Soja (Soybean) Seed
Glycine Soja (Soybean) Seedcake Extract
Glycine Soja (Soybean) Seed Extract
Glycine Soja (Soybean) Seed Powder
Glycine Soja (Soybean) Seed Water
Glycine Soja (Soybean) Sprout Extract

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the majority of these ingredients are reported to function as antioxidants, skin protectants, skin-conditioning agents – miscellaneous, and hair-conditioning agents; several other functions are also reported (Table 1).[1]

Several soy-derived ingredients such as Glycine Soja (Soybean) Oil, Glycine Soja (Soybean) Sterols, Glycine Soja (Soybean) Peptide, Glycine Soja (Soybean) Polypeptide, and Glycine Soja (Soybean) Protein, have been reviewed by the Panel, and were considered safe as used in cosmetics in the present practices of use and concentration described in the safety assessment.[2-4] The full reports on these ingredients can be accessed on the Cosmetic Ingredient Review (CIR)website (https://www.cir-safety.org/ingredients); therefore, data on these ingredients will not be included in this report.

Some of the ingredients reviewed in this safety assessment may be consumed as food, and daily exposure from food would result in much larger systemic exposures than from use in cosmetic products. Although oral studies are included herein, the primary focus of this safety assessment is on the potential for effects from topical exposure to these ingredients as used in cosmetics.

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 list of the typical search engines and websites used, sources explored, and endpoints that the Panel evaluates, is available 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.

Botanicals, such as soy-derived ingredients, may contain hundreds of constituents. However, in this assessment, the Panel is reviewing the potential toxicity of each botanical ingredient as a whole, complex mixture.

It is often not known how the substance being tested in a study compares to the cosmetic ingredient. In the report text, if it is known that the material being tested is a cosmetic ingredient, the INCI naming convention will be used (i.e., the names of cosmetic ingredients are capitalized, without italics (e.g., Glycine Max (Soybean) Leaf Extract)). If it is not known that the test substance is the same as the cosmetic ingredient, the taxonomic naming conventions (i.e. with genus and species name italicized (e.g., a *Glycine max* leaf extract)) or generic terminology (e.g., soybean extract) will be used.

CHEMISTRY

Definition

All ingredients reviewed in this report are derived from the soybean plant (*Glycine max*). *Glycine max* is the domesticated version of its wild progenitor *Glycine soja*.[5] According to the *Dictionary*, *Glycine max* is the accepted scientific name for *Glycine soja*. The definitions of the soy-derived ingredients included in this review are provided in Table 1.[1]

Plant Identification

Soybeans (*Glycine max* and *Glycine soja*) are a species of legume native to East Asia, from where they have spread to Europe and the Americas.[6] Soybean plant height varies greatly, ranging from 0.2 to 2 m. The leaves of the plant are trifoliate, and fall before seeds mature. The fruit is a hairy pod containing 2 - 4 seeds. Soybeans of both subgenera (*Glycine max* and *Glycine soja*) are found in various colors. Typical soybeans are different shades of yellow, brown, green, or black.[7] Compositions of soybeans may vary depending on the seed coat color. Details regarding this variation in composition dependent on color, are described in the Composition section of this report.

According to one study, differences in plant morphological characteristics are attributed between the two subgenera *Glycine max* and *Glycine soja*.[8] The wild soybean, *Glycine soja*, grows in the form of creepers with many lateral branches. These plants flower later than the cultivated soybean and produce small black seeds. *Glycine max* (cultivated soybean) produces large yellow seeds, with a fragile pod. In addition, differences at the genomic level between *Glycine max* and *Glycine soja* have been reported. However, such delineation between these species names is far from ubiquitous and these differences are not expected to affect their role in cosmetics; therefore, the generic terms "soy" and "soybean" are used throughout much of this report.

Method of Manufacture

The majority of the methods below are general to the processing of soy products, and it is unknown if they apply to cosmetic ingredient manufacture.

Glycine Max (Soybean) Leaf Extract

The production of a soy leaf extract involved leaf washing, grinding, freeze-drying, and extraction using a 30-fold volume of 80% ethanol for 4 hours at room temperature.[9] The extracted solution was collected, and a vacuum evaporator was used to remove the ethanol solvent in the supernatant. The amount of extract yielded was 22.3 ± 1.3% on a dry weight basis.

Glycine Max (Soybean) Pulp

To produce a black soybean pulp, black soybeans were soaked in water in a 3:1 ratio for 8 hours.[10] Pulp was obtained after grinding and removing the milk with a muslin cloth, and then freeze-dried.

Glycine Max (Soybean) Seedcoat Extract

In order to make a black soybean seedcoat extract, the black soybean seedcoat was extracted with acidic water and ethanol, purified using absorbent resin, and powdered by spray-drying.[10]

Glycine Max (Soybean) Seed Extract

To obtain a soybean powder, soybean seeds were washed with water, then dried.[11] The dried samples were ground to obtain the powdered form. To produce methanolic and hydroalcoholic extracts of seed powder, samples were extracted separately with methanol (100% and 50% aqueous, respectively) by cold maceration. Methanolic samples were extracted three times with 280 mL methanol for 3 hours in an electrical shaker at 40 ºC. The extracts were then filtered and evaporated. Hydroalcoholic extracts were produced in a similar manner, using alcohol and water as the extraction agents.

Another method to produce seed powder extract involves successive extraction with solvents in increasing order of their polarity (hexane, chloroform, ethyl acetate, ethanol, and water). First, powder materials are passed through a sieve. The sieved powder is then separated via a Soxhlet extractor for 16 hours. The extract is then evaporated to dryness in a rotary vacuum evaporator at 40º C. In order to prepare an ethanolic extract of the black soybean, black bean seeds were dried and ground.[12] The resulting powder was placed into an Erlenmeyer flask and suspended in 500 mL of 99% ethanol. The extract was then filtered and dried using a rotary evaporator.

An n-hexane soybean extract was produced by extracting soybeans (25 g) twice at room temperature by shaking for 48 hours with 500 mL n-hexane.[13] The combined n-hexane extracts were then dried in a vacuum desiccator under reduced pressure and concentrated using a rotavapor at 40 ºC. According to the same study, similar procedures are used in order to prepare ethyl acetate and ethanol soybean extracts.

Glycine Max (Soybean) Sprout Extract

According to one study, the production of black soybean sprout extract begins with soaking of the beans in deionized water.[14] The beans are then germinated, harvested, dried, crushed, sonicated, filtered, and centrifuged to separate the components and collect the supernatant.

Glycine Max (Soybean) Flour

Soybean flour has been reported to be produced by mechanically removing the hull of the soybean, followed by extraction of the oil with hexane.[15] The residual hexane is either removed by indirect heating followed by steam sparging in a desolventizer toaster or by direct contact with superheated hexane in a flash desolventizer. The desolventized soy is then heat-processed, ground, and isolated to the desired particle-size distribution according to product specifications.

Glycine Soja (Soybean) Phytoplacenta Extract

Glycine Soja (Soybean) Phytoplacenta Extract manufacturing information was provided by a cosmetic ingredient manufacturer. The extract was prepared by processing (mechanical grinding/milling) the soybeans, filtration, aqueous extraction, addition of phenoxyethanol, methylparaben, and tetrasodium EDTA, and refiltration.[16] Quality control is performed during the process.

Composition

Powder Extract

Soybeans contain many phytochemicals, such as phenolic acids, flavonoids, isoflavonoids, saponins, phytosterols, and sphingolipids.[17] In order to determine the composition of 24 different soybeans, soybean seeds were ground to a powder and extracted with 80% methanol. The results of this study can be viewed in Table 2. The majorities of the extracts were made up of carbohydrates (30.16 g/100 g), fats (19.94 g/100 g), and proteins (36.49 g/100 g).

Germ Extract

The isoflavone content of dry soybean germ extracts, extracted from ethanol (60 - 70%), methanol (80%), or ethanol (60%), were evaluated. [18] The isoflavone content of each of these extracts were reported to be 40%, 26%, and 30%, respectively.

Soybean Extract

The composition of a black soybean ethanolic extract was studied using thin layer chromatography (TLC).[12] Flavanoids, alkaloids, saponins, tannins, triterpenoids, and glycosides were found. In a different study, the anthocyanins, saponins, and isoflavones of a black soybean extract were examined.[19] Approximately 1.3 g anthocyanins (as tannins) were present per 100 g. Isoflavones were found in the following amounts: daidzin (25 mg/100 g), daidzein (92 mg/100 g), genistin (22 mg/100 g), genistein (51 mg/100 g), and glycitin (16 mg/100 g). In soybeans, isoflavones are strongly associated with proteins.[20] These isoflavones can be dissociated from soy-proteins using alcohol extraction which significantly diminishes the amount of bound-isoflavones.

According to high-performance liquid chromatography (HPLC), an n-hexane soy extract contained a total isoflavone concentration of 27 mg/25 g extract.[13] Among these isoflavones were 40% daidzin, 56% genistin, 2% daidzein, and 2% genistein. An ethyl acetate soy extract and ethanolic soy extract contained total isoflavone concentrations of 48 mg/25 g and 52 mg/25 g, respectively. In a different study, a black soybean extract contained 32.5 mg gallic acid equivalents/g (gallic acid used as sample phenolic compound), 5.7% protein, 80.4 g glucose/100 g, and 5.1% lipid.[21] The total phenolic acid content was 6652.2 µg/g, including gallic acid, protocatechuic acid, caffeic acid, chlorogenic acid, *m*-coumaric acid, ferulic acid, and sinapic acid. The total phytochemical content was 11,776.5 µg/g, including daidzein, genistein, glycitein, daidzin, genistin, glycitin, acetyldaidzin, acetylgenistin, acetylglycitin, malonyldaidzin, malonylgenistin, and malonylglycitin. Flavanols included epigallocatechin (3003.8 µg/g), epicatechin (635.8 µg/g), and epicatechin gallate (735.5 µg/g), and anthocyanins included cyanidin-3-*O*-glucoside (921.4 µg/g), peonidin-3-*O*-glucoside (113.6 µg/g), dephinidin-3-*O*-glucoside (50.9 µg/g), petunidin-3-*O*-glucoside (40.7 µg/g), and pelargonidin-3-*O*-glucoside (38.8 µg/g).

Seedcoat (Hull)

Thirty-nine samples of soybean hulls from feed mills and soy processors throughout the US were collected to examine their chemical composition.[22] The mean values of nutrients and amino acids found in these samples can be seen in Table 3. Samples predominantly consisted of crude fiber, acid detergent fiber, neutral detergent fiber, and nitrogen-free extract. Soybeans vary in composition based on color and area of origin. Black soybeans have unique properties owing to its black hull.[23] The black hull contains polyphenols, such as anthocyanins, procyanidins, and catechins. According to another study, the chemical composition of soybean hulls is dependent upon the efficiency of the dehulling process.[24] The soybean hulls may contain variable amounts of cellulose (29 - 51%), hemicelluloses (10 - 25%), lignin (1 - 4%), pectins (4 - 8%), proteins (11 - 15%), and minor extractives.

Soybean Flour

A comparison of the composition of soybeans differing in seed coat color was examined.[7] Soybeans of a light yellow, dark yellow, brown, and black color were ground to a flour and analyzed for isoflavone content and other chemical composition. Flours were defatted using n-hexane as a solvent for lipid extraction. Lipid, protein, ash, crude fiber, and carbohydrate content were similar among all tested samples. The average amount of lipids, protein, ash, crude fiber, and carbohydrates were 19.05, 37.8, 4.2, 6.3, and 24.7 g/100 g, respectively. Isoflavone content was determined by HPLC. Soybean flour extracted from soybeans with a light-yellow seed coat showed the highest isoflavone content (415.98 mg/100 g), while soybean flour extracted from soybeans with a dark yellow seed coat showed the lowest isoflavone content (220.88 mg/100 g). All samples showed significantly different levels of isoflavone glycosides. Malonyl genistin, for example, was discovered in amounts of 74.98, 95.23, 138.57, and 116.29 mg/100 g, in dark yellow, brown, light yellow, and black soybean samples, respectively.

Pulp

HPLC was used to determine the isoflavone content of a black soybean pulp.[10] The amounts of daidzin, daidzein, genistin, and genistein in the black soybean pulp were determined to be 2.85, 0.27, 1.85, and 0.51 mg/100 g, respectively.

Sprout

The variation of isoflavone content in 17 different types of yellow and green soybean sprouts was studied using HPLC.[25] Yellow soybean sprouts were produced in a dark room. For green soybeans sprouts, seeds were germinated in the dark and then transferred to a box under a yellow light source. Sprouts were separated into cotyledons, hypocotyls, and roots. The average isoflavone concentration in the cotyledon, hypocotyl, and root of the green sprouts was 2167, 1169, and 2399 μg/g, respectively. The average isoflavone concentration in the cotyledon, hypocotyl, and root of the yellow sprouts was 2538, 1132, and 2852 μg/g, respectively.

Leaf Extract/Seed Extract

The phytochemical content of ethanolic leaf and seed extracts were evaluated.[26] The total phenol, flavonoid, beta carotene, and lycopene content in the ethanolic leaf extract was 1092, 877, 40, and 0.69 mg/100 g extract, respectively. The total phenol, flavonoid, beta carotene, lycopene, and ascorbic acid content in the ethanolic seed extract was 938, 274, 11, 10, and 1.3 mg/100 g extract, respectively. In a different study, the phytochemical content of a methanolic soybean leaf extract was studied via various chromatographic procedures.[27] Among the 16 phytochemicals found were 6 isoflavones (4,5,7-trihydroxyisoflavone-7-*O*-β-D-glucopyranoside, 7-dihydroxy-6-methoxyisoflavone, 4,7-dihydroxyisoflavone, 4,7-dihydroxyisoflavone-7-*O*-β-D-glucopyranoside, 4',5,7-trihydroxyflavone, 3',4',5,7-tetrahydroxyflavone, and 3',4',5-trihydroxyflavone-7-*O*-β-D-glucopyranoside), 1 flavanol (3,4',5,7-tetrahydroxyflavonol), 2 pterocarpans (coumetarol and glyceofuran), 2 phytosterols (soyasapogenol B and stigmasterol), 2 phenolic compounds (4-hydroxybenzoic acid and methyl-4-hydroxybenzoate) and 1 sugar alcohol (D-mannitol).

Impurities

Glycine Soja (Soybean) Phytoplacenta Extract

Product specifications for a trade name mixture consisting of water (78.93%), Glycine Soja (Soybean) Phytoplacenta Extract (20%), phenoxyethanol (0.90%), methylparaben (0.15%), and tetrasodium EDTA (0.02%), include the following parameters: < 20 ppm heavy metals, < 10 ppm lead, < 2 ppm arsenic, and < 1 ppm cadmium.[28] Detection limits of certain fragrance allergens were also analyzed for this trade name mixture and can be found in Table 4. These fragrance allergens are those that are required to be specified on cosmetic labels in Europe if certain limits are exceeded. In addition, this trade name mixture did not exceed current US Environmental Protection Agency (EPA) pesticide specifications.

USE

Cosmetic

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

In some cases, VCRP data were submitted under a non-INCI name. For example, Glycine Soja (Soybean) Flour is an INCI name, but *Glycine max* (soybean) flour, is not. VCRP data were available for *Glycine max* (soybean) flour, but not for Glycine Soja (Soybean) Flour; therefore, these data are reported for Glycine Soja (Soybean) Flour, as these names are believed to be synonymous because, according to the *Dictionary*, the accepted scientific name for *Glycine soja* is *Glycine max*.

According to 2020 VCRP data, Glycine Max (Soybean) Seed Extract is reported to be used in 402 formulations, 279 of which are leave-on formulations, and *Glycine max* (soybean) flour (synonymous with Glycine Soja (Soybean) Flour) is reported to be used in 84 formulations (Table 5).[29] All other in-use ingredients are reported to be used in 56 formulations or less. The results of the 2016 concentration of use survey conducted by the Council indicate Glycine Soja (Soybean) Seed Extract has the highest concentration of use; it is used at up to 2% in face and neck products.[30] Ingredients that are not reported to be in use, according to VCRP and Council survey data, are listed in Table 6.

Incidental ingestion of these soy-derived ingredients is possible as Glycine Soja (Soybean) Lipids is used in lipstick formulations at up to 0.65%. Glycine Max (Soybean) Seed Extract and Glycine Soja (Soybean) Seed Extract are also reported to be used in lipstick formulations, however the concentration at which they are used is unknown. In addition, some soy-derived ingredients are used in in products applied near the eye (e.g. in eyeshadows at a maximum concentration of up to 0.09% Glycine Soja (Soybean) Lipids).

Additionally, some of the soy-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Glycine Soja (Soybean) Seed Extract is reported to be used at a concentration of 0.000001% in hair spray formulations. 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 < 10 µm compared with pump sprays.[31,32] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[33,34] In addition, Glycine Max (Soybean) Seed Extract and Glycine Max (Soybean) Lipids are reported to be used in face powders, and could possibly be inhaled; concentration of use data were not reported for these uses. 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.[35-37]

The soy-derived ingredients are not restricted from use in any way under the rules governing cosmetic products in the European Union.[38]

Non-Cosmetic

Food

Soy has been a common staple in Asian diets for thousands of years, and is also a part of modern Western diets. Soybeans can be processed to be used in or as food products such as soy milk, soy sauce, soy curds, tofu, miso, cheese, candies, ice cream, baked goods, and oil.[39] In addition, soy can be found in infant formulas. Soybeans and soybean constituents are commonly used as food fortifiers as their protein content is high. Soybean hulls are commonly used in poultry and swine feeding.[22] In addition, the FDA requires allergen labeling when major allergens are included in food; these allergens include soybeans.[40] According to the FDA, foods, such as soybeans, that have been ingested as food and food products prior to January 1, 1958, are considered GRAS (generally recognized as safe) through experience based on common use in food [21 CFR §170.30].

Industrial

Soybean meal and soybean proteins are used in the manufacture of synthetic fiber, adhesives, varnishes, paints, and pesticides.[17,39] In addition, soybeans are used for biodiesel fuel, upholstery, candles, ink, crayons, lubricants, and hydraulic fluid.[41] Soybean hulls are used in the treatment of wastewater.[24]

Medicine

Soybean germ extract has been reported to be used in herbal medication for the treatment of menopausal symptoms.[18] Soy products are also taken as supplements to alleviate high blood pressure/cholesterol, and to increase bone health.[42] None of the ingredients included in this report are used as active ingredients in US FDA-approved medical preparations; however, soybean oil is used in an FDA-approved, intravenous medication, used to provide a source of calories and essential fatty acids for patients requiring parenteral nutrition when oral or enteral nutrition is not possible or insufficient.[43]

TOXICOKINETIC STUDIES

When rats were given a single oral dose of a soybean extract containing 74 µmol genistein and 77 µmol daidzein/kg as conjugates, the urinary excretion of daidzein and genistein was 17.9% and 11.9%, respectively, over a 48-h post-dose period.[18] No other details regarding this study were provided. In a human study, 11 German post-menopausal women were given a bolus dose of a commercial soy extract.[44] Sulfoglucuronides were the major metabolites of daidzein and genistein in the plasma, and 7-*O*-glucuronides were the predominant metabolites in the urine.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

No acute oral, dermal, or inhalation toxicity studies were discovered in the published literature regarding these soy-derived ingredients, and no unpublished data were submitted. However, a study regarding the oral toxicity of a soybean hull extract was found and is summarized below.

Oral

Glycine Max (Soybean) Seedcoat Extract

Sprague-Dawley rats (n = 6), as well as C57BL/6 mice (n = 6) were given a single oral dose of black soybean hull extract (2.5 g/kg bw) via gavage.[23] Control animals were given purified water (n = 3). Rats were observed for 14 days, and mice were observed for 15 days for signs of morbidity or mortality. No deaths, significant decreases in body weight, or gross pathological abnormalities were observed in either species. The LD_{50} was reported to be greater than 2.5 g/kg bw in rats and mice.

Short-Term Toxicity Studies

Oral

Glycine Soja (Soybean) Extract

The potential toxicity of a hot water extract of black soybeans was studied.[19] Sprague-Dawley IGS rats (6/sex/group) were given 0, 0.5, 1.5, or 5% black soybean extract in the diet for 28 days. No deaths or abnormalities regarding the general conditions of the animals were reported throughout the study. At week 4, a statistically significant increase in urinary potassium values were found in females receiving 5% black soybean extract compared to controls. No treatment-related hematological adverse effects were observed. Platelet count levels were significantly lower in all dosed males; however, changes were minimal and values were within historical control data. Significant elevation of mean corpuscular volumes and reticulocytes levels were noted in the highest dosed males, however, these changes were also minimal and values were within historical control data. A statistically significant increase in alkaline phosphatase enzymes was found in male rats given 1.5% black soybean extract; however, these changes were not dose-dependent. A statistically significant lowering of relative epididymis weights was found in all extract-dosed males. In addition, a statistically significant but non-dose-dependent elevation of relative heart weight was found in females given 0.5% black soybean extract.

Subchronic Toxicity Studies

Oral

Glycine Soja (Soybean) Extract

The systemic toxicity a soybean extract was studied in F344 rats (40 rats/sex).[45] The ground extract was mixed into the diet for 13 weeks at doses of 0, 1.25, 2.5, and 5% (equivalent to doses of 707.2 , 1449.1, and 2830.4 mg/kg/day, respectively, in males and 751.8, 1498.6, and 3028.1 mg/kg/day, respectively, in females). The composition of the extract was 94% saponins and 6% isoflavones (3.78 daidzein, 1.6% glycitein, 0.6% genistein). Neither mortality nor deterioration in general conditions were observed during the course of the study. Results given in this study did not specify which solvent was used when stating extract-induced effects. Statistically significant body weight reductions were noted in males treated with 5% soybean extract, and in all treated females. Statistically significant decreases in red blood cell count, hematocrit levels, and an increase in mean corpuscular volume were detected in males given 5% extract. This effect was not seen in females. Statistically significant, but minimal increases in total protein, albumin, calcium, and aspartate aminotransferase were found in males treated with 2.5% or higher. In females, significant increases of potassium and decreases in chloride were observed in the 5% group. Males in the 5% group displayed a decrease in absolute heart and spleen weights. Dose-dependent decreases in absolute brain weights were observed in male rats dosed with 2.5% and higher. A statistically significant increase in absolute liver weight was observed, in a dose-dependent manner, in all treated animals. Relative kidney weights were also increased in the highest dosed groups of both sexes. Females in the high-dose group displayed a statistically significant decrease in absolute lung weight. Dose-dependent decreases in the absolute weights of the heart and spleen were observed in females at 2.5% and 5%. Soybean-extract related effects were noted in the prostate, vagina, and ovaries. Male rats in the 5% group displayed epithelial atrophy in the ventral prostate, accompanied by cytoplasmic vacuolation and decreases of the luminal secretory fluid. In female rats treated with 2.5% and above, increased incidences of mucification and atrophy of the vaginal epithelium, as well as increased atretic follicles, were observed.

Glycine Soja (Soybean) Fiber

Soluble soybean fiber (SSF) was given in the diet to Sprague-Dawley CD rats (20/sex/group) at concentrations of 2, 3, and 4%, for 3 months.[46] A separate group was given an untreated diet, and served as the control. The SSF was extracted from the fibrous residue in the production process of soy protein. The estimated amount of fiber in the SSF was approximately 72 - 77%. There were no test article-related deaths during the study. In both sexes, weight gain in all dose groups during weeks 2 - 7 was low compared to the controls; however, this effect was not dose-related. By the end of the period, weight gain differences were minimal in dosed groups versus control animals. Decreased food consumption was noted in males (weeks 2 - 5; all dose levels) and in females (weeks 2 - 4; all dose levels). This was followed by a period of increased food intake in both males (weeks 8 - 10; all dose levels) and females (weeks 8 - 11; all dose levels). In all treated males, an increased erythrocyte and decreased reticulocyte count was noted, however, these effects were not dose-dependent. In females, there was a slight, but dose-related increase in the hematocrit and erythrocyte counts of animals of the 3 and 4% dose groups. A reduction in spleen weight was noted in all dosed animals, however this effect was not dose-dependent, and no other histopathological adverse effects were found relating to this matter.

Chronic Toxicity Studies

Oral

Glycine Max (Soybean) Seedcoat Extract

C57BL/6 mice (11 males and 12 females/group) were fed a diet supplemented with 0, 2, or 5% of a black soybean hull extract (acidic water and ethanol used as the extraction agent) for 26 weeks.[23] The mean intake of the extract in males and females was 1468.9 and 2621 mg/kg bw/day, respectively, in the 2% treated group, and 5074.1 and 7619.9 mg/kg

bw/day, respectively, in the 5% treated group. A significant reduction in body weights was noted in 5% extract-exposed males compared to 2% extract-exposed males and control males. At week 26, the abdominal fat of 5% extract-exposed males was 40% lower than that of controls. This effect was not seen in females. The white blood cell count in 5% extract-exposed males and red blood cell count, hemoglobin, and hematocrit levels in 5% extract-exposed females were significantly increased compared to control animals. Triglyceride and chloride levels in males treated with 5% extract were significantly decreased. In female animals, triglyceride and blood urea nitrogen levels were decreased in the 5% extract-exposed group. In males treated with 5% extract, an increase in the relative weights of the kidney, spleen, and brain was apparent. In the same dosing group, a decrease in the relative weight of the spleen was noted. In females treated with 5% extract, absolute weights of the heart, liver, and kidney were decreased. No significant changes in final body weights were noted in any dosed females. In animals dosed with both 2% and 5% soybean seedcoat extract, in the duodenum, slight pigment accumulation in histiocytes of the lamina propria was found. Slight accumulation of pigment in Kupffer cells of the liver was apparent in 5% extract-exposed males and females. The authors considered the no-observed adverse-effect-level (NOAEL) of the 5% black soybean hull extract to be 5074.1 mg/kg bw/day in males and 7617.9 mg/kg bw/day for females in mice.

Glycine Soja (Soybean) Flour

Groups of 20 male Wistar rats were given diets containing 19.1, 42.1, or 79.7% raw soy flour.[47] Each of the three groups was subdivided into two groups, one of which was fed ad libitum, and the other a single 4-h meal per day. Two weeks after the start of the experiment, 5 rats per group were subjected to an injection of azaserine (0.5 mg/100 g bw), dissolved in 0.5 mL sterile saline, to induce pancreatic nodules. Injections were given once a week for 20 weeks. Rats were given their respective diets for up to 12 months. Azaserine injections had no effect on food intake or body weight. A significant decrease in food intake and body weight was noted in animals receiving increased levels of raw soy flour in the diet ($P < 0.01$). Animals fed one meal per day containing 19.1% raw soy flour reached 85% of the body weight of their ad libitum-fed counterparts. Animals fed diets containing 42.1% and 79.7% raw soy flour reached 76 and 62% of the body weight of the ad libitum-fed rats, respectively. Pancreas weights increased as the level of raw soy flour in the diet increased in all treated rats. Approximately 45% of all animals used in the experiment died prior to study termination. In rats fed 19.1% raw soy flour, 25% of rats fed ad libitum were alive at the end of the experiment, while 75% of rats fed only once per day survived until study termination. In rats fed 42.1% raw soy flour, 80% of the meal-fed animals survived vs. 62.5% in the ad libitum group. (Carcinogenic effects observed in this study can be found in the Tumor Promotion section of this report.)

Seventy-two male albino mice/group were fed diets of either raw soy flour, heated soy flour, or casein for up to 18 months.[48] The soy flour diet consisted of soy flour (42.1%), glucose (15%), non-nutritive fiber (5%), corn oil (5.5%), lard (2.5%), DL-methionine (0.1%), choline chloride (0.2%), vitamin mix (2%), mineral mix (5%), and dextrin (22.6%). Animals were also given an injection of either azaserine (10 mg/kg/bw) or 0.9% sodium chloride. Growth of mice was significantly lower ($P < 0.01$) in mice given raw soy flour compared to mice given heated soy flour or casein. The injections with azaserine and sodium chloride did not seem to have an effect.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

No DART studies were discovered in the published literature regarding these soy-derived ingredients, and no unpublished data were submitted. However, a study analyzing the reproductive effects of orally ingested soybean was found and is included below.

The potential reproductive toxicity of the soybean was tested in a study involving 5 male albino rats/group.[49] Male rats were treated with processed soybean meal in the diet at 0, 100, 200, and 300 mg/kg bw for 65 days. Each treated male rat was mated with 3 untreated female rats. No statistically significant effect of soybean meal on the weight of the testes and epididymis was observed. Sperm viability and sperm count were significantly reduced in a dose-dependent manner. In addition, sperm head abnormality was significantly increased in a dose-dependent manner. Rats in the control group displayed seminiferous tubules at various stages of development. Rats in the 100 mg/kg bw group had testicular tissues with compacted interstitial spaces, mild hemorrhaging along the Sertoli's cells, and slight degeneration of the spermatids. Rats treated with 200 mg/kg bw displayed similar effects, and rats treated with 300 mg/kg bw displayed adverse effects such as testicular tissues with inflammation of interstitial cells, severe hemorrhaging along the Sertoli's cells, and excessive degeneration of spermatids, and necrosis. The conception rate of female rats mated with treated males was reduced in a dose-dependent manner when compared to controls.

GENOTOXICITY

No genotoxicity studies were discovered in the published literature, and no unpublished data were submitted.

CARCINOGENICITY STUDIES

No carcinogenicity studies were discovered in the published literature, and no unpublished data were submitted.

Tumor-Promotion Studies

Glycine Soja (Soybean) Flour

Twenty male Wistar rats/group were given diets containing 19.1, 42.1, or 79.7% raw soy flour.[47] Each of the three groups was subdivided into two groups, one of which was fed ad libitum, and the other one 4-h meal per day. Two weeks after the start of the experiment, 5 rats per group were subjected to an injection of azaserine (0.5 mg/100 g bw), dissolved in 0.5 mL sterile saline. Injections were given once a week for 20 weeks. Rats were given their respective diets for up to 12 months. Twenty-seven rats died prior to the end of the study. Among these animals, pancreatic nodules were observed in 1/11, 3/7, and 6/9 rats given 19.1, 42.1, 79.7% raw soy flour, respectively. In rats that were sacrificed after 10 - 12 months, in the absence of azaserine injections, the incidence of nodules was low and unaffected by the feeding regime. Animals that received azaserine injections had a much higher incidence of nodules, which increased with the level of raw soy flour in the diet. No nodules were found in any other organ examined. (Other toxic effects observed during this study can be seen in the Chronic Toxicity Studies section of this report.)

ANTI-TUMORIGENICITY STUDIES

Glycine Soja (Soybean) Flour

In a 15-month study, male Syrian Golden hamsters were divided into four groups and given raw soy flour (15 animals/group), heated soy flour (12 animals/group), raw soy flour/co-administered injection with *N*-nitrosobis(2-oxopropyl) amine (BOP; 15 animals/group), or heated soy flour / injected with BOP (13 animals/group).[48] BOP injections were given at a level of 10 mg/kg bw on days 7 and 14. Animals not given a BOP injection received an injection of 0.9% sodium chloride. Animals fed raw soy flour displayed a slower growth rate ($P < 0.01$) than those fed heated soy flour. At 7 - 8 months, animals injected with BOP lost weight at a significantly ($P < 0.05$) faster rate than animals injected with saline. No significant difference was found in the weights of the pancreas in any of the groups by the end of the study. In groups that did not receive BOP, tumor incidence was quite low; however, in groups that did receive BOP, tumor incidence was increased. Seven out of 8 surviving animals that were given heated soy flour and BOP injections had pancreatic adenomas, and 5 had pancreatic adenocarcinomas. One out of 11 surviving BOP-injected animals given raw soy flour had a pancreatic adenoma, and no adenocarcinomas.

OTHER RELEVANT STUDIES

Effect on Cancer Cell Proliferation

Glycine Soja (Soybean) Extract

The potential anti-proliferative effect of an ethanolic extract of the black soybean on A549 lung cancer cells was studied.[12] The black soy ethanol extract was dissolved in 10% dimethyl sulfoxide (DMSO) at a concentration of 10 mg/mL. The extract was used to prepare final diluted concentrations of 6.25, 12.5, 50, 100, 200, 400, and 800 µg/mL. Cancer cells were cultured for 1 week before exposure to the test substance. The cells were then subjected to 100 µL of each dilution of the test substance as stated above. Each experiment was performed three times, and results were averaged. After incubation for 48 hours, cell viability was measured using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The extract exhibited cytotoxic activity in a concentration-dependent manner in A549 cells. Percent inhibition of A549 lung cancer cells by the soy ethanol extract was 5.2, 4.4, 20.6, 37, 52.8, 60.8, 68.7, and 83.8% when tested at concentrations of 6.25, 12.5, 50, 100, 200, 400, and 800 µg/mL, respectively.

The effect of black soybean extract on the suppression of the proliferation of human gastric cancer (AGS) cells was studied.[21] For this study, the soybean extract was obtained by extracting black soybean with acidified aqueous acetone. AGS cells were plated at a density of 5×10^3 cells/well in 96-well plates. The effect of the extract on the growth of AGS cells was investigated using an MTT assay. After incubation (24 hours), the extract was added to the plates in concentrations of 1 - 5 mg/mL, and incubated for another 48 hours. The extract inhibited growth of AGS cells in a dose-dependent manner. When a concentration of 3 mg/mL extract was used on the AGS cells, cell viability was significantly decreased compared to control cells ($P < 0.05$). Approximately 65.7, 38.8, and 22.5% cells survived after treatment with 3, 4, and 5 mg/mL of black soybean extract. The same procedure was performed on normal rat fibroblast cells. No cytotoxicity was observed when black soybean extract was used on these cells.

Glycine Max (Soybean) Leaf Extract

The anti-proliferative effects of an ethanolic extract of soybean leaves (SLE) were studied in both human colon cancer cells (HCT116) and human lung cancer cells (H1299).[9] The treatment of the HCT116 cells with SLE at concentrations of 125, 250, and 500 µg/mL for 72 hours resulted in a significant inhibition of growth (by 34 - 89%). When HCT116 cells were treated with the same concentrations of SLE for 96 hours, growth inhibition increased (by 62 - 87%). Treatment of H129 cells with SLE (125, 250, and 500 µg/mL) inhibited growth by 45 - 85%. In both types of cancer cells, the growth inhibitory effects of SLE increased with increasing concentrations of SLE, showing a significant dose-response relationship. In addition to inhibition of growth, the effect of SLE on adhesion and migration of the human cancer cells was also studied. When H1299 cells were treated with SLE at 500 µg /mL, a significant inhibition of migration was noted.

Treatment of HCT116 and H1299 cells with SLE also inhibited cell adhesion to fibronectin by 21 - 31% (at 125 - 500 µg/mL) and 14% (at 500 µg/mL), respectively.

Epidermal Hyperplasia Inhibition

Glycine Soja (Soybean) Extract

The possible inhibition of retinoid-induced epidermal hyperplasia was studied in 7 human skin cultures.[50] Cultures of human skin were incubated with 1 µg/mL of 14-all *trans* retinoic acid (14-all *trans* RA) for 8 days. A soy extract was prepared by mixing 250 mg of soy powder in 2 mL of a basal medium. A DMSO extract was also prepared by dissolving 250 mg of soy powder in 1 mL of solvent. All of the soy dissolved in the DMSO, and this solution was used as a control. Hyperplasia-induced organ cultures were treated with soy extracts at 4, 20, or 40 µg/mL. In the presence of 40 µg/mL soy extract, retinoid-induced hyperplasia was reduced by 41% relative to the retinoid response in the absence of soy. Sixteen percent inhibition was observed at 4 µg/mL, and 32% inhibition was observed at 20 µg/mL.

Effects on Pigmentation

Glycine Soja (Soybean) Sprout Extract

An aqueous extract of black soybean sprouts was examined for whitening capacity.[14] Whitening capacity was measured via the measurement of tyrosinase-inhibition. Tyrosinase inhibition capacity of the extract, when used at 40 mg/mL, reached 98%. Inhibition capacity reached 60 - 95% after treatment with 4 mg/mL of the extract, and 40% after treatment with 2 mg/mL of the extract.

Estrogenic Activity

Methanol extracts were prepared from soybeans and analyzed by measuring the MCF-7 (breast cancer cell line) cell proliferation in response to various concentrations of the extract (0.1 – 100 µg/mL).[51] Soybean extract (0.1 µg/mL) caused an increase in proliferation to approximately 35% of what would be expected from 0.1 nM estradiol; while at 100 µg/mL, proliferation was increased to 90%. In order to determine whether the induced cell proliferation was mediated via an estrogen receptor (ER)-dependent mechanism, the soybean extract (100 µg/mL) was tested in combination with the pure estrogen antagonist, fulvestrant. Testing of the soybean extract in combination with fulvestrant resulted in decreased activity. A reporter gene assay was also performed using human embryonic kidney cells (HEK 293 cells) in order to determine whether the effects of the extracts were mediated via ERα and/or ERβ. Preferential agonist activity toward ERβ was observed. For ERβ transcriptional activation, the maximal value obtained at 100 µg/mL was 79.7%, compared to 53.2% for ERα transcriptional activation.

A study was performed to analyze the effects of orally administered soybean extract, obtained using different extraction methods, on the skin of 64 Sprague-Dawley female rats (8/group).[13] The specific soy extracts were administered via gavage each day for one month. Animals in group A were untreated, and animals in group B received carboxymethyl cellulose (0.5%); this solution was also used to dilute the extracts for administration to the experimental animals. Group C received an n-hexane soy extract at a dose of 100 mg/kg and group D received the same extract at a dose of 200 mg/kg. Groups E and F received ethyl acetate soy extracts at doses of 100 and 200 mg/kg, respectively, and groups G and H received an ethanolic soy extract at 100 and 200 mg/kg, respectively. (Details about the preparation of these extracts can be seen in the Method of Manufacturing section of this report.) A statistically significant reduction in the number of estrogen receptor-positive cells (per 10 high-power fields) and an increase in the collagen layer thickness were observed ($P < 0.05\%$) in all groups treated with a soy extract. The thickness of the collagen layer of the rats in group F (1154.93 µM) was significantly higher than that of the rats in group A (864.32 µM). The number of estrogen receptor-positive cells in group D (2.37) was significantly reduced compared to that of group A (6.87), B (8.25), and C (4.75). The number of estrogen receptors in all soy extract–treated groups were decreased compared to that of the controls.

Cytotoxicity

Glycine Max (Soybean) Callus Culture

A trade name mixture containing water (q.b. to 100% w/w), Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%), was tested for cytotoxicity.[52] The product showed a half maximal inhibitory concentration (IC_{50}) greater than 5 µL/mL on human keratinocytes with an MTT assay. No other details regarding this study were provided.

Glycine Soja (Soybean) Phytoplacenta Extract

The cytotoxic potential of a trade name mixture consisting of water (78.93%), Glycine Soja (Soybean) Phytoplacenta Extract (20%), phenoxyethanol (0.90%), methylparaben (0.15%), and tetrasodium EDTA (0.02%) was studied.[53] Human dermal fibroblasts were treated with this trade name mixture at concentrations of 0.01, 0.1, and 1% and incubated for 24 hours. The test substance did not appear to have an effect on cellular viability.

Immunotoxicity

BALB/c mice were dorsally shaved and epicutaneously exposed to a crude soybean extract (50 mg/mL) containing 0.5% sodium dodecyl sulfate in distilled water (n = 9) or distilled water alone (n = 8).[54] Each week, the skin of the animals was shaved and stripped 10 times using adhesive tape. Mice were also intraperitoneally injected with a mixture of midazolam, butorphanol, and medetomidine to control pain. Three times a week for 5 weeks, 50 µL samples were applied epidermally. Various specific immunoglobulin E (IgEs) secreted in response to 7S globulin (Gly m 5), 11S globulin (Gly m 6), profilin (Gly m 3), and PR-10 starvation-associated message 22 (Gly m 4) were measured using enzyme-linked immunosorbent assays or immunoblots. Percutaneous exposure to the soybean extract caused a systemic secretion of soybean-specific IgEs. Of the soy proteins, both 7S and 11S globulins were allergenic in 67% of tested mice. Of the 3 subunits of 7S globulin, it was determined that the β subunit is especially prone to eliciting secretion of soybean-specific IgEs following percutaneous exposure.

DERMAL IRRITATION AND SENSITIZATION

The dermal irritation and sensitization studies summarized below are presented in Table 7.

Irritation

The irritation potential of a cosmetic water-in-oil emulsion incorporating 4% soybean extract was studied in 11 subjects.[55] One gram of base emulsion and emulsion with soy was used to treat sites, and covered with a surgical dressing for 48 h It was not stated whether or not the dressing used was occlusive. No irritation was observed. The irritation potential of a mixture containing water and Glycine Soja (Soybean) Seedcake Extract (13%) was studied in 10 subjects.[56] The test material was applied to the skin at a concentration of 5% and covered with an occlusive patch for 48 h. The test substance was considered to be non-irritating. The irritation potential of a black soybean sprout extract (4 or 40 mg/mL) was studied in 30 subjects (15/sex).[14] Extracts were applied on the arm, under a patch, for 24 h. It was not stated whether or not the dressing used was occlusive. No other details regarding this study were provided. No signs of irritation were observed in any subject.

Sensitization

The sensitizing potential of a trade name mixture containing water (q.b. to 100% w/w), Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%), was tested.[52] In this assay, the expression of CD80 and CD86 were evaluated in a monocyte cell line. The test substance was determined to be

A human repeat insult patch test (HRIPT) was performed on 108 subjects using a leave-on skin care preparation containing 0.3% Glycine Soja (Soybean) Germ Extract under occlusive conditions.[57] The test substance was considered to be non-irritating and non-sensitizing. No irritation or sensitization was observed in a different HRIPT performed on 44 subjects using a skin care preparation containing 0.198% Glycine Soja (Soybean) Seed Extract.[58] In addition, no irritation or sensitization was observed in an HRIPT performed on 59 subjects using a leave-on product containing 3% Glycine Soja (Soybean) Seed Extract.[59]

OCULAR IRRITATION STUDIES

In Vitro

Glycine Max (Soybean) Sprout Extract

The ocular irritation potential of black soybean sprout extract (40 mg/mL and 4 mg/mL) was studied using a hen's egg test chorioallantoic membrane (HET-CAM) assay.[14] Sodium dodecyl sulfate (0.4% and 4%) was used as a positive control, and 0.9% saline was used as a negative control. Similar results were observed in both the negative control group and groups treated with the soybean sprout extract. The test substance was considered to be non-irritating. No other details regarding this study were provided.

Glycine Soja (Soybean) Seedcake Extract

A neutral red release assay was performed to evaluate the ocular irritation potential of a mixture containing water and Glycine Soja (Soybean) Seedcake Extract (13%).[56] Rabbit cornea fibroblasts were exposed to the test substance at concentrations of 5 - 50%. The IC_{50} (i.e., the concentration causing 50% mortality) was greater than 50%. (The percent mortality observed at the dilution of 50% was less than 20%). Thus, the cytotoxicity of the test substance was considered to be negligible, and the mixture non-irritating to the eye.

CLINICAL STUDIES

Case Reports

A 55-year-old woman with a 5-month history of reacting to a facial cosmetic cream developed erythema and swelling of the face after using a night cream containing soybean extract.[60] Patch tests were performed using different dilutions of soybean extract, the night cream itself, components of the night cream, and standard cosmetic/facial ingredients.

The following allergens were tested: para-phenylenediamine (1% in petrolatum (pet.)), fragrance mix (8% pet.), cocamidopropyl betaine (1% pet.), night cream, ceramide 3 and soybean extract (2% pet.), ceramide 3 (5%), ceramide 3 (2%), and three different dilutions of soybean extract (1, 10, and 20%). When the soybean extract dilutions were applied under occlusive patches to the forearm and read at 30 minutes, slight erythema was observed at the 20% dilution. Palpable erythema was observed after 36 hours at the 10 and 20% dilution. Patch tests using both concentrations of ceramide 3 were negative, however, the patch test using ceramide 3 and soybean extract (2%), yielded positive results. Positive results were obtained for all dilutions of the soybean extract on days 2 and 7. Cocamidopropyl betaine and *p*-phenylenediamine resulted in positive results on day 4, and the fragrance mix yielded positive results on day 2 and 4. The patient reported previous consumption of soybeans without adverse reactions and was subjected to an allergen-specific IgE test to soybean, which was negative.

A 30-year-old female esthetician with atopic dermatitis and severe hand eczema developed anaphylactic symptoms (systemic urticaria, dyspnea, and hypotension) after consuming soy products.[61] Prior to working as an esthetician, she did not experience hand eczema or soy food allergies. Beginning at the age of 23, she began to touch cosmetic lotions frequently at the work place. Several months later, she noticed eczema on her fingers. At 28 years old, she experiences severe symptoms such as systemic urticaria and dyspnea after consumption of soy products. Examinations revealed the following: a total serum immunoglobulin (IgE) level of 3280 international units (IU)/mL, thymus and activation-regulated chemokine level of 715 pg/mL, and lactase dehydrogenase levels of 274 units (U)/L. Specific IgE antibodies were detected for soy (19.3 U_A/mL), Japanese cedar (4.72 U_A/mL) and Japanese white birch (1.24 U_A/mL). Skin pricks test were preformed using soy extract (10 mg/mL), the cosmetic lotion containing soy extract used by the patient, and commercially available soy milk. All tests yielded positive results. Skin prick tests performed on three healthy volunteers using the same cosmetic lotion yielded negative results.

Occupational Exposure

The allergenicity to soybean hull in subjects exposed to different levels of soybean dust inhalation (SDI) in Argentina was studied.[62] Exposure to SDI was defined as follows: (1) direct = occupational, (2) indirect = proximity to soybean fields or grain elevators, and (3) urban = urbanized areas without a known source of SDI. Two different types of groups were studied. Group 1 consisted of 365 patients who were clinically diagnosed with asthma or allergic rhinitis. Group 2 consisted of 50 healthy subjects. All participants were given a standard questionnaire, and were subjected to a prick skin test (ST) with common allergens and a soybean hull extract. In addition, specific IgE and immunoglobin G4p (IgG4) secreted in response to soybean hulls were measured in the sera of 51 patients from group 1 with a positive ST to soybean hull, and in all subjects from group 2. From group 1, 15.3% of subjects had a positive ST to soybean hulls. No subjects from group 2 had a positive ST. Of those with a positive ST to soybean hulls, 38.7, 20.3, and 8.2% of the affected subjects were associated with direct, indirect, and urban exposures, respectively. The percentage of positive soybean hull-specific IgE secretion in groups 1 and 2 were 39.2% and 10%, respectively, and for IgG4 were 27.4% and 12%, in groups 1 and 2, respectively. IgG4 levels in group 1 were significantly higher in subjects with direct exposure compared to subjects with indirect or urban exposure.

In a different study, effects in workers from three soybean-processing plants in South Africa were evaluated using a respiratory questionnaire and estimation of atopy.[63] A total of 144 employees completed the questionnaire, and 136 gave blood samples for analysis of specific IgE levels. The processes in all three worksites were based on similar milling techniques. Soybeans arrive at the processing mill, are off-loaded, and stored. The beans are then de-hulled, subjected to cooking, milled, and bagged. According to the questionnaire, 38 individuals reported either an upper or lower work-related respiratory symptom. Among these individuals, eight employees reported upper respiratory symptoms in the absence of any lower respiratory symptoms. Twenty-two employees reported lower-respiratory symptoms only (cough, wheezing, or chest tightness). The remaining eight employees reported both upper and lower respiratory symptoms. Cough and chest tightness were the most commonly reported symptoms, followed by nasal irritation and wheezing. Altogether, 33.1% (45/136) of workers were atopic, and 14% (19/136) of workers exhibited sensitization to soybean allergens.

SUMMARY

The safety of 28 soy-derived ingredients as used in cosmetics is reviewed in this safety assessment. All ingredients reviewed in this report are derived from the soybean plant (*Glycine max* or *Glycine soja*). According to the *Dictionary*, most of these ingredients are reported to function as antioxidants, skin protectants, skin-conditioning agents – miscellaneous, and hair-conditioning agents; however, other functions are also reported. Soybeans and ingredients made from soybeans are commonly used in foods. Because daily exposure via ingestion would result in much greater systemic exposure than what is expected from cosmetic use, potential for effects from topical exposure is the focus of this report.

Soybeans contain many phytochemicals, such as phenolic acids, flavonoids, isoflavanoids, saponins, phytosterols, and sphingolipids. These phytochemicals vary based on geographic location, specific plant parts, and color of the bean/plant.

According to 2020 VCRP survey data, Glycine Soja (Soybean) Seed Extract is reported to be used in 402 formulations, 279 of which are leave-on formulations, and Glycine Soja (Soybean) Flour is reported to be used in 84 formulations. The results of the concentration of use survey conducted by the Council indicate Glycine Soja (Soybean) Seed

Extract has the highest concentration of use; it is used at up to 2% in face and neck products. Additionally, inhalation of Glycine Soja (Soybean) Seed Extract is possible, as it was reported to be used at 0.000001% in hair sprays.

When rats were given a single oral dose of a soybean extract containing 74 µmol genistein and 77 µmol daidzein/kg as conjugates, the urinary excretion of daidzein and genistein was 17.9% and 11.9%, respectively, over a 48-hour post-dose period. When humans were given a bolus dose of a commercial soy extract, sulfoglucuronides were the major metabolites of daidzein and genistein in the plasma, and 7-*O*-glucuronides were the predominant metabolites in the urine.

Six Sprague-Dawley rats and six C57BL/6 mice were given a single oral dose of black soybean hull extract (2.5 g/kg/bw) via gavage; the LD_{50} was reported to be greater than 2.5 g/kg bw in both species. In a different study, Sprague-Dawley IGS rats (6/sex/group) were given up to 5% black soybean extract in the diet for 28 days. No deaths were reported throughout the study, however a statistically significant increase in alkaline phosphatase enzymes was found in male rats given 1.5% black soybean extract. In addition, a statistically significant but non-dose-dependent elevation of relative heart weight was found in females given 0.5% black soybean extract. In a different study, SSF was given to Sprague-Dawley CD rats (20/sex/group) at concentrations up to 4% for 3 months. A slight, but dose-related increase in the hematocrit and erythrocyte count at the 3 and 4% level was noted. In a 13-week toxicity study, the systemic toxicity of aqueous and ethanolic soybean extracts (up to 5%) was studied in F344 rats (40 rats/sex). Statistically significant body weight reductions were noted in males treated with 5% soybean extract, and in all treated females. Statistically significant, but minimal increases in total protein, albumin, calcium, and aspartate aminotransferase were found in males treated with 2.5% or higher. Dose-dependent, statistically significant changes in organ weights compared to control animals were also noted. In a study in which 33 male and 35 female C57BL/6 mice were given up to 5% black soybean hull extract in the diet for 26 weeks, significant body weight reduction was noted in high-dosed males and significant reductions in triglyceride, hemoglobin, and hematocrit levels were noted in high-dosed females. Relative weights of the kidney, spleen, and brain were increased in high-dosed males. In animals dosed with either 2% or 5% soybean hull extract, in the duodenum, slight pigment accumulation in histiocytes of the lamina propria was found. Slight accumulation of pigment in Kupffer cells of the liver was apparent in 5%-dosed males and females.

A chronic toxicity study was performed on 60 male Wistar rats given up to 79.7% raw soy flour, ad libitum or as a single meal per day. Azaserine injections were also given to select animals. Approximately 45% of all animals died prior to the termination of the experiment. Pancreas weights increased as the level of raw soy flour in the diet increased in all treated rats. In a different study, 72 male albino mice/group were given either raw soy flour, heated soy flour, or casein for up to 18 months. Growth of mice was significantly lower ($P < 0.01$) in mice given raw soy flour compared to mice given heated soy flour or casein.

The reproductive toxicity of soybeans was tested in 5 male albino rats/group. Rats were given processed soybean meal at up to 300 mg/kg bw for 65 days. Rats in the 100 mg/kg/bw group had testicular tissues with compacted interstitial spaces, mild hemorrhaging along the Sertoli's cells, and slight degeneration of the spermatids. Rats treated with 200 mg/kg/bw displayed similar effects, and rats treated with 300 mg/kg /bw displayed adverse effects such as testicular tissues with inflammation of interstitial cells, severe hemorrhaging along the Sertoli's cells, and excessive degeneration of spermatids, and necrosis. Each treated rat was mated with 3 untreated female rats. The conception rate of female rats sired by males in the control and treated groups were reduced in a dose-dependent manner.

Twenty male Wistar rats/group were given up to 79.7% raw soy flour in the diet in a tumor-promotion study. Injections of azaserine were also given to select rats. Animals that received azaserine injections had a much higher incidence of nodules, which increased with the level of raw soy flour in the diet. In a study involving male albino mice, mice fed raw soy flour in comparison to heated soy flour or casein displayed a significant decrease in growth. In a 15-month study, male Syrian Golden hamsters were divided into four groups and given raw soy flour (15 animals/group), heated soy flour (12 animals/group), raw soy flour/co-administered injection with BOP (15 animals/group), or heated soy flour / injected with BOP (13 animals/group). Groups that did not receive BOP had a low tumor incidence. All but one animal displayed either pancreatic adenomas or adenocarcinomas when given heated soy flour and a BOP injection, while only one out of 11 animals given BOP injections and raw soy flour displayed a pancreatic adenoma.

Studies were performed in order to analyze the effects of soy-derived extracts on cancer cell proliferation. An ethanolic soybean extract inhibited cytotoxic activity in A549 cells in a concentration-dependent manner. The potential of a soybean extract to inhibit the proliferation of cancer cells was also studied on AGS cells. Approximately 65.7, 38.8, and 22.5% cells survived after treatment with 3, 4, and 5 mg/mL of black soybean extract. The same procedure was performed on normal rat fibroblast cells. No cytotoxicity was observed when black soybean extract was used on these cells. In a different assay, HCT116 and H1299 cells were exposed to an ethanolic extract of soybean leaves. In both types of cancer cells, the growth inhibitory effects of SLE increased with increasing concentrations of SLE, showing a significant dose-response relationship. In addition to inhibition of growth, the effect of SLE on adhesion and migration of the human cancer cells was also studied. When H1299 cells were treated with SLE at 500 µg /mL, a significant inhibition of migration was noted. Treatment of HCT116 and H1299 cells with SLE also inhibited cell adhesion to fibronectin by 21 - 31% (at 125 - 500 µg/mL) and 14% (at 500 µg/mL), respectively.

The possible inhibition of retinoid-induced epidermal hyperplasia was studied in 7 human skin cultures. In the presence of a 40 µg/mL soy extract, retinoid-induced hyperplasia was reduced by 41% relative to the retinoid response in the absence of soy.

An aqueous extract of black soybean sprouts was examined for whitening capacity via the measurement of tyrosinase-inhibition. Tyrosinase inhibition capacity of the extract, when used at 40 mg/mL, reached 98%.

A methanolic soybean extract (0.1 µg/mL) caused an increase of cell proliferation to approximately 35%, while at 100 µg/mL, proliferation was increased to 90%. Testing of the soybean extract in combination with fulvestrant resulted in decreased proliferation (below 0%). A reported gene assay was also performed using human embryonic kidney cells (HEK 293 cells) in order to determine whether the effects of the extracts were mediated via ERα and/or ERβ. Preferential agonist activity toward ERβ was observed. For ERβ transcriptional activation, the maximal value obtained at 100 µg/mL was 79.7%, compared to 53.2% for ERα transcriptional activation. A study was performed to analyze the effects of orally administrated soybean extract obtained using different extraction methods on the skin of 64 Sprague-Dawley female rats (8/group). The number of estrogen receptors in all soy extract–treated groups were decreased compared to that of the controls.

A percutaneous immunotoxicity study was performed on BALB/c mice. Mice were dermally exposed (after tape stripping 10x) to crude soybean extract (50 mg/mL, 3 times a week). Exposure to the soybean extract resulted in an increase of circulatory soybean-specific IgEs. Of the soy proteins, both 7S and 11S globulins were allergens in 67% of tested mice.

A trade name mixture containing water (q.b. to 100% w/w), Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%) and a trade name mixture consisting of water (78.93%), Glycine Soja (Soybean) Phytoplacenta Extract (20%), phenoxyethanol (0.90%), methylparaben (0.15%), and Tetrasodium EDTA (0.02%) displayed no cytotoxic potential in cytotoxicity assays performed on human keratinocytes and human dermal fibroblasts.

A 48-h patch test was performed on 11 subjects using a cosmetic formulation containing 4% soybean extract. No irritation was observed. No irritation was observed when a 48-h patch test was performed in 10 subjects using a mixture containing water and Glycine Soja (Soybean) Seedcake Extract (13%) at a concentration of 5%. A 24-h patch test performed on 30 subjects using 4 or 40 mg/mL black soybean sprout extract yielded negative results. No sensitizing potential was observed (test details not provided) with a trade name mixture containing water, Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%). No sensitization or irritation was observed when an HRIPT was completed with 108 subjects using a leave-on formulation containing 0.3% Glycine (Soja) Soybean Germ Extract. A skin care preparation containing 0.198% Glycine Soja (Soybean) Seed Extract did not cause irritation or sensitization in an HRIPT performed on 44 subjects. No irritation or sensitization was observed in an HRIPT performed on 59 subjects using a test substance consisting of 3% Glycine Soja (Soybean) Seed Extract.

A HET-CAM assay performed using a soybean sprout extract revealed no potential ocular irritation. In a different study, a mixture consisting of water and Glycine Soja (Soybean) Seedcake Extract was predicted to be non-irritating to the eye in a neutral red release assay.

According to a case study, a 55-year-old woman with a 5-month history of reacting to a facial cosmetic cream developed erythema and swelling of the face after using a night cream containing soybean extract. Patch tests were performed using different dilutions of soybean extract, the night cream itself, components of the night cream, and standard cosmetic/facial ingredients. Positive results were obtained for all dilutions of the soybean extract on days 2 and 7. In a different case study, a 30-year-old female esthetician with atopic dermatitis and severe hand eczema developed anaphylactic symptoms after consuming soy products. Skin pricks test were preformed using soy extract (10 mg/mL), the cosmetic lotion containing soy extract used by the patient, and commercially available soy milk. All tests yielded positive results.

Allergenicity to soybean hull was studied in an occupational exposure study. Positive skin prick tests to soybean hull were reported for 38.7, 20.3, and 8.2% in subjects with direct (occupational), indirect (proximity to soybean fields or grain elevators), or urban (no known source of soy dust inhalation) exposures, respectively. Another occupational study was performed, assessing soybean-processing plant workers in South Africa. In 38/144 individuals that reported either an upper or lower work-related respiratory symptom, eight employees reported upper respiratory symptoms in the absence of any lower respiratory symptoms, 22 reported lower-respiratory symptoms only (cough, wheezing, or chest tightness), and the remaining eight employees reported both upper and lower respiratory symptoms.

DISCUSSION

The ingredient group reviewed in this safety assessment (*Glycine max* and *Glycine soja*-derived ingredients) was formed based on the supposition that ingredients from a given genus and species, and on a closely related species (i.e., *max* and *soja*), would have constituents in common (indeed, the *Dictionary* states that these two names refer to the exact same species). These ingredients have been ingested as food and food products for many years. As exposure via oral ingestion would be much higher than exposure from cosmetics, concerns regarding systemic toxicity have been mitigated. In addition, the Panel noted the lack of genotoxicity and carcinogenicity data, but considered those data to be unnecessary to assess safety due to the long-term use of these ingredients as food.

Potential reproductive effects following oral ingestion of soybean and soybean extract were noted by the Panel; however, these effects were likely attributed to ingestion of the isoflavone and phytoestrogen content of the soybean. The concern for these reproductive effects were mitigated considering the total isoflavone and phytoestrogen content would be relatively low in cosmetics, and dermal exposure to these ingredients would be far lower than oral exposure.

In addition, the Panel noted the occupational exposure study in which workers displayed asthmatic symptoms after inhaled exposure to soy. The Panel attributed the respiratory symptoms to the prolonged duration of exposure, which would not be a relevant issue in cosmetic use.

Tyrosinase inhibition was reported in a study involving Glycine Soja (Soybean) Sprout Extract; however, the Panel decided that this was not of concern for skin depigmentation as this was an in vitro study, and the doses used in this study were much higher than what would be used in cosmetics.

The Panel noted the immunotoxicity study regarding IgE-mediated allergy to ingested soy proteins. The Panel has previously reviewed the safety of soy proteins and peptides, and in that safety assessment noted that soy proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. The Panel was not concerned that such reactions would be induced by dermal exposure because these soy proteins are water soluble, would not penetrate the skin, and have molecular weights that are well below that which would cause IgE-cross-linking. Additionally, the Panel noted there were no reported cases of Type I immediate hypersensitivity reactions from cosmetic use of soy protein or peptide ingredients.

The Expert Panel expressed concern regarding 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 these impurities.

The Panel discussed the issue of incidental inhalation exposure from powders and hair sprays. The Council survey results indicate that Glycine Soja (Soybean) Seed Extract is being used in hair sprays at concentrations up to 0.000001%. Also, Glycine Max (Soybean) Seed Extract and Glycine Max (Soybean) Lipids are used in face powders; concentration of use data were not reported for these uses. 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 composition 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 Panel determined that there are insufficient data to evaluate the safety of Glycine Max (Soybean) Callus Culture, Glycine Max (Soybean) Callus Culture Extract, Glycine Max (Soybean) Callus Extract, and Glycine Max (Soybean) Phytoplacenta Conditioned Media. In order to make a determination of safety for these ingredients, the Panel has requested composition, impurities, method of manufacture, 28-day dermal toxicity, and sensitization and irritation data.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 24 soy-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Glycine Max (Soybean) Fiber*
Glycine Max (Soybean) Flower/Leaf/Stem Juice*
Glycine Max (Soybean) Leaf Cell Extract*
Glycine Max (Soybean) Leaf Extract*
Glycine Max (Soybean) Phytoplacenta Extract
Glycine Max (Soybean) Pulp*
Glycine Max (Soybean) Seed Extract
Glycine Max (Soybean) Seedcake Extract*
Glycine Max (Soybean) Seedcoat Extract*
Glycine Max (Soybean) Seed Powder*
Glycine Max (Soybean) Sprout Extract*
Glycine Soja (Soybean) Extract
Glycine Soja (Soybean) Fiber*
Glycine Soja (Soybean) Flour
Glycine Soja (Soybean) Germ Extract
Glycine Soja (Soybean) Hull*
Glycine Soja (Soybean) Lipids
Glycine Soja (Soybean) Phytoplacenta Extract*
Glycine Soja (Soybean) Seed
Glycine Soja (Soybean) Seedcake Extract*
Glycine Soja (Soybean) Seed Extract
Glycine Soja (Soybean) Seed Powder*
Glycine Soja (Soybean) Seed Water*
Glycine Soja (Soybean) Sprout Extract*

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

The Panel also concluded that the available data are insufficient to make a determination of safety for the following 4 ingredients:

Glycine Max (Soybean) Callus Culture**
Glycine Max (Soybean) Callus Culture Extract**
Glycine Max (Soybean) Callus Extract**
Glycine Max (Soybean) Phytoplacenta Conditioned Media**

** There are currently no uses reported for these ingredients.

TABLES

Table 1. INCI names, definitions, and functions of the soy-derived ingredients in this safety assessment[1]

Ingredient	Definition	Function
Glycine Max (Soybean) Callus Culture	Glycine Max (Soybean) Callus Culture is a suspension of the cultured callus cells of *Glycine max*.	Antioxidants; Humectants; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Callus Culture Extract	Glycine Max (Soybean) Callus Culture Extract is the extract of a culture of the callus of *Glycine max*.	Antifungal Agents; Antioxidants; Hair Conditioning Agents; Skin-Conditioning Agents - Humectant
Glycine Max (Soybean) Callus Extract	Glycine Max (Soybean) Callus Extract is the extract of the callus of *Glycine max* grown in culture.	Antimicrobial Agents; Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Fiber	Glycine Max (Soybean) Fiber is the fiber obtained from the pulp of the soybean, *Glycine max*.	Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Flower/Leaf/Stem Juice	Glycine Max (Soybean) Flower/Leaf/Stem Juice is the juice expressed from the flowers, leaves and stems of *Glycine max*.	Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Leaf Cell Extract	Glycine Max (Soybean) Leaf Cell Extract is the extract of a culture of the leaf cells of *Glycine max*.	Antioxidants; Skin Protectants
Glycine Max (Soybean) Leaf Extract	Glycine Max (Soybean) Leaf Extract is the extract of the leaves of *Glycine max*.	Antioxidants; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Phytoplacenta Conditioned Media	Glycine Max (Soybean) Phytoplacenta Conditioned Media is the growth media removed from cultures of the phytoplacenta of *Glycine max* after several days of growth.	Antimicrobial Agents; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Phytoplacenta Extract	Glycine Max (Soybean) Phytoplacenta Extract is the extract of the phytoplacenta cells directly isolated from the plant *Glycine max* or grown in culture.	Antimicrobial Agents; Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents - Humectant
Glycine Max (Soybean) Pulp	Glycine Max (Soybean) Pulp is the pulp of *Glycine max*.	Skin-Conditioning Agents - Humectant
Glycine Max (Soybean) Seedcake Extract	Glycine Max (Soybean) Seedcake Extract is the extract of the seedcake of *Glycine max*.	Skin-Conditioning Agents - Emollient
Glycine Max (Soybean) Seedcoat Extract	Glycine Max (Soybean) Seedcoat Extract is the extract of the seedcoat of *Glycine max*.	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Seed Powder	Glycine Max (Soybean) Seed Powder is the powder obtained from the dried, ground seeds of *Glycine max.*	Exfoliants; Skin-Conditioning Agents - Miscellaneous
Glycine Max (Soybean) Sprout Extract	Glycine Max (Soybean) Sprout Extract is the extract of the sprout of the soybean, *Glycine max.*	Skin-Conditioning Agents - Miscellaneous.
Glycine Soja (Soybean) Extract	Glycine Soja (Soybean) Extract is the extract of the whole plant, *Glycine soja.* The accepted scientific name for *Glycine soja* is *Glycine max.*	Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Fiber	Glycine Soja (Soybean) Fiber is the fiber obtained from the pulp of the soybean, *Glycine soja*. The accepted scientific name for *Glycine soja* is *Glycine max.*	Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Flour 68513-95-1	Glycine Soja (Soybean) Flour is the powder prepared from the fine grinding of the soybean, *Glycine max.* The accepted scientific name for *Glycine soja* is *Glycine max.*	Abrasives; Bulking Agents; Viscosity Increasing Agents - Aqueous
Glycine Soja (Soybean) Germ Extract	Glycine Soja (Soybean) Germ Extract is the extract of the germ of *Glycine soja.* The accepted scientific name for *Glycine soja* is *Glycine max.*	Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Hull	Glycine Soja (Soybean) Hull is the outer covering of the soybean, *Glycine soja.* The accepted scientific name for *Glycine soja* is *Glycine max.*	Exfoliants; Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Lipids	Glycine Soja (Soybean) Lipids is the alcohol soluble fraction of the gummy portion obtained during the refining of Glycine Soja (Soybean) Oil. It is a blend consisting predominantly of phospholipids, sterols and triglycerides. The accepted scientific name for *Glycine soja* is *Glycine max.*	Hair Conditioning Agents; Skin-Conditioning Agents - Occlusive
Glycine Soja (Soybean) Phytoplacenta Extract	Glycine Soja (Soybean) Phytoplacenta Extract is the extract of the phytoplacenta cells directly isolated from the plant *Glycine soja* or grown in culture. The accepted scientific name for *Glycine soja* is *Glycine max.*	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Seed	Glycine Soja (Soybean) Seed is the bean of *Glycine soja*. The accepted scientific name for *Glycine soja* is *Glycine max.*	Not Reported
Glycine Soja (Soybean) Seedcake Extract	Glycine Soja (Soybean) Seedcake Extract is the extract of the seedcake of *Glycine soja*. The accepted scientific name for *Glycine soja* is *Glycine max.*	Skin Protectants
Glycine Soja (Soybean) Seed Extract	Glycine Soja (Soybean) Seed Extract is the extract of the seeds of *Glycine soja*. The accepted scientific name for *Glycine soja* is *Glycine max.*	Skin-Conditioning Agents - Miscellaneous
Glycine Soja (Soybean) Seed Powder	Glycine Soja (Soybean) Seed Powder is the powder obtained from the dried, ground seeds of *Glycine soja*. The accepted scientific name for *Glycine soja* is *Glycine max.*	Abrasives; Bulking Agents; Skin-Conditioning Agents - Miscellaneous

Table 1. INCI names, definitions, and functions of the soy-derived ingredients in this safety assessment[1]

Ingredient	Definition	Function
Glycine Soja (Soybean) Seed Water	Glycine Soja (Soybean) Seed Water is an aqueous solution of the steam distillate obtained from the seeds of *Glycine soja*. The accepted scientific name for *Glycine soja* is *Glycine max*.	Skin-Conditioning Agents - Humectant
Glycine Soja (Soybean) Sprout Extract	Glycine Soja (Soybean) Sprout Extract is the extract of the young shoots of the soybean, *Glycine soja*. The accepted scientific name for *Glycine soja* is *Glycine max*.	Skin-Conditioning Agents - Miscellaneous

Table 2. Average constituents in 24 methanolic soybean seed extracts (g/100 g)[17]

Carbohydrates	30.16	Alanine	1.915
Sugars	7.33	Aspartic acid	5.112
Fat	19.94	Glutamic acid	7.874
Protein	36.49	Glycine	1.880
Tryptophan	0.591	Proline	2.379
Threonine	1.766	Serine	2.375
Isoleucine	1.971	Water	8.54
Leucine	3.309	Calcium	0.277
Lysine	2.706	Iron	0.0175
Methionine	0.547	Magnesium	0.280
Phenylalanine	2.122	Phosphorus	0.704
Tyrosine	1.539	Potassium	1.797
Valine	2.029	Sodium	0.002
Arginine	3.153	Zinc	0.00489
Histidine	1.097		

Table 3. Mean nutrient and amino acid values for 38 samples of soybean hulls (%)[22]

Moisture	8.18
Crude fiber	33.32
Nitrogen-free extract	39.18
Ash (residual upon burning)	4.87
Calcium	0.52
Phosphorous	0.15
Lysine	0.86
Methionine	0.16
Threonine	0.48
Tryptophan	0.15
Arginine	0.65
Histidine	0.31
Leucine	0.82
Isoleucine	0.48
Phenylalanine	0.54
Valine	0.55

Table 4. Detection limits of fragrance allergens in a trade name mixture containing Glycine Soja (Soybean) Phytoplacenta Extract[64]

Allergen	ppm
Alpha-IsoMethyl Ionone	< 0.02
Amyl Cinnamal	< 0.10
Anise Alcohol	< 0.00
Benzyl Alcohol	< 0.01
Benzyl Benzoate	< 0.09
Benzyl Cinnamate	< 0.30
Benzyl Salicylate	< 0.06
Butylphenyl Methylpropional	< 0.50
Cinnamal	< 0.01
Cinnamyl Alcohol	< 0.30
Citral	< 1.00
Citronellol	< 0.00
Coumarin	< 0.00
Eugenol	< 0.70
Farnesol	< 0.04
Farnesol	< 0.04
Geraniol	<0.08
Hexyl Cinnamal	< 0.40
Hydroxycitronellal	< 1.00
Hydroxymethylpentyl 3-Cylcohexene carboxaldehyde	< 0.30
Isoeugenol	< 0.06
Limonene	< 0.05
Linalool	< 0.00
Methyl 2-Octynoate	< 0.20
Evernia prunastri	< 0.02
Evernia furfuracea	< 0.00
Amylcinnamyl Alcohol	< 1.00

Table 5. Frequency (2020) and concentration (2016) of use of soy-derived ingredients.[29,30]

	# of Uses	Conc of Use (%)	# of Uses	Conc of Use (%)	# of Uses	Conc of Use (%)
	Glycine Max (Soybean) Seed Extract		**Glycine Max (Soybean) Phytoplacenta Extract**		**Glycine Soja (Soybean) Extract (also listed as Glycine Max) Soybean Extract in VCRP)**	
Totals*	**402**	**0.0066 - 1**	**16**	**NR**	**14**	**NR**
Duration of Use						
Leave-On	*279*	*0.0066 – 1*	*13*	*NR*	*11*	*NR*
Rinse-Off	*122*	*0.0066*	*3*	*NR*	*3*	*NR*
Diluted for (Bath) Use	*1*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	37	0.0066	1	NR	NR	NR
Incidental Ingestion	22	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	6; 93[a]; 74[b]	NR	1; 6[a]; 3[b]	NR	2[a]; 4[b]	NR
Incidental Inhalation-Powder	5; 74[b]	0.0066[c]	2[b]; 3[c]	NR	4[b]	NR
Dermal Contact	241	0.0066 - 1	14	NR	10	NR
Deodorant (underarm)	1[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	138	NR	2	NR	4	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	28	NR	NR	NR	NR	NR
Baby Products	NR	NR	3	NR	1	NR

	Glycine Soja (Soybean) Flour (also listed as Glycine Max (Soybean) Flour in VCRP)		**Glycine Soja (Soybean) Germ Extract (also listed as Glycine Max (Soybean) Germ Extract in VCRP)**		**Glycine Soja (Soybean) Lipids (also listed as Glycine Max (Soybean) Lipids in VCRP)**	
Totals*	**84**	**0.0001**	**56**	**0.00002 – 0.45**	**54**	**0.086 – 0.65**
Duration of Use						
Leave-On	*82*	*0.0001*	*46*	*0.0002 – 0.45*	*44*	*0.086 – 0.65*
Rinse-Off	*2*	*NR*	*10*	*0.00002 – 0.00014*	*10*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	6[d]	0.01	6	0.09
Incidental Ingestion	NR	NR	NR	NR	2	0.65
Incidental Inhalation-Spray	78[a]; 1[b]	NR	12[a]; 17[b]	NR	22[a]; 7[b]	NR
Incidental Inhalation-Powder	1[b]	0.0001[c]	17[b]	0.005 – 0.45[c]	1; 7[b]	NR
Dermal Contact	82	0.0001	52	0.00002 – 0.45	46	0.09
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	4	0.00014 – 0.11	5	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	1	NR
Mucous Membrane	1	NR	2	NR	2	NR
Baby Products	NR	NR	2	NR	NR	NR
	Glycine Soja (Soybean) Seed (also listed as Glycine Max (Soybean) Seed in VCRP)		**Glycine Soja (Soybean) Seed Extract**		**Glycine Soja (Soybean) Sprout Extract (also listed as Glycine Max (Soybean) Sprout Extract in VCRP)**	
Totals*	**1**	**NR**	**NR**	**0.000001 – 2**	**1**	**NR**
Duration of Use						
Leave-On	*NR*	*NR*	*NR*	*0.000001 – 2*	*1*	*NR*
Rinse-Off	*1*	*NR*	*NR*	*0.00008 – 0.7*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*0.0004*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.0001	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	0.000001; 0.005[a]	1[a]	NR
Incidental Inhalation-Powder	NR	NR	NR	0.002 – 2[c]	NR	NR
Dermal Contact	1[d]	NR	NR	0.0004 – 2	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.000001 – 0.01	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	0.001	NR	NR
Mucous Membrane	NR	NR	NR	0.0001 – 0.0004	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

NR = Not Reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum 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. Soy-Derived Ingredients not reported to be in use

Glycine Max (Soybean) Callus Culture
Glycine Max (Soybean) Callus Culture Extract
Glycine Max (Soybean) Callus Extract
Glycine Max (Soybean) Fiber
Glycine Max (Soybean) Flower/Leaf/Stem Juice
Glycine Max (Soybean) Leaf Cell Extract
Glycine Max (Soybean) Leaf Extract
Glycine Max (Soybean) Phytoplacenta Conditioned Media
Glycine Max (Soybean) Pulp
Glycine Max (Soybean) Seedcake Extract
Glycine Max (Soybean) Seedcoat Extract
Glycine Max (Soybean) Seed Powder
Glycine Max (Soybean) Sprout Extract
Glycine Soja (Soybean) Fiber
Glycine Soja (Soybean) Hull
Glycine Soja (Soybean) Phytoplacenta Extract
Glycine Soja (Soybean) Seedcake Extract
Glycine Soja (Soybean) Seed Powder
Glycine Soja (Soybean) Seed Water

Table 7. Dermal irritation and sensitization

Ingredient	Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
DERMAL IRRITATION						
HUMAN						
Glycine Soja (Soybean) Extract	Cosmetic water-in-oil emulsion incorporating 4% soybean extract	100%; 1000 mg	11	Patches containing test substance were applied to a 5 cm x 4 cm area on the forearm. One gram of base emulsion and emulsion with soy were used to treat sites. After application, a surgical dressing was used to cover the area. It was not stated whether the dressing was occlusive or not. After 48 hours, the dressing was removed and forearms were washed with saline.	Non-irritating	[55]
Glycine Soja (Soybean) Seedcake Extract	Mixture containing water and Glycine Soja (Soybean) Seedcake Extract (13%)	5%; dose not stated	10	The mixture was applied to the skin and covered with an occlusive patch for 48 hours.	Non-irritating	[56]
Glycine Max (Soybean) Sprout Extract	Black soybean sprout extract	4 or 40 mg/mL	30 (15/sex)	Extracts were applied on the arm, under a patch, for 24 hours. It was not stated whether the dressing used was occlusive or not.	Non-irritating	[14]
SENSITIZATION						
IN VITRO						
Glycine Max (Soybean) Callus Culture	Trade name mixture containing water (100% w/w), Glycine Max (Soybean) Callus Culture (13 – 18%), citric acid (1.5%), sodium benzoate (0.2%), and potassium sorbate (0.1%)	100%	THP-1	Investigated the expression of CD80 and CD86 on immunocompetent cells (monocyte cell line THP-1)	Non-sensitizing	[52]
HUMAN						
Glycine Soja (Soybean) Germ Extract	Leave-on skin preparation containing 0.3% Glycine Soja (Soybean) Germ Extract	100%; dose not stated	108	An HRIPT was performed. The undiluted test substance was placed on the skin under an occlusive patch 3 times a week for a total of 9 applications during the induction period. After a 2-week rest period, challenge patches were applied to previously untreated sites. After 24 hours, patches were removed and the test sites were evaluated.	Non-irritating; Non-sensitizing	[57]
Glycine Soja (Soybean) Seed Extract	Skin-care preparation containing 0.198% Glycine Soja (Soybean) Seed Extract	100%; 0.2 mL	44	An HRIPT was performed. The test article was placed onto a 2 cm x 2 cm square of cotton fabric affixed to semi-occlusive surgical tape. The patch was then applied to the back every Monday, Wednesday, and Friday, until 9 applications had been completed. After a 2-week rest period, a challenge patch was applied to a previously unpatched test site.	Non-irritating; Non-sensitizing	[58]
Glycine Soja (Soybean) Seed Extract	Leave-on product containing 3% Glycine Soja (Soybean) Seed Extract	100%; 0.02 mL	59	An HRIPT was performed. The test article was placed on the skin under a semi-occlusive patch for 48 hours per induction period. A 2-week rest period followed the 9th induction patch. A challenge patch was then placed on a virgin test site and evaluated 48 and 72 hours after application.	Non-irritating; Non-sensitizing	[59]

HRIPT = Human Repeated Insult Patch Test

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2020 FDA VCRP DATA Soybean-derived Ingredients

***red indicates VCRP data were reported**

1. **Glycine Max (Soybean) Phytoplacenta Extract – Total = 16**

Baby Shampoos	1
Baby Lotions, Oils, Powders, and Creams	2
Eye Lotion	1
Hair Spray (aerosol fixatives)	1
Cleansing	2
Face and Neck (exc shave)	3
Moisturizing	5
Night	1

2. **Glycine Max (Soybean) Extract – Total = 14**

Other Baby Products	1
Rinses (non-coloring)	1
Shampoos (non-coloring)	2
Other Hair Preparations	1
Foundations	1
Face and Neck (exc shave)	4
Moisturizing	2
Other Skin Care Preps	2

3. **Glycine Soja (Soybean) Flour (listed as g. max) – Total = 84**

Eye Shadow	1
Hair Conditioner	1
Tonics, Dressings, and Other Hair Grooming Aids	1
Blushers (all types)	1
Bath Soaps and Detergents	1
Body and Hand (exc shave)	1
Moisturizing	76
Night	1
Other Skin Care Preps	1

4. **Glycine Soja (Soybean) Germ Extract (listed as g. max) – Total = 56**

Baby Shampoos	1
Baby Lotions, Oils, Powders, and Creams	1
Eyebrow Pencil	1

Eye Lotion	2
Other Eye Makeup Preparations	3
Shampoos (non-coloring)	1
Tonics, Dressings, and Other Hair Grooming Aids	2
Foundations	1
Other Makeup Preparations	1
Bath Soaps and Detergents	2
Cleansing	5
Face and Neck (exc shave)	9
Body and Hand (exc shave)	8
Moisturizing	8
Night	1
Paste Masks (mud packs)	1
Other Skin Care Preps	8
Indoor Tanning Preparations	1

5. Glycine Soja (Soybean) Lipids (listed as g. max) – Total = 54

Eye Lotion	4
Other Eye Makeup Preparations	2
Hair Conditioner	1
Shampoos (non-coloring)	4
Face Powders	1
Foundations	1
Lipstick	2
Other Makeup Preparations	2
Other Manicuring Preparations	1
Shaving Cream	1
Cleansing	3
Face and Neck (exc shave)	6
Body and Hand (exc shave)	1
Moisturizing	20
Night	2
Paste Masks (mud packs)	1
Other Skin Care Preps	2

6. Glycine Soja (Soybean) Seed (listed as g. max) – Total = 1

Paste Masks (mud packs)	1

7. Glycine Soja (Soybean) Seed Extract – Total = 402

Other Bath Preparations	1
Eye Shadow	13
Eye Lotion	13
Mascara	1
Other Eye Makeup Preparations	10
Hair Conditioner	39
Hair Spray (aerosol fixatives)	6
Hair Straighteners	2
Permanent Waves	2
Shampoos (non-coloring)	44
Tonics, Dressings, and Other Hair Grooming Aids	31
Other Hair Preparations	14
Blushers (all types)	2
Face Powders	5
Foundations	1
Lipstick	22
Other Makeup Preparations	5
Bath Soaps and Detergents	2
Deodorants (underarm)	1
Other Personal Cleanliness Products	3
Aftershave Lotion	3
Shaving Cream	2
Other Shaving Preparation Products	1
Cleansing	17
Depilatories	1
Face and Neck (exc shave)	60
Body and Hand (exc shave)	14
Moisturizing	42
Night	16
Paste Masks (mud packs)	9
Skin Fresheners	2
Other Skin Care Preps	16
Suntan Gels, Creams, and Liquids	2

8. Glycine Soja (Soybean) Sprout Extract (listed as g. max) – Total = 1

Moisturizing	1

No Reported Uses

1. **Glycine Max (Soybean) Callus Culture**
2. **Glycine Max (Soybean) Callus Culture Extract**
3. **Glycine Max (Soybean) Callus Extract**
4. **Glycine Max (Soybean) Fiber**
5. **Glycine Max (Soybean) Flower/Leaf/Stem Juice**
6. **Glycine Max (Soybean) Leaf Cell**
7. **Glycine Max (Soybean) Leaf Extract**
8. **Glycine Max (Soybean) Phytoplacenta Conditioned Media**
9. **Glycine Max (Soybean) Pulp**
10. **Glycine Max (Soybean) Seedcake Extract**
11. **Glycine Max (Soybean) Seedcoat Extract**
12. **Glycine Max (Soybean) Seed Powder**
13. **Glycine Max (Soybean) Sprout Extract**
14. **Glycine Soja (Soybean) Extract (listed as g. max)**
15. **Glycine Soja (Soybean) Fiber**
16. **Glycine Soja (Soybean) Hull**
17. **Glycine Soja (Soybean) Phytoplacenta Extract**
18. **Glycine Soja (Soybean) Seed Powder**
19. **Glycine Soja (Soybean) Seed Water**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: December 3, 2019

SUBJECT: Draft Tentative Report Safety Assessment of Soy-Derived Ingredients as Used in Cosmetics (draft prepared for the December 2019 CIR Expert Panel meeting)

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

Key Issue

Discussion - Regarding tumor promotion, the Discussion states: "However, the Panel noted that those with a high propensity to develop skin cancer should take caution during the long-term use of cosmetics containing these ingredients." As the tumor promotion study involved azaserine exposure and oral exposure to high doses of raw soy flour (19-79% of the diet), it is not appropriate to infer that low levels of soy-derived ingredients may increase the risk of skin cancer based on this study. This sentence should be deleted.

Additional Considerations

Method of Manufacture, Glycine Max (Soybean) Seed Extract - "Glycine Soja (Soybean) Extract" needs to be deleted at the end of the second paragraph.

Composition, Germ Extract - The information on effects of isoflavone compounds (estrogen-like effects, anti-carcinogenicity potential, genotoxicity) does not belong in the Composition section.

Composition, Seedcoat (Hull) - The first sentence says that samples were collected from throughout the United States (reference 19). The results says composition varies by "country of origin". If samples were collected from countries other than the United States, the first sentence needs to be revised. If only US samples were analyzed, "perhaps "country" should be corrected to "county".

Impurities - It should be made clear that the fragrance ingredients included in Table 4 are those required to be on the label of cosmetic products in Europe if they exceed a certain limit.

Subchronic, Oral, Glycine Soja (Soybean) Extract - It should be made clear that only one extract was studied in reference 42. The reference is not clear as it does state "aqueous or

ethanolic soybean extract". The more important information is the composition that is stated. The amount of individual isoflavones (3.78% diadzein, 1.6% glycitein, 0.6% genistein) should also be stated in the CIR report. The description of this study should also include the mg/kg/day doses as given by the authors (707.2, 1449.1, 2830.4 mg/kg/day for males, and 751.8, 1498.6, 3028.1 mg/kg/day for females).

DART; Summary - It should be made clear that only male rats were treated in the rat study of soybean meal. Each treated male rat was mated with 3 untreated female rats. Although the study may have used the word "sired", it would be clearer if it stated "the conception rate of female rats mated with treated males...."

Anti-Tumorigenicity - This section states: "The soy flour composition is the same as was used in the experiment above." The composition of the soy flour is not stated in the experiment described in the previous section.

Sensitization; Summary - The description of the study on the Callus Culture should reflect what is said in Table 4. This was an *in vitro* study that examined the expression of CD80 and CD86 in a monocyte cell line.

Summary - The Summary incorrectly states that the highest use concentration reported was 0.65% Glycine Soja (Soybean) Lipids in lipstick.

Please correct: "and genistein the in the plasma"

Discussion - As this report does not include any information about protein molecular weights, perhaps information on the molecular weights of ingredients reviewed in the 2015 CIR report on soy proteins and peptides should be added to this report. The Discussion of that report states: "The Panel noted that soy proteins are known food allergens that can elicit Type I immediate hypersensitivity reactions when ingested by sensitized individuals. However, the Panel was not concerned that such reactions would be induced by dermal exposure, because these ingredients are water soluble, would not penetrate the skin, and have molecular weights that are well below that which would cause IgE-cross-linking. The Panel reviewed studies showing no relevant ocular irritation in animals, no dermal irritation or sensitization in animals and human subjects, and no reported cases of Type I immediate hypersensitivity reactions from cosmetic use, which support their conclusion for these ingredients." As some of the ingredients, in this report may contain proteins, the Discussion should state that proteins in these ingredients should be below that which would cause IgE-crosslinking (≤3,500 Dalton).

Table 4 - For the *in vitro* sensitization study, the test population should be listed as the monocyte cell line THP-1 rather then NR.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 14, 2020

SUBJECT: Tentative Report: Safety Assessment of Soy-Derived Ingredients as Used in Cosmetics (release date: December 16, 2019)

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

Key Issues

Composition, Soybean Extract - There are three sentences in this section (associated with references 17, 10 and 18) that included the words daidzein and genistein twice. Reference 10 was checked. The CIR report currently states: "Among these isoflavones were 40% daidzein, 56% genistein, 2% daidzein and 2% genistein." This needs to be corrected to: "40% daidzin [no e], 58% genistin [no e], 2% daidzein, and 3% genistein." References 17 and 18 were not checked, but it is likely a similar error (changing genistin to genistein and changing daidzin to diadzein) occurred during spell checking.

DART; Summary - As only male rats were treated in the study described in the CIR report (reference 46), the last sentence ("No other effects regarding treated female rats were observed.") needs to be deleted from both the DART section and the Summary. If they also completed a study in which female rats were treated, the methods and results of that study need to be described in the CIR report.

Discussion - The Chemistry section of the report indicates that the Dictionary is using two names, *Glycine max* and *Glycine soja* for the same plant. The Discussion currently states they are closely related species. How these two names are described should be consistent with the Dictionary and should be consistent throughout the CIR report.

In the paragraph about Type I allergy (IgE-mediated) it is not clear what is meant by "these cosmetic ingredients". This appears to be referring to proteins as described in soy protein and peptide report, but may be misinterpreted as applying to the ingredients in this report . What is known about the proteins that may be found in the ingredients in this report? It would be helpful if the Discussion stated that proteins in the ingredients in the

current report should have molecular weights below that which would cause IgE cross-linking.

Additional Considerations

Method of Manufacture - The first paragraph of this section should make it clear that the method of manufacture for Glycine Max (Soybean) Phytoplacenta Extract came from a cosmetic ingredient supplier. It currently states the it is "unknown if they apply to cosmetic ingredient manufacture."

Non-Cosmetic Use, Food - As there is no doubt that soy is in modern western diets, please delete: "reported to be present".

Non-Cosmetic Use, Medicine - Please provide a reference for the last sentence of this subsection.

Estrogenic Activity - What was the concentration of estradiol used in comparison to the concentration of the soy extract (reference 48)? Please correct: "in all soy extracted-treated groups" [delete "ed"]

Dermal Irritation - It would be helpful to add a human subheading or indicate that all of the studies in the section were completed in humans.

Summary - Please change "phosphatase enzymes" to "alkaline phosphatase enzymes"

Discussion - On what "chemical and biological" properties of these ingredients is inhalation safety based? Perhaps, this should be changed to composition.

Table 1 - Rather than "Function", "Reported Product Categories" are stated in the Function row of Table 1 for Glycine Max (Soybean) Sprout Extract. The Function for this ingredient is listed as: "Skin Conditioning Agents - Miscellaneous".

Table 2 - Please state the solvent(s) used to make the soybean seed extracts described in this table.

Reference 15 - The second 2017 needs to be deleted.