
Safety Assessment of *Scutellaria baicalensis*-Derived Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 21, 2020
Panel Date: September 14-15, 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 report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst, CIR
Date: August 21, 2020
Subject: Safety Assessment of *Scutellaria baicalensis*-Derived Ingredients as Used in Cosmetics

Enclosed is a Draft Final Report on 4 *Scutellaria baicalensis*-derived ingredients (*scutel092020rep*). Report comments that were received from the Council prior to the June 2020 Expert Panel for Cosmetic Ingredient Safety (Panel) meeting (*scutel092020pcpc1*) have been addressed and are also enclosed for the Panel's review.

At the June 2020 Panel meeting, a Tentative Report with the following conclusions was issued: *Scutellaria Baicalensis* Root Extract and *Scutellaria Baicalensis* Root Powder are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The available data are insufficient to make a determination that *Scutellaria Baicalensis* Extract and *Scutellaria Baicalensis* Sprout Extract are safe under the intended conditions of use in cosmetic formulations. Comments on the Tentative Report that were received from the Council (*scutel092020pcpc2*) have been addressed and are enclosed for the Panel's review. The Council's comments relating to the tentative report discussion deserve the Panel's consideration.

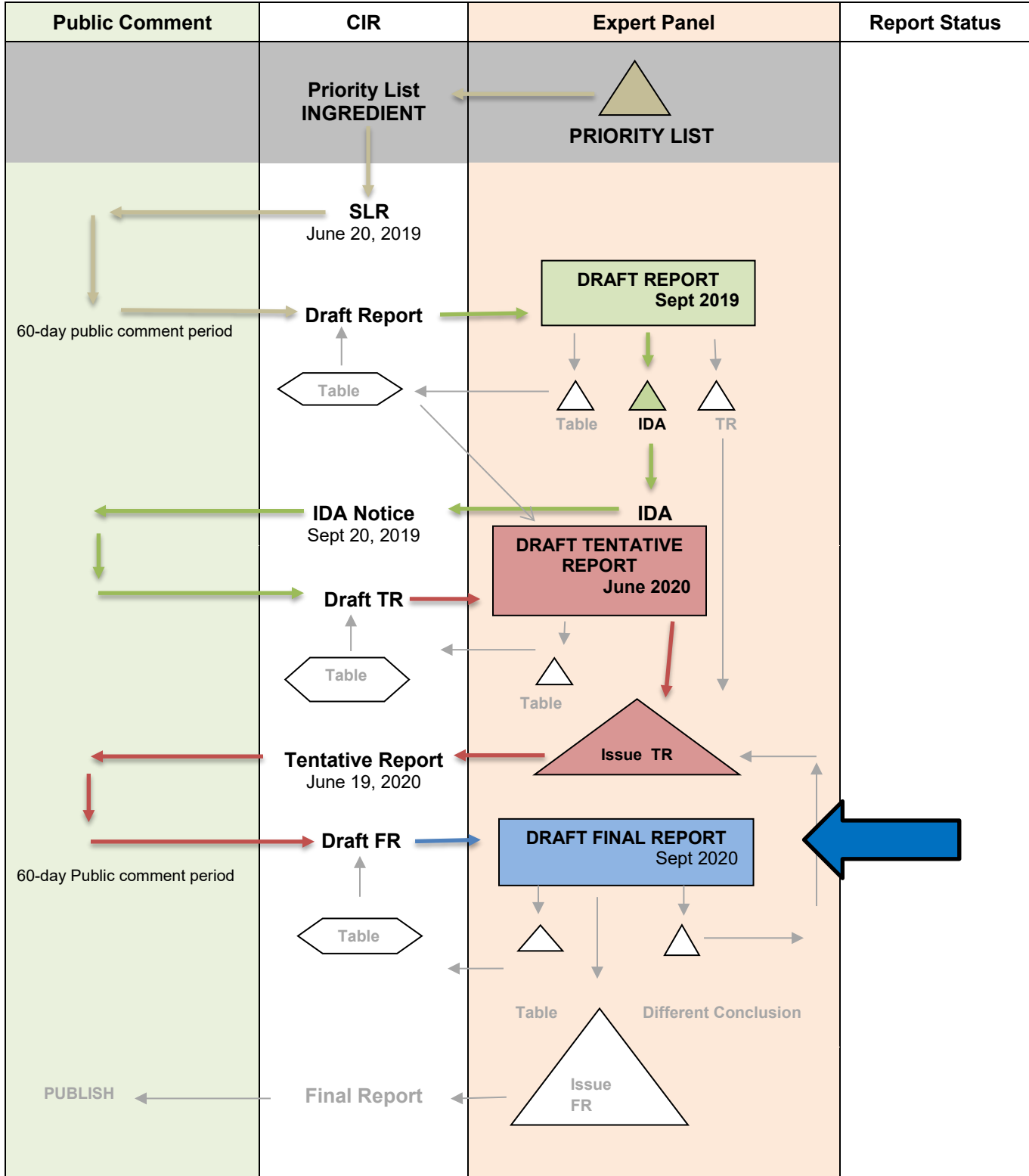
Also included in this package for your review are the report history (*scutel092020hist*), flow chart (*scutel092020flow*), literature search strategy (*scutel092020strat*), ingredient data profile (*scutel092020prof*), 2020 FDA VCRP data (*scutel092020FDA*), and minutes from the September 2019 and June 2020 Panel meetings (*scutel092020min*).

After reviewing these documents, the Panel should issue a Final Report with the split conclusion stated in the second paragraph above.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Scutellaria baicalensis-derived Ingredients

MEETING September 2020



CIR History of:

***Scutellaria baicalensis*-derived Ingredients**

A Scientific Literature Review (SLR) on *Scutellaria baicalensis* -Derived Ingredients was issued on June 20, 2019. Comments and unpublished data were received from the Council before/after announcement of the SLR.

Draft Report, Teams/Panel: September 16-17, 2019

The draft report has been revised to include the following unpublished data that were received from the Council:

- (1) Use concentration data on all *Scutellaria baicalensis*-derived Ingredients
- (2) Use concentration data on Scutellaria Baicalensis Sprout Extract
- (3) Method of manufacture data on Scutellaria Baicalensis Root Extract (different extractants)
- (4) Chemical characterization data on Scutellaria Baicalensis Root Extract trade name materials
- (5) Impurities data on a Scutellaria Baicalensis Root Extract trade name material
- (6) Human skin irritation and sensitization data on Scutellaria Baicalensis Root Extract trade name materials

Comments on the safety assessment that were received from the Council have been addressed, and the report has been updated to include unpublished data (stated above) that were received from the Council.

An insufficient data announcement (IDA) with the following data requests on *Scutellaria baicalensis*-derived ingredients was issued:

Scutellaria Baicalensis Extract

Scutellaria Baicalensis Root Extract

Scutellaria Baicalensis Root Powder

Scutellaria Baicalensis Sprout Extract

- Genotoxicity (in vitro and mammalian); for ingredient extracts, methanol and aqueous extracts should be tested
- Phototoxicity

Scutellaria Baicalensis Root Extract and Scutellaria Baicalensis Root Powder

- A NOAEL for skin pigmentation and anti-inflammatory effects, including the suppression of delayed contact hypersensitivity, is needed

Scutellaria Baicalensis Extract

- Skin irritation and sensitization
- 28-day dermal toxicity; if dermal absorption occurs, additional data may be needed

Scutellaria Baicalensis Sprout Extract

- Method of Manufacture
- Composition
- Impurities
- Dermal absorption; if dermal absorption occurs, additional data may be needed
- Skin irritation and sensitization

Draft Tentative Report, Teams/Panel: March 16-17, 2020

The following data were received from the Personal Care Products Council in response to the IDA that was issued at the September 2019 Panel meeting: (1) Method of Manufacture of Scutellaria Baicalensis Root Extract (aqueous extract), (2) in vitro genotoxicity data on a trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract), (3) in vitro phototoxicity data on a trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract), and an HRIPT on a leave-on product containing 0.001% Scutellaria Baicalensis Root Extract. In addition to the unpublished data, 3 additional case reports that involve patch testing/photopatch testing with Scutellaria Baicalensis Root Extract or Scutellaria Baicalensis Extract have been added to the report text.

The report has been revised to include the new data, and a draft discussion has been added. Also, comments that were received from the Council prior to the September 2019 Panel meeting have been incorporated.

Genotoxicity and phototoxicity data on *Scutellaria Baicalensis* Root Extract were received from the Council, and the Panel determined that these data also support the safety of *Scutellaria Baicalensis* Root Powder. The existing data requests on *Scutellaria Baicalensis* Extract and *Scutellaria Baicalensis* Sprout Extract remain valid. Thus, the Panel issued a tentative report with the following conclusions: *Scutellaria Baicalensis* Root Extract and *Scutellaria Baicalensis* Root Powder are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The available data are insufficient to make a determination that *Scutellaria Baicalensis* Extract and *Scutellaria Baicalensis* Sprout Extract are safe under the intended conditions of use in cosmetic formulations.

Draft Final Report, Teams/Panel: September 14-15, 2020

Report comments that were received from the Council prior to the June 2020 Panel meeting have been addressed. The same is true for the Council's comments on the tentative report.

Scutellaria baicalensis-derived Ingredients Data Profile* -September 14-15, 2020 - Wilbur Johnson, Jr.

						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
Scutellaria Baicalensis Extract	X			X	X		X																							X
Scutellaria Baicalensis Root Extract	X		X	X	X		X								X	X				X	X		X	X	X					X
Scutellaria Baicalensis Root Powder																														
Scutellaria Baicalensis Sprout Extract	X																													

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

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Scutellaria Baicalensis-Derived Ingredients – 5/10/2019; 7/29/19; 2/3/20; 8/6/20

Ingredient	CAS #	InfoBase	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Scutellaria Baicalensis Root Extract	94279-99-9	Yes	6/3	92/3	No	Yes	No	No	No	No	No	No	No	No	No	No	
Scutellaria Baicalensis Extract	94279-99-9	Yes	191/14	293/11	No	Yes	REACH PreReg. – No Dossier	No	No	No	No	No	No	No	No	No	
Scutellaria Baicalensis Root Powder	94279-99-9	Yes	0	7/0	No	Yes	No	No	No	No	No	No	No	No	No	No	
Scutellaria Baicalensis Sprout Extract	94279-99-9	Yes	0	2/0	No	No	No	No	No	No	No	No	No	No	No	No	
94279-99		Yes	0	717/14	No	Yes	REACH PreReg. – No Dossier	No	No	No	No	No	No	No	No	No	

Search Strategy

[document search strategy used for PubMed and Toxnet]

[identify total # of hits /# hits that were useful or examined for usefulness]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - <http://www.personalcarecouncil.org/science-safety/line-infobase>
SciFinder (usually a combined search for all ingredients in report; list # of this/# useful) - <https://scifinder.cas.org/scifinder>
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - <http://www.ncbi.nlm.nih.gov/pubmed>
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) - <https://toxnet.nlm.nih.gov/> (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm> (CFR); then, list of all databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>; then, <http://www.accessdata.fda.gov/scripts/fcn/fcnavigation.cfm?rpt=eafuslisting&displayall=true> (EAFUS); <http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm> (GRAS); <http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm> (SCOGS database); <http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives> (indirect food additives list); <http://www.fda.gov/Drugs/InformationOnDrugs/default.htm> (drug approvals and database); <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf> (OTC ingredient list); <http://www.accessdata.fda.gov/scripts/cder/iig/> (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - <http://ec.europa.eu/growth/tools-databases/cosing/>

ECHA (European Chemicals Agency – REACH dossiers) – <http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1>

IUCLID (International Uniform Chemical Information Database) - <https://iuclid6.echa.europa.eu/search>

OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- <http://webnet.oecd.org/hpv/ui/Search.aspx>

HPVIS (EPA High-Production Volume Info Systems) - <https://ofmext.epa.gov/hpvis/HPVISlogon>

NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- <https://www.nicnas.gov.au/>

NTIS (National Technical Information Service) - <http://www.ntis.gov/>

NTP (National Toxicology Program) - <http://ntp.niehs.nih.gov/>

WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

FAO (Food and Agriculture Organization of the United Nations) - <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/> (FAO);

FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

Web – perform general search; may find technical data sheets, published reports, etc

ECETOC (European Center for Ecotoxicology and Toxicology Database) - <http://www.ecetoc.org/>

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>

Fragrance Websites, if applicable

IFRA (International Fragrance Association) – <http://www.ifraorg.org/>

RIFM (the Research Institute for Fragrance Materials) should be contacted

SEPTEMBER 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team –September 16, 2019

DR. BELSITO: Shall we scuttle along to Scutellaria?

DR. LIEBLER: Yes. Before we get to Sulfites.

DR. BELSITO: Oh, my God. This is endless. Okay. Safety assessment. This is the first time we're looking at it, so feel free to comment away. There's a fragrance use, of course, which is not our purview. I guess the first question I had is, this is the first time we're reviewing a group where none of them have the same function. Is this an issue?

DR. SNYDER: I didn't catch that.

DR. BELSITO: Yeah. Read the sentence. PDF Page 9, the first full paragraph. It says, "However, these ingredients do not have any functions in common."

MS. FIUME: If I were to channel Bart, he doesn't necessarily feel that all the functions are truly representative of what the ingredients do. So, while sometimes it might provide useful information, it shouldn't be a reason to not include the ingredients together.

DR. BELSITO: Okay. I'm just saying, because we said before we'd do add-ons if they were no-brainers and they had similar functions. And here, we're starting with a group where we say none of them have similar functions. I'm just reading what I saw and asking the questions.

On PDF Page 9, under Physical and Chemical Properties, I think you have this completely backwards. The absorption peak between 200 and 250 is within the mid-wavelength of UVC, not UVB. And then absorption between 250 and 300, crossing both UVC and short-wavelength UVB. UVB is 290-320. UVC is less than 290. So, for every C, you've got to change it to B, and for every B, you've got to change it to C in that paragraph.

And then, for method of manufacture we need the extract and the sprout. And I didn't know if we needed the root powder since we have the root extract. If you read how the root extract is made, they make the powder first and then they water it down. So, I didn't really think we needed the manufacture for the powder.

DR. LIEBLER: So I think we need it for the extract.

DR. BELSITO: And the sprout.

DR. LIEBLER: Right. But for the extract, we need to know, what is it an extract of, roots, whole plant, stem, leaves?

DR. BELSITO: Right. Yeah, which we would get from the method of manufacture?

DR. LIEBLER: Right. So, if we had the method of manufacture, then that in turn could help us with safety data for some of the other ingredients.

DR. BELSITO: Right.

DR. LIEBLER: I had this insufficient for method of manufacture and composition for the whole extract.

DR. SNYDER: We have composition for the extract, the root extract and the root powder. We don't have anything on the sprout.

DR. BELSITO: Well, that was another question that I had on composition. I mean, they basically just gave you general categories. You were happy with the composition on the root extract and the root powder?

DR. LIEBLER: There was enough information for the root extract and the root powder. I think the thing I was unclear about for the extract, the scutellaria baicalensis, was whether or not that's distinct from the roots. In other words, does the extract contain roots?

DR. SNYDER: Since the extract was Table 2, it lists everything that's in there. Actually, there's more data than we have on the other one.

DR. LIEBLER: I'll take another look.

DR. SNYDER: Page 19.

DR. LIEBLER: Yeah. That's a listing of chemicals in it. I'm just trying to get the definition. Oh, it's the extract of the whole plant. Duh. Okay, there it is. That includes, therefore, roots.

DR. SNYDER: I thought we were good on everything except for the sprout. We don't have any data on the sprout.

DR. LIEBLER: Right.

DR. BELSITO: Okay. What did you think of the DART study on PDF 13, Paul?

DR. SNYDER: Well, there were two negative studies. And there was one, but the only effects were on maternal and there was no developmental effects. It was maternal so I had cleared that.

DR. BELSITO: Okay. What about the genotox? For genotox, I didn't understand. Results were positive for methanol and negative for aqueous. PDF 13, bottom of the page. It's the only one that's positive with two -- this was in the rec-assay. We had negative Ames and we had no mammalian genotoxicity. So, we only had two in vitros and no carcinogenicity.

MS. FIUME: And then, the second study, it was actually positive results seen in the aqueous and not the methanol.

DR. BELSITO: Right.

MS. FIUME: So, they were contradictory. Yeah.

DR. SNYDER: We go to Tom and there's those random positive ones, because the majority of them appears to be negative.

DR. BELSITO: No. We don't have a majority. We have a rec-assay and we have an Ames; and each had a positive result, one in methanol and one in aqueous.

DR. LIEBLER: Yeah. This is problematic. I'd like to hear what Tom thinks. But his point is frequently that sometimes you get conflicting results with botanicals.

DR. BELSITO: But we have no mammalian. We have no backups for this. We just have in vitro. And then we don't have a No-Adverse-Effect-Level for melanogenesis.

DR. KLAASSEN: Correct.

DR. LIEBLER: This is just in mouse melanoma cells, right?

DR. BELSITO: Yeah.

DR. LIEBLER: These are pretty high concentrations.

DR. BELSITO: I understand. But we have a report and we don't have a concentration at which nothing happens.

DR. LIEBLER: So, if you see an effect on melanogenesis in a cell culture system only, without any positive in vivo data, then you need a No-Effect-Level in vivo.

DR. BELSITO: You need some data.

DR. LIEBLER: In the previous report we did have cell data, but we also had in vivo data that was melanin-suppressing. But we didn't have a No-Effect-Level. Here, we don't have any in vivo data at all.

DR. BELSITO: I understand. But we have suggested evidence that this could occur.

DR. SNYDER: It inhibits melanogenesis, yeah.

DR. BELSITO: Without any data to suggest that it does not occur either in vivo or at concentrations that are used in cosmetics.

DR. LIEBLER: Okay.

DR. BELSITO: Then, for the antiallergenic effects -- here there were three concentrations used, Wilbur. It says 1, 10, and 100 micrograms per mL. The one, two, three, four, fifth line from the bottom of that paragraph it says, "following treatment with the extract (both concentrations)."

So, if there were three concentrations, did the 1 micron per mL not have an effect? Do we have a No-Effect-Level? Because there were three concentrations used and then they're counted as both concentrations.

MR. JOHNSON: I'll have to check that, but I think that that referred to the 10 and the 100. But I'll check that publication to see whether or not there was an affect and at what.

DR. BELSITO: Because if it has an anti-inflammatory effect, then we also need a NOAEL because cosmetics should not have biological functioning. Right? Or it becomes an OTC anti-inflammatory or prescription anti-inflammatory.

DR. SNYDER: Right. Not under our purview.

DR. BELSITO: Right. So, we need more information on melanogenesis.

DR. SNYDER: Which one was that that's supposed to function as an -- root extract?

DR. BELSITO: The baicalensis extract. Ethanol extract, plant part not stated. Then we also have suppression of DNCB-induced contact dermatitis, aqueous extract of the root. They stated the results indicated a topical application, suppressed DNCB-induced contact dermatitis. This was 0.1 percent aqueous extract.

DR. SNYDER: No, we didn't get the data needs.

DR. BELSITO: So we need a no-observed-effect-level for melanogenesis, IgE, or our anti-inflammatory suppression of contact allergy. In terms of sensitization for the root extract --

DR. SNYDER: We have that.

DR. BELSITO: Well, yeah. Theoretically, you're supposed to have 20 test animals, they only had 10 in the Buehler, but it was negative.

And the human HRIPT on the root extract, theoretically, you're supposed to have 100 subjects in the same panel, but they had 49 and 54. So I thought, overall, even though the studies didn't meet the usual defined criteria in terms of ends, they were okay when put together for the root extract.

DR. SNYDER: Okay.

DR. BELSITO: So, I thought insufficient for the root extract and powder. We need more data on the no-observed-effect-level for pigment effects and anti-inflammatory effects. For the extract, we need sensitization and irritation and a 28-day dermal. And if absorbed, other studies. And for the sprout, we need everything.

MR. JOHNSON: Could you go over that again?

DR. BELSITO: For the root extract and powder, we need a no-observed-adverse-effect-level for pigmentation, anti-inflammatory effects including suppression of contact dermatitis. For the extract of the whole plant we need sensitization and irritation and a 28-day dermal. If absorbed, additional studies may be needed. For the sprout, we need manufacturing, impurities, sensitization, composition, irritation, dermal absorption.

MR. JOHNSON: Manufacture, impurities.

DR. BELSITO: Impurities, dermal absorption. If absorbed, other studies may be needed. Sensitization and irritation.

MS. FIUME: Do you need a method of manufacture for the whole plant extract?

DR. BELSITO: I didn't put that down.

DR. SNYDER: Dan had it at first, but I think it went away, right? You mentioned that at first?

DR. LIEBLER: Well, it's just defined in Table 1 as the entire plant extract, all parts of the plant. Because my question was, what parts of the plant is it?

DR. BELSITO: So, you need composition for extract?

DR. LIEBLER: We've got composition for the extract. We're okay on that.

DR. BELSITO: Okay. You got that, Wilbur?

MR. JOHNSON: Let me read it back. For the whole plant extract, skin irritation and sensitization data and 28-day dermal toxicity data. If absorption occurs, then additional data may be needed. For the sprout extract, method of manufacture, impurities, dermal absorption. If absorbed, additional studies may be needed. Skin sensitization and skin irritation.

DR. BELSITO: Right.

DR. LIEBLER: Did we need more mutagenesis? We needed an in vivo mutagenesis?

DR. BELSITO: Well, if absorbed.

MS. FIUME: Oh, were you going to wait to see what Tom says tomorrow?

DR. BELSITO: Yeah, we're going to wait to see what Tom says about mutagenesis.

DR. LIEBLER: Okay.

DR. BELSITO: And then for the extract and powder we needed the no-observed-adverse-effect-levels for pigmentation, anti-inflammatory effects, and suppression of delayed type hypersensitivity. Then Tom comments on the mutagenicity studies.

MR. JOHNSON: Dr. Belsito, are there any concerns about teratogenicity? Because we had positive results in the teratogenicity study.

DR. KLAASSEN: But they were kind of repaired with time. It was more of a delay, I think. I didn't think it was necessary, if I recall correctly.

MR. JOHNSON: You said there's no concern, and what's the reasoning?

DR. KLAASSEN: Well, it wasn't a true teratogenic effect. It was kind of a delay in development.

DR. SNYDER: No. No, no. There were maternal effects but only at high doses, 32 milligrams per kilogram with two negative studies. That's fine. Opps. I'm on the wrong report. Sorry.

MR. JOHNSON: I guess what I was talking about the statistical significant dose-dependent increase in the incidence of skeletal variations.

DR. KLAASSEN: Right. But then I thought, if you read a little further, at a little later date they're back to control. So, it's kind of a delayed. And that's usually not considered a --

DR. SNYDER: Skeletal variations.

MR. JOHNSON: Okay.

DR. SNYDER: Yeah, if they would lose weight or anything -- it's not a . It's not a very good one.

DR. BELSITO: Yeah. It says the author stated that the results of the study suggested the appearance of lumbar ribs induced by the test material is a transient fetal variation rather than teratogenicity or maternal toxicity.

DR. KLAASSEN: And I agree.

DR. SNYDER: Yeah. I do.

Marks Team – September 16, 2019

DR. MARKS: Okay. Are we ready? Everybody's back. Okay. Let's move on now to *Scutellaria B. Baicalensis* perhaps is the way you say that. Mint. There we go. On the next memo, Wilbur, would you put mint? At any rate, this is the first review of these four ingredients. As you mentioned, they're herbs or mint. Ron and Tom, first, the four ingredients okay? The extract, the root extract, root powder, sprout extract?

DR. SLAGA: Yes.

DR. SHANK: Yes.

DR. MARKS: Yeah. I don't think -- we can't eliminate them. We have no good reason. What needs do we have for them? First of all, they're herbs. Are they GRAS food? I assume, but, Tom, you're going to comment.

DR. SLAGA: I thought there was plenty of data, and I'd say safe.

DR. MARKS: We certainly have data for the extract and the root extract.

DR. BERGFELD: What about the sprout?

DR. MARKS: Well, we're going to get to the -- yeah, there's nothing. Ron, what do you think?

DR. SLAGA: The sprout comes from the root, the seed.

DR. SHANK: We have data on the root extract, but I don't know if you can read across to all of the other forms. The root extract inhibited melanin production in cultured melanoma cells, so we might need data on depigmentation in animals. It's also used in sun lotions, so we may need phototox data. You could try to do UV absorption, but these are such mixtures I'm not too sure how those data would be interpreted.

The root extract in a developmental toxicity study produced lumbar ribs in rats. And I need to ask Dr. Snyder what does that really mean. I've never encountered that before.

So I did have some needs. We have a little toxicology data on, quote, extract. Is that whole plant extract? And we don't have data on the sprout extract, but these are used at much lower concentrations than the root extract. So maybe if we can read across, we could cover them. And what else?

DR. MARKS: I'll address the irritation and sensitization. I thought it was fine. It was okay for the root extract at 100 percent and in animal at 10 percent. And the use concentration was 0.5, so it's way, way above the use concentration.

DR. SHANK: Right.

DR. MARKS: I felt the root extract we could read over to the extract itself, perhaps. And then the other, the extract itself, again, as you mentioned, there's low concentration, 0.3 percent in the extract, and 0.0005 percent in the sprout. So I thought the concentrations of use were so low that at least irritation and sensitization would not be an issue.

So it's mint. Does that have any bearing in terms of the systemic toxicity? I guess you'd say is this a GRAS? Is it food? And if so, does it eliminate some of those systemic needs, other than, as you said, the issue of could the root extract cause depigmentation? Do we need phototox data. And then the developmental issue, Ron? And I might ask you tomorrow -- although we're seconding it -- to comment on those three needs.

DR. SHANK: This is mint? I thought this was Chinese skullcap.

DR. MARKS: I'm going on.

DR. SHANK: Pardon me?

MR. GERMILLION: It says it's in the mint family on page 9 of the report, but it's Chinese skullcap and Baikal skunk. So the mint family is what it says.

DR. SHANK: Okay.

DR. MARKS: What is the -- what is China skullcap?

DR. SHANK: Herbal medicine used for everything.

DR. MARKS: Yeah. So it's really a medicine rather than a food. Then it wouldn't be GRAS.

DR. SHANK: That's my understanding.

MR. ANSELL: Yeah. But GRAS is not a driver as to whether or not it's ingested as part of the human diet.

DR. MARKS: Yeah.

MR. GERMILLION: And things can be GRAS. Companies can self-determine that a substance is GRAS that they're using. I'm not really sure. Sometimes FDA is asked to give a voluntary opinion on whether they'd like more data. But I'm a little confused about the references to GRAS and what the significance of that is.

MS. SADRIEH: There's no significance. GRAS doesn't apply to cosmetics.

MR. GERMILLION: Yeah. I guess what my point was is just things are GRAS. FDA hasn't contested that interpretation, but it doesn't necessarily mean that there's really any kind of meaningful safety assessment.

MR. ANSELL: Well, that's a point of some discussion. But it's really not relevant to the criteria within the context of the CIR review. What we're saying is that if it's been part of the human diet for a substantial period of time, that that is responsive to the question of systemic toxicity, and that we should be focusing on topical effects and concentrations. The GRAS discussion is a very specific regulatory scheme within the U.S. And it not being GRAS does not suggest it's not an item of food.

The GRAS finding, however, I would argue is a substantial finding. It's generally recognized by experts. It is a regulatory scheme, and FDA does have to formally not object. So it doesn't suggest -- we could argue whether the current affirmation versus notification is effective. But what we're interested here is that it's been part of the diet.

DR. MARKS: We've had extensive conversations in our team about what GRAS is and what it means. So I guess tomorrow we'll most likely be seconding a motion for an insufficient data announcement, perhaps, getting the needs for the root extract concerning it's inhibition of melanin. Is there depigmentation? Perhaps phototox data. And then we'll question the developmental issue, too. Does that sound reasonable?

DR. SHANK: Yes. Are the sensitization data enough? There's an animal study when they use the dry powder. Is that reasonable? How do you do that? And then the human study, there's very little detail. So I was wondering if that's enough data to say we can read across for everything else. It's page 16 in the report. In the animal data, they used a dry powder. I don't know how you do that.

DR. MARKS: Basically, you just apply it on there. And I thought it was okay.

DR. SHANK: Okay. And then the human data, 49 subjects and then another one 54 subjects. And 32 --

DR. MARKS: And that was at 10 percent. And, again, which is much higher than the use concentration.

DR. SHANK: But there are no data.

DR. MARKS: You mean in terms of the actual testing. Yeah. I guess I assume that when they do an HRIPT that it's done in the usual manner; HRIPT, or it wouldn't be identified as such. Did you get any sense that it was other than the usual methodology?

MR. JOHNSON: I think it's the usual.

DR. MARKS: So I accept it at face value.

DR. SHANK: Okay.

DR. MARKS: Since HRIPT is a standardized testing methodology.

MR. JOHNSON: Because in that submission, data relating to the test protocol were not included. So that's just an assumption about the protocol.

DR. MARKS: And actually, I thought the 100 percent powder was pretty impressive, actually.

DR. SHANK: How do you do such a test? Do you have to put it on a gauze pad and then just tape it to the animal's skin?

DR. MARKS: Presumably, yes.

DR. SHANK: You wouldn't make a paste out of it or something? Never mind.

DR. MARKS: They say a spray dried extract.

DR. SHANK: Applied as a powder.

DR. MARKS: I know when I sometimes don't have the actual patch testing allergens, in either petrolatum or water, I will take the whole -- if it's a plant part, I'll actually take the plant part and apply it directly to the skin and get sensitization.

DR. SHANK: Really.

DR. MARKS: Yes.

DR. SHANK: Thank you.

DR. MARKS: You're welcome.

MR. JOHNSON: One question, Dr. Marks. The data need, the depigmentation data, specifically, what type of testing is being requested in the IDA?

DR. SHANK: I would use pigment in animal, a guinea pig that has pigment in skin, and then apply it to the skin. Again, these are, I think, standardized tests.

DR. MARKS: That's what's been used in the past.

DR. BERGFELD: Are you allowed to use animal testing now?

DR. SHANK: In the United States, yes.

DR. MARKS: And presumably, this may actually -- data may exist, we just didn't find it. What page is that?

DR. SHANK: Let's see.

MS. FIUME: 14.

DR. BERGFELD: It had some very interesting characteristics. It supposedly lighten skin. It dampened inflammation. I don't think you can read across to sprout.

DR. SHANK: I agree.

DR. MARKS: Okay. So I don't think our -- let's go back. So again, insufficient data announcement is what we would propose. And we need more information concerning the depigmentation for the root extract and potentially the other three ingredients. We need phototox data and developmental data. Did I clarify that, Ron?

DR. SHANK: We have developmental tox, but I don't know how to interpret it. It's a rat study, and they found in the embryos lumbar ribs. Rats don't have lumbar ribs. And there seemed to be a transient response. So something's going on, but I don't know how to interpret it. So maybe Dr. Snyder can help us out on that.

DR. MARKS: And that was which page for that?

DR. SHANK: Let's see. Page 13, in the middle.

DR. MARKS: Okay. Any other comments? So presumably, we'll have an insufficient data announcement tomorrow.

MR. JOHNSON: Dr. Marks and other members of the team, you'll notice throughout the report text that sometimes you will see a scutellaria baicalensis root extract, meaning that we're not sure what was actually tested is the INCI name ingredient. And in particular, that's true with respect to the genotoxicity studies. So with that in mind, would there be any need for any additional genotoxicity data?

DR. SLAGA: Since it is the first time, we could ask for it and see if we get it.

DR. BERGFELD: Are you going to do it on the root and the sprout since you're asking?

DR. SLAGA: Yeah. Just ask for both, the sprout and root.

MR. JOHNSON: Now, the phototoxicity data --

DR. MARKS: Let's go back to that. So Tom, you think we should ask for mutagenicity?

DR. SLAGA: Well, if we're asking for other things.

DR. MARKS: If we don't get it, are we going to say it's insufficient?

DR. SLAGA: No, it's not really needed.

DR. MARKS: Well, if we don't need it then we shouldn't ask for it. Because I don't want to put out ask for things and then we go back and say, well, we really didn't need it. And that's what I question, Tom, when you said initially you didn't have a need for it.

DR. SLAGA: I didn't initially have any needs.

DR. MARKS: Okay. So I know you were talking about whether it's the INCI ingredient or not, and we have that with other botanicals. When they're testing, we're not sure whether it's truly a cosmetic formulation or another formulation of it. And that's the uncertainty, I think, when we're dealing with these botanicals. Monice, you had a comment. So I'm going to say, Wilbur, we don't need that --

MR. JOHNSON: Okay.

DR. MARKS: -- based on Tom's comment.

MS. FIUME: So I actually have two questions, but the first is with the genotox. So for the purposes of the discussion, then, it says that a methanol extract had positive results, but the aqueous extract had negative results. So for the purposes of the discussion, can you provide some language?

DR. SLAGA: That can be discussed in the discussion. In this case, the aqueous is the most important, right?

MS. FIUME: Do we have what the extract is for the ingredient because there's ethanol extract, butylene glycol, but it doesn't say if it's --? Okay. So then the specific language, Dr. Slaga, what should be said about it?

DR. SLAGA: I can't explain the methanol, to be honest, but the fact that it was more soluble in water I thought gave more realistic response.

DR. SHANK: In a lot of the toxicology data, the adverse response was very much dependent on which solvent was used to make the extract. That would suggest probably that the flavonoids are the toxic agents here because you can separate them based on which solvent you use. What's used in cosmetics I'm not sure.

MS. FIUME: Since an IDA is going out, do you want additional method of -- would that help clarify?

DR. SHANK: I'm not sure it would clarify because -- unless there's just one extract used, say water, yes, that would clarify it. But if there's several different methods, no, it won't clarify it.

MS. FIUME: Thank you. My second --

DR. SHANK: Let me see what's here on methods.

MR. JOHNSON: PDF page 10.

DR. SHANK: So it looks like you could use ethanol, butylene glycol, water.

MS. FIUME: Thank you. And then, I guess, my other question --

DR. MARKS: Well, have we settled it? We don't need these, Tom?

DR. SLAGA: You could ask for data to clarify the methanol aqueous. I read that, but at the same time, these things have a long history of use. And there's really no alert for cancer genotoxicity as being a problem. And without -- you can have the genotox, but if you have no irritation, the odds that you would get cancer are very slim.

MR. JOHNSON: So Dr. Slaga, you want to know whether or not methanol is in fact used in the production of either of those extracts?

DR. SLAGA: Right.

DR. SHANK: Well, genotox in one study -- the methanol extract was positive and the water negative and in the Ames assay the opposite. So it's very hard to interpret that.

DR. MARKS: So then the question is how can we clarify it. Do we use the reasoning you just said, Tom, in the discussion that a long use of this and no alerts?

DR. SLAGA: Well, that's one study. We could ask for repeat studies, both in bacteria and mammalian mutagenesis just for a complete on both the methanol and aqueous. But other solvents were used, and they weren't tested.

DR. SHANK: A toxicological response is very much dependent on what solvent is used to extract the plant.

DR. MARKS: So it sounds like -- I'm not sure how we can clarify it. I guess that's my question. If we call it insufficient because of -- do you want to say mutagenicity or carcinogenicity?

DR. SLAGA: No. We just need to clarify the genotoxicity with repeat studies, additional studies on both aqueous and methanol extract; both in bacteria, the Ames in this case, which was used, and mammalian system.

MR. JOHNSON: This is just for the root extract?

DR. SLAGA: Huh?

MR. JOHNSON: Just for the root extract ingredient, or what about the other extract?

DR. SHANK: I don't think you can read across from the root to the leaf and stem and sprout. Unless we have the data showing that the composition is pretty much the same regardless of the source.

DR. SLAGA: We could ask for it all right now.

MR. JOHNSON: On all?

DR. SLAGA: Yeah.

MR. JOHNSON: Even the root powder?

DR. SLAGA: Yeah.

MR. JOHNSON: Okay.

DR. MARKS: What page was that, Wilbur, in the document?

DR. SLAGA: Was it 10?

DR. MARKS: Ten. And then how about the phototox data? Which page was that, Ron Shank?

DR. SHANK: Let me see. Well. Hmm.

MS. FIUME: Is it page 14 you're talking about, the melanogenesis study?

DR. SHANK: Yes. Thank you.

DR. MARKS: Okay. Good. So it seems pretty clear tomorrow we're going to have an insufficient data announcement. And at least our team would like clarification of depigmentation of the root extract and also the sprout, suggest using a depigmented animal model. We'll clarify that tomorrow.

Some phototox data based also on that melanogenesis section, developmental clarification. The question is these ribs that you're talking about, Ron, we'll get Paul's input on that. And I'll probably ask you to clarify your concerns, Ron. And then, clarify the genotoxicity studies with the methanol and water extracts. And we can't read across for all the ingredients. And, Tom, I may ask you to comment on that.

DR. SLAGA: We want additional studies to clarify that. We want to have the weight of evidence going one way or the other. With the Ames assay, it's very difficult to tell after one study. It's usually repeated a number of times to see how it kind of unfolds.

DR. MARKS: And Tom, I'll probably ask you to comment on that tomorrow. Okay. Any other questions?

MR. JOHNSON: Yes, Dr. Marks. The phototoxicity data request is on which ingredient?

DR. SHANK: The root extract for sure.

MR. JOHNSON: The root extract, the sprout extract?

DR. BERGFELD: I think your sprout is needing everything, composition especially, concentrations of use --

DR. SHANK: Yeah. We don't know anything about the sprout.

DR. BERGFELD: -- special studies.

DR. SHANK: It is used, isn't it?

DR. MARKS: The extract, the concentration, I believe, is 0.03 percent. It has 102 uses.

MS. FIUME: And the whole plant extract, also, has use.

MR. JOHNSON: Yeah.

DR. SHANK: Yeah. We don't have any tox data or sensitization data on whole plant extract or sprout extract. Now, root powder is just dried root extract? That's how I read it.

DR. MARKS: Yes. I wondered whether the sensitization and the irritation data were necessary for the extract at 0.03 percent use concentration. And then for the sprout extract, the use concentration leave on was 0.0005 percent. So one might use the same reasoning on the sprout extract that so little of it's used, are we concerned about the other toxicologic endpoints. But we can ask for them.

At 0.0005 -- I assume that concentration is correct. It's really low. So that's why I didn't particularly identify those since we had the root extract as a non-sensitizer. I didn't feel compelled with the others. I felt we could read-across the root powder. And then the extract itself and the sprout extract I felt were low concentrations would be okay from a sensitization point of view. That was my reasoning.

DR. SHANK: That sounds good.

DR. MARKS: Okay. Well, we have it looks like four data needs for tomorrow. We'll suggest the issue with depigmentation, the phototox, maybe developmental. We'll get clarification of that tomorrow concerning those ribs that you were talking about, Ron. And then also clarify/additional studies on genotoxicity. Does that sound good, Tom?

DR. SLAGA: Yeah.

DR. MARKS: Sound good, Ron?

DR. SHANK: Yes.

DR. MARKS: Okay. And we'll see what the Belsito team suggests also, but I have a feeling it's going to be an IDA, Wilbur, no matter what. Okay

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DR. BELSITO: So this is the first time we're looking at the Chinese skullcap-derived ingredients. And based upon the data that was provided to us, first of all there was a report of it being used as a fragrance, which we would like acknowledged it is not our purview. We did discuss the fact that all of these seem to have a different function and whether that was an issue, but we did not think so.

Overall we felt that it was insufficient for the root extract and the powder, we needed more data on constituents. We also needed a NOAEL for the pigment effects and the anti-inflammatory effects of these materials.

DR. BERGFELD: Is there a second or a comment?

DR. MARKS: Yes, we second the insufficient data announcement. We had a few other concerns. One was phototox data on all the ingredients. And then Ron Shank had a concern and wanted Paul's comments about developmental effects. Where in one system -- you want to elaborate on that, Ron, the issue of the ribs?

DR. SHANK: I just would like to ask Dr. Snyder, what is the significant in a rat study where you see lumbar ribs.

DR. SNYDER: The general consensus is that if you see skeletal variations in a study where there are maternal effects or any even slight effects, that they're not considered significant, unless you see other malformation or something. But them as a standalone doesn't give you very much evidence of teratogenicity.

DR. SHANK: Okay, thank you.

DR. KLAASSEN: In fact, often those kind of repair themselves with time. It's basically kind of a slowing down of the maturation. And in fact in the study they did look at the ribs at a later time and they did catch up. So, that's not considered a teratogenic effect.

DR. SHANK: Okay, right. This is the first time I've come across lumbar ribs, so I had to ask.

DR. SNYDER: Yeah, I sent the staff the review paper on the anogenital distant things and the skeletal variations and how to interpret those. I sent that to the staff as a reference for them to have.

DR. BERGFELD: Thank you.

DR. BELSITO: And, we had a question over to Tom about the mutagenicity studies. We have no mammalian genotox, but in a rec-assay the methanol extract was positive, and the aqueous extract was negative. And then in an Ames test it was flipped; the methanol extract was negative, and the aqueous extract was positive. How do we interpret that, and do we need a mammalian genotoxicity?

DR. SLAGA: That was one of the data needs that we would like to see that repeated. When you only have one trial like that, where one's positive and one's negative, it would be nice to have several other -- a repeat of that, plus another assay, be it a mammalian system, so that you could develop a weight of evidence one way or the other.

So, that was one of our discussions that we thought that it's better not to leave it that way. More data since we're asking for others, it would be good to have that.

DR. LIEBLER: So are you suggesting repeats on the in vitro -- analyses for an in vivo?

DR. SLAGA: Yeah, repeats on the in vitro, plus additional assays or two. You know, it'd be nice to have a mammalian system.

DR. LIEBLER: Right, okay

DR. SLAGA: Yeah.

DR. LIEBLER: Yeah.

DR. BELSITO: And so, this is the one on the sprout also that we -- so on the root powder and extract we need more data on constituents and a NOAEL for pigment, infection and anti-inflammatory. For the extract we need sensitization, irritation, 28-day dermal, and if effects, additional. And for the sprout we need method of manufacturing, impurities, sensitization, irritation and a 28-day dermal and if absorbed, other data may be necessary. And then, the comments we just had on mutagenesis.

DR. BERGFELD: I'd like to ask a question regarding is this a food? I mean, if it's in the mint family -- it's not only medicinal as the Chinese use it, but it's possible it's used in our country as a food substance, and herb.

DR. BELSITO: I couldn't find anything where it was used as a food.

DR. HELDRETH: Not that we're aware of.

DR. SLAGA: It's a mint.

DR. BELSITO: Yeah, but mint is *Mentha piperita* or something like that.

DR. BERGFELD: Well, anyhow, it is a consideration if we could find anything on food.

DR. BELSITO: It's a different species or genus for sure.

DR. BERGFELD: All right, well we've had a second -- an amended second, I gather, because we've had some added needs put in. So, any other comments?

And seeing none, I'll call the question. All those in favor with an insufficient report? Yes, thank you, unanimous. And, the insufficiencies have been outlined, and you all have them? Okay, fine.

Belsito Team – June 8, 2020

DR. BELSITO: Just kill me, man. I've never seen a report with so many different data needs for different groups of ingredients. Okay. So I'm not going to read them all. You have them, right?

DR. SNYDER: Yes.

DR. BELSITO: We all have the agenda. So what we got back was manufacturing for the root extract, genotoxicity for the root extract, phototoxicity for the root extract, and an HRIPT for root extract. So it seems like industry was most concerned about getting root extract taken care of.

There were a good amount of comments from the council on this though and really having to do a lot with the root extract and the root powder. But then they also mentioned that the extract -- there were two case reports of irritation and sensitization, but actually they were positive reports. And not much else except 3T3 assay, which is in this report.

The interesting thing is, though, when you look at the absorption, it's 250-300 nanometers. So it barely makes it into the UVB range, which starts at 290. And it's pretty far away from the UVA. And almost every photosynthesis hazard that I know or phototoxic material absorbs UVA. So I'm not sure why we are so concerned about photo. This is PDF page 20.

DR. LIEBLER: Yeah. Don, I think it's one thing to use UV spectra to assess pure compounds but not to assess mixtures because mixtures have abundant ingredients that may absorb but will not necessarily be photo excited to product any necessarily hazardous affects. I think that it's not a good yardstick to use.

DR. BELSITO: Okay.

DR. LIEBLER: So I don't think that there is a reason for concern here, you know, unless we had constituents that were clearly associated with phototoxicity.

DR. BELSITO: Okay. And we have composition on the root, and the root powder is pretty similar.

DR. LIEBLER: We still don't have anything on the sprout.

DR. BELSITO: Right. We don't really have much on the extract. And the extract, when it's spread orally, seems to go everywhere. If you look at the ADME studies on page 22, it was detected in heart, liver, lung, kidney, stomach, spleen, brain, and intestines.

DR. KLAASEN: And look at the toxicological studies, non-existent. I don't think we have this in DART.

DR. BELSITO: There are no tox studies. We do have a DART study on the root extract, which was pretty negative. No effects on the fetus. We have genotox on the weed extract, no carcinogenicity. But when you bring in the weed extract, we have the pigment affect again, which I suppose -- I think the council also said we could handle as we've handled it before -- that this would be a non-cosmetic use, and manufacturers should formulate to avoid levels that could potentially affect pigmentation.

DR. LIEBLER: Yeah. This is, I think, kind of a bogus alert on pigmentation because this is one of those studies that was just on toxicity affect in the mouse melanoma cells exposed to very high concentrations of the ingredient. And there's no evidence for any in vivo effect. So I agree. We can handle this in the discussion. But we should point out that the model, from which the data come, really isn't a good model for pigmentation affects.

DR. BELSITO: Okay.

DR. LIEBLER: Paul, do you share my view, or do you have another take?

DR. SNYDER: No, I concur with that. My only concern is the root extract is used at 0.5 percent in a leave-on, and we don't have any -- we asked for 28-day dermal for the extract. But I don't remember why we didn't ask for fruit extract from the council.

DR. LIEBLER: We really are thin on tox.

DR. SNYDER: Yes, that's the only one that bothers -- the extract doesn't bother me. It's the 0.03 percent. And with the maximum dermal at -- whether they have the dermal, maximum leave-on is 0.00027. It's that root extract at 0.5 percent.

DR. LIEBLER: And we can't really fall back on GRAS with this. It is apparently the root. *Scutellaria radix* is an herbal medicine in China. *Scutellaria baicalensis* Georgi is one of 50 fundamental herbs in Chinese medicine. So we really don't have a lot to fall back on on tox.

DR. BELSITO: Since this is a Chinese herbal medicine, it may work by killing people with those diseases. Oh, lord. Sick joke, sorry.

DR. LIEBLER: I think we're probably okay now on genotox. The March to June supplement indicates some additional in vivo, the mammalian tox and genotox. So that clears up one concern I had about genotox -- that we didn't have mammalian, but now we do. And that's on the Chinese medicine that is an extract of the root.

DR. BELSITO: Mm-hmm. Well, can we say the root extract and the root powder by extension are safe and the others are insufficient for essentially what we asked for before? Or are you still concerned with the lack of tox data since the root extract has the highest use at 0.5?

DR. SNYDER: Well, yeah. But if you look at this, we do have three DART studies there, and there was nothing -- no signal of toxicity in there maternally or fetal-ly. So I think we're okay.

DR. BELSITO: And just for the root extract and powder, not for the others.

DR. SNYDER: Correct.

DR. BELSITO: And the others we essentially need everything we asked for before, correct?

DR. SNYDER: Yes.

DR. BELSITO: Okay. So Wilbur, basically you can just get rid of what we asked for in the root extract. We already sort of discussed how to handle the hyperpigmentation and depigmentation. So what we did for pomegranate, *Punica granatum*, was - - we noted that skin might be considered it to be a drug affect and should not occur during use of cosmetic products. Because of that, based on low concentration of use of these extracts in cosmetic products, clinical experience, concern for this affecting cosmetics was mitigated. Nevertheless, cosmetic formulators should only use, in this case, *Punica granatum* extracts and products in a manner that does not cause depigmentation.

DR. SNYDER: Yes.

DR. BELSITO: So I think you could just take that language. The only part of the language I got rid of -- it said, "the known mechanism of action," which was no in this case, is not known in the case we're looking at. Why this happens, we don't know. So I just got rid of that part of the explanation. Anything else on this?

MR. JOHNSON: So Dr. Belsito, just delete that data request on the root extract and the root powder and add the boilerplate from the pomegranate report on depig?

DR. BELSITO: Right. Except that in the pomegranate report we said there was a known mechanism of action. There's no mechanism of action for this, so you just get rid of that.

MR. JOHNSON: Okay.

DR. BELSITO: And it's in my comment.

MR. JOHNSON: Okay. Thanks.

DR. BELSITO: And so we're going to go safe as used for the root and the root powder and insufficient for all the others for the same reasons that we originally went insufficient.

DR. SNYDER: Agree.

DR. BELSITO: Okay. That was an entire page in our annotated agenda there.

Marks Team –June 8, 2020

DR. MARKS: Also known as Chinese skullcap, it's a mint and medical herb. So this is a draft tentative report on these four *Scutellaria*-derived ingredients. And we issued an insufficient data announcement at the September meeting last year. And there were a number of deficiencies. I'm not going to go through all those. They're listed there, both for the root extract, root powder, the extract itself, and then the sprout extract. And we did receive data since that request. And let me see. We got data on the root extract, method of manufacture, genotox, phototox, HRIPT. They all look good to me.

Maybe I'll just jump right in and give you my conclusion, so I had a mixed conclusion. Lisa, Ron, Tom, do you want to jump in, or do you want me to give where I think we could go? I thought perhaps two of them -- these ingredients, the root extract and the power -- could be safe, but we have to deal with the skin lightning pigmentation and suppression of the delayed type hypersensitivity for the root extract.

And my feeling was is we could use the same reasoning as with skin lightening by pomegranate. There's three botanicals this time which all have skin lightening potential or effect. And so I thought the discussion with pomegranate was quite good in dealing with it. And then I thought the extract and the sprout extract there was insufficient for what's listed below.

But, Lisa, Ron, and Tom, why don't you weigh in because these botanicals -- fortunately, there are just four ingredients, but they oftentimes get pretty complex because the number of ingredients, the different plant parts, et cetera. So what was your

take of it? And let me see. Did Alex comment? She wondered whether "formulate to not cause pigmentation" -- I think was mentioned in her memo. (Inaudible), I asked you to weigh in too.

I just thought that the discussion in the pomegranate was quite good, that paragraph. We'll see that. I won't ask everybody to switch to that. If you want, I can read that paragraph from pomegranate. Would you like to hear that, everybody, or just switch to the pomegranate ingredient?

DR. SLAGA: Yeah.

MS. KOWCZ: Sure. Go ahead.

DR. MARKS: Okay. "Data included in this report indicate that extracts of parts of pomegranate, *Punica granatum*, may have skin lightening effect. The Panel noted that skin lightening is considered to be a drug effect and should not occur during the use of cosmetic products." I thought that was a very important sentence.

DR. PETERSON: Mm-hmm. I agree.

DR. MARKS: "Because of that caveat and based on the low concentrations of use of these extracts in cosmetic products, the Panel's knowledge of mechanism of action --" that is inhibition of tyrosinase activity by polyphenols. Obviously, this would have to be adjusted a little bit based on the ingredient. "-- the results of the in vitro study of pomegranate fruit extract, and clinical experience, concern for this effect in cosmetics was mitigated. Nevertheless, cosmetic formulators should only use *Punica granatum* extracts in products in a manner that does not cause depigmentation."

I thought that was really -- it almost could have a resource document on skin lightening. And I think it was just, for some reason, a cluster of these ingredients that we have three different ones: this one, the next one we'll be doing, which is the Ascorbyl Glucoside, and then lastly pomegranate. So I kind of thought that could be included in the discussion, only tailoring it for Chinese skullcap, and that would take care of the issue with the skin pigmentation.

But, again, Lisa, Ron, Tom, your comments. How do you want to proceed forward because we're going to be issuing a tentative report with a conclusion?

DR. SHANK: I thought the discussion handled the skin lightening effects satisfactorily as it is now. So issue an insufficient data report with the needs that have been identified.

DR. PETERSON: Yeah. I thought it was still insufficient. And there was a paper suggested in the memo. I didn't think that paper was appropriate because it was mixing this herb with three others, and it wasn't really looking at just the herb alone. So I didn't think that paper was helpful.

MR. GREMILLION: I'd like to ask a question if that's okay. This is Thomas at CFA.

DR. MARKS: Of course.

MR. GREMILLION: The HRIPT that was submitted, it's mentioned on the first page and described -- oh, I lost it but anyway - - on the first page, it says that it was a leave-on product containing 0.001 percent of the root extract. Did that involve experimenting with some other stuff? It just seems like a really low concentration.

DR. MARKS: That definitely is a low concentration but let me go back and look at my original -- in the original report, I had that for the root extract, we had human studies showing that 10 percent was okay. I could go back and look at that. And in animal, as far as dermal sensitization, we had a hundred percent which was a non-sensitizer. So even though we got that HRIPT at 0.001 percent, to me, that added nothing. I was relying on the original data.

MR. GREMILLION: Yeah. I noticed -- it's on page 27 that it's described. I noticed, yeah, just below the new study summary that mentions that HRIPT that you refer to -- the Panel had called for more data. And so I just wondered if that was responsive to data on irritation.

DR. MARKS: Actually, when you look at the needs under the memo for the root extract and the root powder, all that we requested was a NOAEL for the skin pigmentation and the anti-inflammatory effects. And it's kind of interesting because I actually thought suppression of delayed type hypersensitivity, when you're talking about a topical, would be a good thing, not a bad thing. So I wasn't as much concerned about suppression of delayed hypersensitivity as I was about the skin pigmentation.

I heard you right, Ron. Lisa, you would still go with an insufficient data announcement because we didn't get a NOAEL for the skin pigmentation. Is that correct?

DR. SHANK: Yes.

DR. PETERSON: Yep.

DR. MARKS: Okay.

DR. EISENMANN: This is Carol. Can I say something quick about botanicals and skin? Identifying a NOAEL for a botanical for skin pigmentation is really kind of problematic because you could have one and then add another. This is similar

to how you do for botanicals when formulated to be nonsensitizing because another botanical -- you might have the same type of composition.

So if you identify a NOAEL for that plant, this still may be pretty meaningless because you can add another plant that has a similar component that would bring it up. So if you set a limit -- so I think that's why the statement on pomegranate is so helpful because the idea is the product should not cause depigmentation.

DR. MARKS: So Carol, if I hear what you're saying, you would say safe root extract and powder when formulated to be -- not cause skin depigmentation.

DR. EISENMANN: Well, you're more or less doing that for the pomegranate one, but you're not putting it in the conclusion. But, yes.

DR. MARKS: Yeah. I have no problems. Ron Shank and Lisa, I don't feel --

DR. SHANK: That's okay.

DR. MARKS: I don't have any problems putting that qualifier in because I had questions, as you could tell, right from the get-go how we would handle the depigmentation issue. So we could put it as a -- as Carol, I like your interpretation -- just the same way we do with the sensitizers when formulated to be. Okay. And then we have a robust discussion in the report about -- similar to pomegranate -- adjusted to, in this case, the *Scutellaria*. So Lisa, does that sound okay to you --

DR. PETERSON: Yeah. That sounds fine.

DR. MARKS: -- when formulated to not cause depigmentation. That can be ordered a little bit, but that's the point. What about the delayed hypersensitivity? As you can tell my bias is, man, this is good. I like that idea, but that was not as big an alert by any means for me. And that was, again, a need.

I would have not asked that as an insufficient, but what's your take on that, Lisa? Because I think it's very important. There, the only two needs for the root extract and the powder in my mind is how to handle the depigmentation and how to handle the delayed contact sensitivity.

DR. PETERSON: Yeah. I would defer to you on the delayed contact sensitivity. It's not my area of expertise.

DR. MARKS: Tom, Ron Shank?

DR. SHANK: We have several ingredients here, and, in the current discussion, it says we have data needs. We can't handle all of those data needs by just saying -- using the pomegranate verbiage for skin pigmentation.

DR. MARKS: No.

DR. SHANK: There's genotox data needed, phototox needed, dermal, 28-day dermal, methods of manufacture, composition, a whole bunch of stuff.

DR. MARKS: Oh, yeah. That's for the --

DR. SHANK: Those remain. Those data needs remain.

DR. MARKS: Oh, absolutely. Oh, absolutely. I would put that as the two in which we cannot -- that would be insufficient. That remains the same.

DR. SHANK: Okay.

DR. PETERSON: And there is (inaudible).

DR. MARKS: For me, it would only be the root extract and the root powder that we could say safe. The extract itself and the sprout extract would be insufficient.

DR. PETERSON: Well, actually, the geno --

DR. SHANK: The root extract still needs genotox, especially mammalian, and phototox.

DR. MARKS: I thought we got phototox, and I thought we got more data on the root extract that it was genotox and a phototox and were all okay. But Tom, weigh in on that when you look at the needs as --

DR. SLAGA: I agree with you.

DR. SHANK: Those were two in vitro studies, were they not? I think so. The genotox was an Ames?

DR. PETERSON: Yep.

DR. SHANK: And the phototox was a cell culture, which is not enough.

DR. MARKS: Okay. So what you're pointing out, Ron, is that with all the ingredients, the genotox and the phototox -- and you feel we don't have enough of that to move forward.

DR. SHANK: Right.

DR. MARKS: So basically, it still remains insufficient as you, I think, Lisa, started right off -- insufficient for everything. We got some data, but we still have lots of needs for all of the ingredients. And we could handle the skin pigmentation as perhaps - - as we move onto a final report to formulate when to not cause depigmentation, but obviously that doesn't address the genotox and phototox.

DR. SHANK: Correct.

DR. MARKS: Tom, you're fine with we don't have enough genotox data for the root extract or the root powder?

DR. SLAGA: Yeah. No, the root and the root powder are (Inaudible).

DR. MARKS: I couldn't hear you, Tom.

DR. SLAGA: Huh?

DR. MARKS: Okay. So we're going to move forward insufficient data. So our team will move tomorrow that we issue a tentative report with an insufficient conclusion and that basically everything that's been listed here is a need still remain for the root. For all of them, we need genotox and phototox. Perhaps a skin pigmentation, we would handle with a formulate to avoid skin pigmentation.

I didn't think the inflammatory issues were really significant, but we'll see what the Belsito team says again tomorrow. And then listed for the extract: irritation and sensitization, 28-day dermal; and for the sprout extract, those bullets -- those five bullets: M.O.M., composition, and impurities. Ron Shank, do I -- and Lisa -- do I have that? That we will issue an insufficient for all four ingredients?

DR. SHANK: You got it.

DR. PETERSON: Yep.

MR. JOHNSON: About tomorrow, may I interrupt please?

DR. MARKS: Oh -- you aren't interrupting, Wilbur.

MR. JOHNSON: Okay.

DR. MARKS: You're open.

MR. JOHNSON: So all the data needs remain, with the exception of the request for the N-O-A-E-L for skin pigmentation?

DR. SHANK: Correct.

DR. MARKS: That would be my take, but we'll see what the Belsito take will be tomorrow. Carol, I don't know if you're still on, but I think your point is very well taken as, if you combine several different botanicals and they all have a skin lightening effect, we don't know exactly what the composition ingredient is that's causing that -- that we would want to avoid depigmentation in that case. So I think we can get around the NOAEL based having a conclusion that takes that into consideration. But we'll see what the Belsito team says tomorrow. Again, it's going out as a tentative report, so both industry and we will have another crack at it.

MR. JOHNSON: Dr. Marks, what is your conclusion?

DR. MARKS: Pardon?

MR. JOHNSON: What is your conclusion?

DR. MARKS: Insufficient for all four ingredients.

MR. JOHNSON: Okay. Thank you.

DR. EISENMANN: I have one other comment. You know there is a little bit of human photo data, as a case report, that's negative.

DR. MARKS: Yeah.

DR. EISENMANN: So if combined with the in vitro study and the concentration of use, I'm not sure why you'd still need the photo.

DR. MARKS: And you're talking about all the ingredients or specific ones that --

DR. EISENMANN: Um.

DR. MARKS: -- because I agree with you in terms of the concentration.

DR. EISENMANN: Whatever the -- well, unfortunately, the human, it just says the extract rather than a root extract. But whatever the photo -- the in vitro was a root extract. I mean it's an OECD guideline study. That's what's being accepted most

everywhere else as being acceptable to screen for phototox. It was negative, and then you have a hint -- I wish I knew more about what this -- if this was really a whole plant extract or if it was root extract. Unfortunately, sometimes the naming is not as clear as it should be.

DR. MARKS: Yeah. I guess one of the things that stood out --

DR. EISENMANN: We could discuss it with the other team tomorrow, but I think it's disappointing to hear that you're not going to accept an OECD-accepted in vitro study for phototoxicity.

DR. MARKS: See, I had on my notes phototox okay, but let's see what happens tomorrow. And then the other comment I had was you brought up the concentration. Am I right that the sprout use concentration is 0.0005 percent?

DR. EISENMANN: That's what somebody reported. I mean, I only report what they tell me.

DR. MARKS: Yeah. It's hard to believe that that low a concentration, unless maybe it's aflatoxin.

DR. EISENMANN: Well, you know, with plants, sometimes they sell them as very complex mixtures of multiple plants all into one, and then they put a -- so they have a small amount in the ingredient itself, and then they put a small amount of the mixture. So that ends up to be a small amount of the one plant.

DR. MARKS: Yeah. Any rate, I just want to point out that the sprout concentration is really low, at least what is reported. Okay. So insufficient conclusion tomorrow, and basically all the needs which were outlined in the memo are still there. We can have the discussion about skin pigmentation and the anti-inflammatory with the root extract and the root powder. I know we're going to do that again in the future. And the phototox, Carol, if that's not brought up tomorrow, you can bring that up. I thought the phototox -- I was ready to move on to that.

Any issues, Lisa, Ron, Tom to enhance the discussion? The concern about the ribs, I think Paul addressed that. I thought the discussion was fine, genotox, pigment, photo, all that in the discussion. That look good?

DR. SHANK: Yes.

DR. MARKS: Yeah. Okay.

MR. JOHNSON: Dr. Marks, I know you had mentioned that the issue of skin depigmentation should be addressed in the discussion. Other than that, which other concerns should be specifically mentioned?

DR. MARKS: I think what you have in there already, Wilbur. Again, we'll see how the things go between the two teams tomorrow. And you can enhance the discussion tomorrow based on our discussion tomorrow.

MR. JOHNSON: Okay. Thank you.

DR. MARKS: And then I think the skin pigmentation, that's going to be an interesting discussion tomorrow whether we handle it in the same way as we did with pomegranate. Okay. So I'm going to move tomorrow a tentative report with an insufficient conclusion. Okay. Any other comments before we move on to the next ingredient? Is everybody good, or do you want to take a five-minute break?

DR. PETERSON: I would like a five-minute break, please.

DR. MARKS: Okay. I think what I'm going to do then is let's everybody leave however they pulled up. Hopefully, if we don't -- I may hit my little mouse once in a while to make sure everything doesn't disappear. But hopefully, if we're not talking, Microsoft Team won't go down on us. It's 10:53. Let's plan on getting back together again at 11:00. Does that sound good? Does that give everybody enough time?

MS. KOWCZ: Yeah. It sounds great. Thank you.

DR. PETERSON: Thanks.

DR. MARKS: Okay. You're welcome. Tom's already gone.

Full Panel – June 9, 2020

DR. MARKS: Wilma, I'll probable use the non-scientific term, the lay term, Chinese Skull Cap, which is a mint.

DR. BERGFELD: Okay.

DR. MARKS: And, Wilbur, on February 21st sent us a memo with a draft tentative report on these ingredients. At the September 2019 Panel meeting an insufficient data announcement was issued. And, in that memo were all the data needs among these four ingredients and what they were. I'm not sure I need to re-read all these. I may just pick out a couple things.

So, for all the four ingredients we wanted genotox and phototox. We got more genotox and phototox data on the Root Extract, which supported as safety of the Root Extract. Then under the Root Extract and Root Powder, we wanted a NOAEL for the

skin pigmentation. And, also, it appeared to have anti-inflammatory effects, a reduction and delayed hyposensitivity reactions. So, we wanted more data about that.

And then, for the Extract we wanted irritation and sensitization, 28-day dermal tox. And the Sprout Extract, method of manufacture, composition, impurities, dermal absorption, and skin irritation and sensitization.

We got, as I said, some data that appeared to add to the Root Extract. And, so, our team thought that we could move forward with a tentative report that all four ingredients are still insufficient with the needs outlined below, although we have the information as far as the genotox and phototox on Root Extract. Or, we could have two of the ingredients safe, the Root Extract and the Powder when formulated to not cause skin lightening.

And, the issues we discussed was whether or not we really needed the NOAEL for skin pigmentation, or whether we could use the -- similar to what we do with sensitivity with a combination of botanical, we didn't want to see skin lightening occur. And, as far as the depressed DTH, delayed type hyposensitivity, I didn't -- actually I thought that was an asset rather than a concern. So, I'm not sure which one; we could continue with the insufficiencies, and do all four ingredients insufficient, or we could have a split conclusion. And, Don, I'd be very interested in how your team handled these four ingredients.

DR. BELSITO: Yeah, so, we felt that the Root Extract, and by extension, the Root Powder were safe as used, and the others were insufficient. We did not put the skin pigment effects in the conclusion, that was part of the discussion as we've done for - - blanking on the moment -- the other one, because that would be an over-the-counter drug effect and not a cosmetic effect.

DR. MARKS: Yeah, I think that was --

DR. BELSITO: And, so, we would put that in the discussion, but not in the conclusion.

DR. MARKS: That's fine. That was in, I believe, Pomegranate.

DR. BELSITO: Yeah.

DR. MARKS: A very nice discussion there. Okay, so, I will modify my motion that two of the ingredients are safe, the Root Extract and Powder, handle the skin lightening in the discussion, and the other two are insufficient for the data needs listed in the memo.

DR. BELSITO: Exactly.

DR. BERGFELD: Are you seconding that, Don?

DR. BELSITO: Yes.

DR. BERGFELD: Any further discussion regarding this ingredient, this botanical? Seeing none, I'm going to call the question then. All those in favor of this conclusion, please indicate by raising your hands. Thank you. Opposed? Hearing none, this is unanimous and approved.

Safety Assessment of *Scutellaria baicalensis*-Derived Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 21, 2020
Panel Date: September 14-15, 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 report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, CIR.

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ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 4 *Scutellaria baicalensis*-derived ingredients in cosmetic products; these ingredients are reported to have the following functions in cosmetics: antimicrobial agent, skin conditioning agent, abrasives, fragrance ingredients, skin protectants, and antioxidants. The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations, and concluded that *Scutellaria Baicalensis* Root Extract and *Scutellaria Baicalensis* Root Powder are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the available data are insufficient to make a determination that *Scutellaria Baicalensis* Extract and *Scutellaria Baicalensis* Sprout Extract are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of the following 4 *Scutellaria baicalensis*-derived ingredients, as used in cosmetics, is reviewed in this safety assessment.

Scutellaria Baicalensis Extract
Scutellaria Baicalensis Root Extract

Scutellaria Baicalensis Root Powder
Scutellaria Baicalensis Sprout Extract

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients, collectively, have the following reported functions in cosmetics: antimicrobial agent, skin conditioning agent, abrasives, fragrance ingredients, skin protectants, and antioxidants (See Table 1).¹ However, these ingredients do not have any functions in common.

Botanicals, such as *Scutellaria baicalensis*-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, the Panel is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex mixture. The Panel is not reviewing the potential toxicity of the individual constituents.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that the Panel evaluates, is available on the Cosmetic Ingredient Review (CIR) website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

In many of the published studies, it is not known how the substance being tested compares to the cosmetic ingredient. Therefore, if it is not known whether the substance being discussed is a cosmetic ingredient, the test substance will be identified by genus and species (e.g., “a *Scutellaria baicalensis* extract”). If it is known that the substance is a cosmetic ingredient, INCI nomenclature (e.g., “*Scutellaria Baicalensis* Extract”) will be used; italics are not used in INCI names.

CHEMISTRY

Definition

The definitions and functions in cosmetics of the 4 *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment are presented in Table 1.¹ All of these ingredients are derived from either the root or the sprout plant parts. The root is defined as an organ of the plant that absorbs and transports water and nutrients, lacks leaves and nodules, and is usually underground.¹ The sprout is defined as a seedling, germinating seed, and any new growth of a plant from a stem such as a new branch or a bud.

Plant Identification

Scutellaria baicalensis Georgi is an herb of the Lamiaceae family (i.e., mint family) and Scutellarioideae subfamily.^{2,3} Baikal skullcap and Chinese skullcap are common names for this herb, which is native to the Asia-Temperate geographical region that includes Siberia, Mongolia, Russian (far east), China, and Korea. *Scutellaria radix* is defined as the root of *Scutellaria baicalensis* Georgi.⁴

Chemicals Properties

Scutellaria Baicalensis Root Extract

In an ultraviolet (UV) spectral analysis of a *Scutellaria baicalensis* root extract (aqueous ethanol extract), an absorption peak between 200 and 250 nm (within the short-wavelength UV (UVC)) and an absorption peak between 250 and 300 nm (crossing both mid-wavelength UV (UVB) and UVC)) were observed.⁴

Method of Manufacture

Scutellaria Baicalensis Root Extract

Data on the methods of manufacture of *Scutellaria Baicalensis* Root Extract (using different extractants) were provided via the Personal Care Products Council (Council).^{5,6} According to one method, the dried raw material (*Scutellaria*

baicalensis root) is extracted with 90 vol% ethanolic solution.⁵ Extraction is followed by filtration, concentration of the filtrate (and then concentration adjustment with 50 vol% ethanolic solution). The next steps include sedimentation, filtration, and then packaging. Another method uses a lower concentration of the extractant.⁵ The first step in this production process is extraction of the dried raw material with 30 vol% ethanolic solution.⁵ Extraction is followed by filtration and concentration of the filtrate. Squalene is then added, and this step is followed by sedimentation, filtration, and then packaging. A third production method involves extraction of the dried raw material with 50 vol% 1,3-butylene glycolic solution.⁵ Extraction is followed by filtration and then sedimentation. This step is followed by additional filtration and then packaging. The production of *Scutellaria Baicalensis* Root Extract via aqueous extraction of *Scutellaria baicalensis* has also been described. The botanical raw material (*Scutellaria baicalensis* root) is cut and cleaned. This is followed by water extraction, a concentration phase, and then spray drying.⁶

A method of preparation of a *Scutellaria baicalensis* root extract (aqueous extract) from a published study is summarized as follows.⁷ Briefly, the dried roots of *Scutellaria baicalensis* are ground into powder (60-mesh) and 250 g are extracted twice with 10 volumes of boiling purified water for 1 h. The supernatants are then combined, filtered, and lyophilized. The extract (powder) is then stored at 4 °C until use.

In a method of preparation from another study, *Scutellaria baicalensis* roots were chopped into pieces, immersed in distilled water for 1 h, and then extracted under thermal reflux for 1 h, twice.⁸ The extract was filtrated using analytical filter paper and evaporated to dryness using a rotary evaporator at 60 °C under reduced pressure. The dried residue was dissolved in distilled water to yield a final concentration of 0.3 g/l.

Composition

Scutellaria Baicalensis Extract

Phytochemical analyses have detected and quantified the flavonoids baicalin, baicalein, scutellarin, wogonin, and the human neurohormones, melatonin and serotonin, in leaf and stem tissues from *Scutellaria baicalensis*.⁹ The extraction of dried slices of *Scutellaria baicalensis* with ethanol has yielded a number of chemical constituents, including various glucuronides and flavones (See Table 2).¹⁰

Scutellaria Baicalensis Root Extract

Scutellaria baicalensis root extract contains flavonoid glucuronides (baicalin, wogonoside, and oroxylin A 7-O- β -D-glucuronide) and their aglycones (baicalein, wogonin, and oroxylin A).⁷ The content of these major flavonoids in a *Scutellaria baicalensis* root extract (250 g, aqueous extract) has been determined to be: baicalin (406 mg/g extract), wogonoside (155 mg/g extract), 7-O- β -D-glucuronide (53.8 mg/g extract), baicalein (31.7 mg/g extract), wogonin (30.5 mg/g extract), and oroxylin A (7.24 mg/g extract). The total content of these 6 main flavonoids accounted for 68.5% of the extract.

A *Scutellaria Baicalensis* Root Extract trade name mixture (30% ethanol extract) is reported to contain flavonoid compounds.⁵ Another *Scutellaria Baicalensis* Root Extract trade name mixture (90% ethanol and butylene glycol extract) contains tannin and flavonoid compounds.

Scutellaria Baicalensis Root Powder

A *Scutellaria baicalensis* root (dried root) contains a variety of flavones, phenylethanoids, amino acids, sterols, and essential oils.⁷ The major flavonoid glycosides of this material include baicalin, wogonoside, oroxylin A 7-O- β -D-glucuronide, and their aglycones baicalein, wogonin and oroxylin A.^{7,11} Baicalin is the most abundant flavonoid constituent of this *Scutellaria baicalensis* root. Minor flavonoids that have been identified in this *Scutellaria baicalensis* root include: viscidulin III-2-O- β -D-glucoside; 5,7,2,5-tetrahydroxyflavone; (-)-eriodictyol; rivularin; chrysin 8-C- β -D-glucopyranoside; and 5,2'-dihydroxy-6,7,8,3'-tetramethoxyflavone.¹²

Impurities

Scutellaria Baicalensis Extract

The results of a high-performance thin-layer chromatographic analysis of a *Scutellaria baicalensis* extract have indicated the absence of *Teucrium chamaedrys* (Gemander), which has been reported as an adulterant of *Scutellaria lateriflora* (American skullcap) herbal preparations.¹³ *Teucrium chamaedrys* is a species of ornamental plant native to Mediterranean region of Europe and North Africa, and to the Middle East as far east as Iran.

Scutellaria Baicalensis Root Extract

A *Scutellaria Baicalensis* Root Extract trade name mixture (ethanol and butylene glycol extract) is reported to contain no more than 20 ppm heavy metals and no more than 2 ppm arsenic.⁵

USE

Cosmetic

The safety of *Scutellaria baicalensis*-derived ingredients is evaluated based on data received from the United States Food and Drug Administration (US FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics.

Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.¹⁴ Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Council, of maximum reported use concentrations by product category.^{15,16}

According to 2020 VCRP data, *Scutellaria Baicalensis* Root Extract is reported to be used in 514 cosmetic products (419 leave-on products, 95 rinse-off products).¹⁴ Of the *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency. The results of concentration of use surveys conducted by the Council in 2018 and 2019 indicate that *Scutellaria Baicalensis* Root Extract is used at maximum use concentrations up to 0.5% in leave-on products (moisturizing products).^{15,16} This is the highest use concentrations in leave-on products that is reported for the *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment. According to VCRP and Council survey data, *Scutellaria Baicalensis* Root Powder is not currently in use in cosmetic products. Further use data are presented in Table 3.

Cosmetic products containing *Scutellaria baicalensis*-derived ingredients may be applied to the skin or, incidentally, may come in contact with the eyes (e.g., *Scutellaria Baicalensis* Root Extract at concentrations up to 0.07% in eye shadows). *Scutellaria Baicalensis* Root Extract and *Scutellaria Baicalensis* Sprout Extract are used in products that come in contact with mucous membranes during product use (maximum ingredient use concentrations of 0.0045% (lipstick) and 0.0002% (bath soaps and detergents), respectively). Additionally, *Scutellaria Baicalensis* Root Extract could be incidentally ingested (maximum use concentrations up to 0.0045% (lipstick)). Products containing *Scutellaria baicalensis*-derived ingredients may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

The *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.¹⁷

Non-Cosmetic

Scutellaria Baicalensis Root Extract and *Scutellaria Baicalensis* Root Powder

Scutellaria Radix, known as Huangqin in Chinese, is the dried root of *Scutellaria baicalensis* Georgi. It is a well-known traditional herbal medicine that is used to treat inflammation, cardiovascular diseases, and respiratory and gastrointestinal infections.⁷ *Scutellaria baicalensis* Georgi is one of the 50 fundamental herbs of traditional Chinese medicine, and pharmacological effects of *Scutellaria baicalensis* have been described.^{7,12,18}

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Scutellaria Baicalensis Extract

The toxicokinetics of *Scutellaria baicalensis* extract (ethanol extract) was studied using groups of Sprague-Dawley rats.¹⁹ *Scutellaria baicalensis* herb (plant part not stated) was extracted in this study. In an oral absorption experiment, a *Scutellaria baicalensis* extract (single dose of 2.5 ml/kg) was administered (method not stated) to 6 Sprague-Dawley rats, after which blood samples were collected. The blood concentration of baicalin (a flavone component of the extract) quickly reached its peak, suggesting that it was absorbed rapidly and eliminated slowly. In the distribution experiment, the extract (2.5 ml/kg) was administered orally to 30 Sprague-Dawley rats. The animals were killed and tissue samples from the following organs were collected at various intervals (15, 30, 60, 120, 360, and 600 min): heart, liver, lung, kidney, stomach, spleen, brain, and intestines. Baicalin was detected in all of the tissues that were collected. The amount of baicalin that was found in the brain indicated that this flavone could pass the blood-brain barrier. Baicalein (another flavone component) was also detected in the liver, heart, lung, kidney, stomach, and intestine. Another experiment that was performed involved 6 rats that were dosed orally (method not stated) with the extract (2.5 ml/kg). Urine and feces were collected at different time points (0 - 4 h, 4 - 8 h, 8 - 12 h, 12 - 24 h post-dosing). Baicalin and baicalein were detected in the urine and feces after dosing. The urinary cumulative excretion of baicalin was 0.12% and the fecal cumulative excretion of baicalin was 0.48% of the dose up to 24 h post-administration. The urinary cumulative excretion of baicalein was 0.05% and the fecal cumulative excretion of baicalein was 0.04% of the dose up to 24 h post-administration.

Scutellaria Baicalensis Root Extract

Metabolism and excretion of an orally (gavage)-administered *Scutellaria baicalensis* root extract (aqueous extract) were evaluated using groups of male Sprague-Dawley rats.⁸ The first experiment involved 2 groups of 6 fasted rats (test and control groups). The aqueous extract (dissolved in distilled water prior to dosing) was administered by gavage at a dose of 4.5 g/kg bw. Control animals received distilled water (5 ml). Urine and feces samples were collected at 12 h post-dosing. In the second experiment, another group of 6 fasted rats was dosed by gavage with the test substance, and bile samples were collected from the cannulated bile duct within 12 h. Four parent components (from *Scutellaria baicalensis* root) and a total

of 15 metabolites (sulfate and glucuronide conjugates, and hydroxylated, methylated, acetylated, and deoxygenated products) were detected, with most present in the urine. The metabolites identified are presented in Table 4.

A *Scutellaria baicalensis* root extract (suspended in an aqueous 0.5% carboxymethyl cellulose sodium salt solution, to a concentration of 100 mg/ml) was administered orally (method not stated) to fasted male Sprague-Dawley rats (number not stated) at a dose of 800 mg/kg (equivalent to baicalin (324.80 mg/kg), wogonoside (124.00 mg/kg), oroxylin A 7-*O*- β -D-glucuronide (43.04 mg/kg), baicalein (25.36 mg/kg), wogonin (24.40 mg/kg), and oroxylin A (5.79 mg/kg)).⁷ Blood samples (250 μ l) were obtained from the jugular veins and collected at the following times after dosing: 0.083, 0.167, 0.25, 0.33, 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 36, and 48 h. The peak plasma concentration (C_{max}) and the time reaching C_{max} (T_{max}) were obtained directly from the experimental data. The three tested flavonoid glucuronides (baicalin, wogonoside, and oroxylin A 7-*O*- β -D-glucuronide) and their aglycones (baicalein, wogonin and oroxylin A) exhibited rapid absorption ($T_{max} < 12$ min) and exhibited a multiple-peak phenomenon. Focusing on the dose in the extract, because the dose of baicalein is much higher than that of oroxylin A, one would expect that the systemic exposure of baicalein would have been greater, but it was comparable to that of oroxylin A. Therefore, the potential for systemic exposure per unit time would be greater for oroxylin A (when compared to baicalein). Because the doses of baicalein and wogonin in the extract are comparable, the expectation is that the systemic exposure would have been comparable, but the systemic exposure of baicalein was much less than that of wogonin. Therefore, the potential for systemic exposure per unit time would be greater for wogonin (when compared to baicalein). These data indicate that the systemic absorption, over time, of baicalein would be less when compared to the other 2 constituents.

Human

Oral

Scutellaria Baicalensis Root Powder

A study was performed to investigate the urinary pharmacokinetics of flavone constituents of a *Scutellaria baicalensis* root powder (contains baicalin, baicalein, wogonoside and wogonin flavones).²⁰ Quantitation (using high performance liquid chromatography) of the commercial powder indicated that baicalin and wogonoside were the major flavone constituents, and that their aglycones, baicalein and wogonin, were less abundant. The powder (5.2 g) and 200 ml water were administered orally to 10 subjects after an overnight fast. Urine samples were collected before and after dosing. The glucuronides and sulfates of baicalein and wogonin in urine were hydrolyzed with β -glucuronidase and sulfatase, respectively. Study results indicated that the mean cumulated renal excretion of baicalein glucuronides and sulfates were 43.1 ± 4.5 μ mol (2.9% of dose) and 64.8 ± 6.3 μ mol (4.3% of dose), respectively. Wogonin glucuronides and sulfates were 21.6 ± 2.0 μ mol (5.9% of dose) and 20.7 ± 1.7 μ mol (5.7% of dose), respectively. The renal excretion of conjugated metabolites of wogonin (11.6% of dose; number of μ mol not stated) were higher than that of baicalein (7.2% of dose; number of μ mol not stated). The baicalein sulfates predominated when compared to the corresponding glucuronides; whereas, the presence of wogonin sulfates was comparable to the corresponding glucuronides.

TOXICOLOGICAL STUDIES

General toxicity studies of *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Scutellaria Baicalensis Root Extract

The teratogenicity of a *Scutellaria baicalensis* root extract (aqueous extract) was evaluated using groups of 30 pregnant, Sprague-Dawley female rats.²¹ The test substance was administered by gavage to 3 groups, at doses of 0.25, 12.49, and 24.98 g/kg/day, on gestation days 7 to 17 (11 d). Control rats were administered distilled water. Two-thirds of pregnant females in each group were killed on day 20 of gestation, and their fetuses were examined. The remaining dams were allowed to litter naturally, and postnatal development of the offspring was evaluated. A statistically significant ($p < 0.05$), dose-dependent increase in the incidence of skeletal variations (presence of lumbar ribs) was observed. A dose-dependent increase in the frequency of dilatation of the ureter was also reported. However, the incidence of this abnormality was comparable between the 12.49 and 24.98 g/kg/day dose groups. Dilatation was observed along the entire length of the ureter, not in localized segments. Various minor abnormalities were also observed in the 24.98 g/kg/day dose group, and hydrocephaly was observed in one of the control litters. There were no statistically significant differences in the following between control and treated groups: maternal body weight, intake of diet and water, efficiency of diet, hematologic values, resorbed and dead fetuses, corpora lutea, separation of eyelids, emergence of abdominal hair and incisors, traction test values, sex organ function in fetuses, and the growth of fetuses.

A *Scutellaria baicalensis* root extract (aqueous extract) was administered by gavage to 20 pregnant Sprague-Dawley rats.²² The extract, in saline (15 g in 750 ml), was administered slowly (186 mg/kg bw) daily, from day 7 to day 17 of gestation. The authors noted that the administered dose was equivalent to 25 g/kg of *Scutellaria baicalensis* root (starting material), representing a 100-fold increase over the typical human intake level. The control group (20 pregnant rats) was

administered equal volumes of saline. Ten maternal animals in each group were killed on gestation day 20, and the fetuses were delivered by cesarean section. The following were then determined: number of dead fetuses, live fetuses, resorption sites, and corpora lutea; fetal sex; and fetal body weights. Skeletal examinations of fetuses were also performed after the animals were killed on day 20. Skeletons of offspring obtained by natural delivery were evaluated at postnatal day 50 by necropsy. The remaining animals were allowed to naturally deliver their offspring, and all of the weanlings were maintained to postnatal day 50 for the reversibility study. In fetuses obtained by cesarean section on gestational day 20, the incidence of fetal lumbar rib was increased in the treated group ($11.54 \pm 0.15\%$) when compared to the vehicle control group. However, in the groups obtained by natural delivery, the fetal lumbar rib incidence of the treated group ($0.81 \pm 0.01\%$) was decreased on postnatal day 50 when compared to the fetuses that were delivered by cesarean section on day 20. This means that the lumbar rib had been recovered by postnatal day 50. The weights of fetuses in the treated group tended to be less when compared to those in the control group. Alkaline phosphatase in treated dams was increased on gestation day 20, but was decreased on postnatal day 50. There were no significant differences between the control and treated group with respect to the following: maternal body weight, or embryological, histopathological, hematological, or serum biochemical changes. The authors stated that the results of this study suggest that the appearance of lumbar rib induced by the test material is a transient fetal variation rather than teratogenicity or maternal toxicity.

The effect of a *Scutellaria baicalensis* root extract (aqueous extract) on embryonic development was studied using groups of 18 pregnant ICR mice that received oral (gavage) doses of 2, 8, or 32 g/kg/day.²³ The doses (dose volume = 0.5 ml/30 g bw) were administered from gestation day 6 to 15. The control group (18 pregnant mice) was administered water. The animals were killed on gestation day 18, and the following parameters were evaluated: live and dead fetuses, resorptions, external and skeletal malformed fetuses, maternal body weights, and maternal liver, kidney, and heart weights. When compared to the negative control group, no statistically significant differences in fetal parameters were observed. Maternal absolute liver and kidney weights in the 32 g/kg/day group were significantly higher ($p < 0.05$) when compared to the control group. Additionally, increases in relative liver and kidney weight values in this group were statistically significant ($p < 0.05$). The authors concluded that the oral administration of this extract at or below a dose of 32 g/kg/day during organogenesis did not cause statistically significant fetal external or skeletal malformations. However, dosing with 32 g/kg/day presented potential maternal toxicity.

GENOTOXICITY STUDIES

In Vitro

Scutellaria Baicalensis Root Extract

The genotoxicity of a trade name mixture containing 33.33% *Scutellaria Baicalensis* Root Extract (aqueous extract) was evaluated in the Ames test using the following *Salmonella typhimurium* strains with and without metabolic activation: TA97a, TA98, TA100, TA102, and TA1535.⁶ The tradename mixture was evaluated at doses up to 5 µl/dish, and testing was performed in accordance with Organization for Economic Co-Operation and Development (OECD) Test Guideline (TG) 471. The test procedure included a negative/solvent control (not stated). The trade name mixture did not cause significant cytotoxicity and was non-genotoxic over the range of doses tested in all bacterial strains.

The Ames test was also used to evaluate the genotoxicity of *Scutellaria baicalensis* root extracts (methanol extract and aqueous extract), using *S. typhimurium* strains TA98 and TA100, with and without metabolic activation.²⁴ The bacterial suspension + extract (0.1 ml) was incubated for 2 d, and the revertant colonies formed were scored. AF-2 and benzo[a]pyrene served as positive controls. Results for the aqueous extract were positive in strain TA100 with, but not without, metabolic activation. All strain TA98 results for the aqueous extract were negative. Results were also negative for the methanol extract, with or without metabolic activation, in both strains.

The genotoxicity of *Scutellaria baicalensis* root extracts (methanol extract and aqueous extract) was evaluated in the *Bacillus subtilis* rec-assay using strains H17 Rec⁺ and M45 Rec⁻ without metabolic activation.²⁴ A filter-paper disk containing the extract (100 mg/ml; 60 µl) and a bacterial strain was incubated overnight. The diameter of inhibition zones formed around the disk was measured, and Rec⁺ and Rec⁻ spore plates were compared. Mitomycin C and furylfuramide (AF-2) served as positive controls. Results were positive for the methanol extract and negative for the aqueous extract.

In Vivo

Data on the in vivo genotoxicity of *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

OTHER RELEVANT STUDIES

Effect on Melanogenesis

Scutellaria Baicalensis Root Extract

The effect of a *Scutellaria baicalensis* root extract (powder, ethanol extract) on melanogenesis was studied using B16F10 mouse melanoma cells.²⁵ B16F10 cells were cultured for 24 h with a *Scutellaria baicalensis* root extract at concentrations of 7, 35, and 70 µg/ml. Linoleic acid (100 µM) served as the positive control. Incubation with a *Scutellaria baicalensis* root extract for 24 h resulted in a statistically significant ($p < 0.01$) decrease in melanin levels in a dose-dependent manner as the dose was increased from 35 µg/ml to 70 µg/ml. At a concentration of 70 µg/ml, the extract inhibited melanin formation more effectively than did the positive control (100 µM linoleic acid). It should be noted that results also indicated that 2 flavone components of *Scutellaria baicalensis* root (wogonin and wogonoside) consistently inhibited melanogenesis in both B16F10 melanoma cells and melanocytes. In order to determine the most efficient extraction of *Scutellaria baicalensis* root, the inhibition of melanogenesis by each extract generated from the following 4 organic solvents was evaluated: n-hexane, ethyl acetate, methanol, and water. The solvents n-hexane, ethyl acetate, methanol and water resulted in 83.2, 109.2, 177.6, and 84.4 mg of the crude extract (a *Scutellaria baicalensis* root extract) from the ratio of powder/solvent (20.3 g/100 ml, 10.1 g/50 ml, 1.0 g/5 ml, and 1.0 g/30 ml), respectively. Melanin content was assessed after treatment of B16F10 cells with each extract for 24 h. The methanol extract caused a statistically significant ($p < 0.05$) decrease in melanin content, whereas no decrease was observed after treatment with the other three extracts. The extract eluted by ethyl acetate tended to increase melanin content and produced toxicity. These results suggest that *Scutellaria baicalensis* root extract (methanol extract) is capable of inhibiting melanogenesis (strong inhibitory effect, without cytotoxicity), and its active components can be efficiently extracted. The authors stated that the difference in results depending on the extractant used is that certain flavonoids in a *Scutellaria baicalensis* root extract (present in one extract versus the other) were responsible for the inhibition of melanogenesis.

Antiallergic Effects

Scutellaria Baicalensis Extract

Antiallergic effects of a *Scutellaria baicalensis* extract (ethanol extract, plant part not stated) were evaluated using the following groups of 6 Sprague–Dawley rats: rats sensitized with anti-dinitrophenyl (anti-DNP) immunoglobulin E (IgE); rats sensitized with anti-DNP IgE and treated with a *Scutellaria baicalensis* extract; normal control group; and negative control group.²⁶ The rats received intradermal injections of anti-DNP IgE at each of three dorsal skin sites. At 48 h post-injection, each rat received an intravenous injection of DNP-HSA in saline containing 4% Evans blue. A *Scutellaria baicalensis* extract (28 mg/100 g body weight) was administered orally prior to this injection. The rats were then killed, dorsal skin was removed, and the pigment area was measured. Additionally, rat peritoneal mast cells (RPMCs) were cultured and purified to investigate histamine release. RPMC's were incubated for 10 min with a *Scutellaria baicalensis* extract at concentrations of 1, 10, and 100 µg/ml. Histamine release was evoked by adding compound 48/80. Also, in vitro, human mast cells (HMC-1) were pretreated with a *Scutellaria baicalensis* extract (1, 10, and 100 µg/ml) for 1 h before stimulation with phorbol 12-myristate-13-acetate (PMA) plus A23187 (a calcium ionophore). The effects on pro-inflammatory cytokine expression and mitogen activated protein (MAP) kinase expression were investigated using tumor necrosis factor-alpha (TNF- α) and interleukin-8 (IL-8) assays, and Western blotting analysis of HMC-1 cells. Treatment with a *Scutellaria baicalensis* extract inhibited the passive cutaneous anaphylaxis reaction, when compared to the control group. Following treatment of RPMCs with a *Scutellaria baicalensis* extract (all 3 concentrations), histamine release decreased significantly. In HMC-1 cells, a *Scutellaria baicalensis* extract restored IL-8 and TNF- α expression and inhibited MAP kinase expression in compound 48/80-induced HMC-1 cells. The authors noted that these data suggest that a *Scutellaria baicalensis* extract may prove to be a useful anti-inflammatory agent through its downregulation of the expression of various inflammatory mediators.

Scutellaria Baicalensis Root Extract

The antiallergic effect of a topically applied *Scutellaria baicalensis* root extract (aqueous extract) in suppressing 2,4-dinitrochlorobenzene (DNCB)-induced allergic contact dermatitis was studied.²⁷ This *Scutellaria baicalensis* root extract (aqueous extract) was defined as a spray dried extract with the following components: baicalin (6.45%), wogonoside (3.37%), baicalein (2.07%), and wogonin (0.48%). *Scutellaria baicalensis* root extract (aqueous extract) was evaluated using the following 6 groups (5 mice per group) of female BALB/c mice: negative control group (cream base alone); positive group (dinitrochlorobenzene (DNCB) + cream base); dexamethasone group (DNCB + 0.1% dexamethasone cream); 0.1% *Scutellaria baicalensis* root extract (aqueous extract) group (DNCB + 0.1% *Scutellaria baicalensis* root extract (aqueous extract) cream); and 0.5% *Scutellaria baicalensis* root extract (aqueous extract) (DNCB + 0.5% *Scutellaria baicalensis* root extract (aqueous extract) cream). Each gram of cream contained (w/w) 1 mg of dexamethasone and a *Scutellaria baicalensis* root extract (aqueous extract) (1 and 5 mg) in an emollient cream base consisting of the following components: propylene glycol, stearyl alcohol, acetyl alcohol, sorbitan monostearate, polysorbate 60, mineral oil and purified water. The mice received topical applications (on dorsal skin) of ~20 mg dexamethasone cream, a *Scutellaria baicalensis* root extract (aqueous extract) cream, or emollient cream base alone daily on days 1 to 14. Allergic sensitization was induced according to the following procedure: A 1-cm² gauze patch containing 0.1 ml of 1% DNCB in acetone/olive oil (3:1) was applied for 4 h (on days 1 and 4) to the back. After a 4-d non-treatment period, the mice were challenged (dorsal skin) with a patch

containing 0.2% DNCB on days 8 and 11. On day 14, the mice were killed and blood samples were collected. Dorsal skin samples from each mouse were subjected to histopathological and biochemical examination.

Topical application of a *Scutellaria baicalensis* root extract (aqueous extract) attenuated the epidermal thickness and mast cell infiltration into the skin in DNCB-induced contact dermatitis. Additionally, a *Scutellaria baicalensis* root extract (aqueous extract) suppressed DNCB-induced production of serum IgE as well as IL-4, IFN- γ , and TNF- α in the skin. Topical application of a *Scutellaria baicalensis* root extract (aqueous extract) also ameliorated the significant decrease in dermal glutathione and superoxide dismutase levels. The researchers stated that these results indicated that the topical application of *Scutellaria baicalensis* suppressed DNCB-induced contact dermatitis.

Cytotoxicity

Scutellaria Baicalensis Root Extract

A *Scutellaria baicalensis* root extract (aqueous extract) was tested in apoptosis experiments involving the following cell types from 26 children with acute lymphoblastic leukemia: the NALM-6 cell line (human peripheral blood leukemia pre-B cells), peripheral blood leukocytes, and bone marrow cells.²⁸ The 3 cell types were incubated for 48 h with a *Scutellaria baicalensis* root extract (aqueous extract) at concentrations up to 200 $\mu\text{g/ml}$ / 2×10^6 cells. Peripheral blood (from 16 healthy children) tested with the same concentrations served as the control. The percentage of living peripheral blood leukocytes and bone marrow cells after 24 h of incubation oscillated around 90% (test and control cells). However, on day 2, the number of living bone marrow cells from patients with acute lymphoblastic leukemia decreased to only 65%. A *Scutellaria baicalensis* root extract (aqueous extract) enhanced the apoptosis of peripheral blood leukocytes in bone marrow cells of leukemic children. The percentage of peripheral blood leukocytes that underwent apoptosis increased from 11% in the control to 17% and 24% for the doses of 100 $\mu\text{g/ml}$ and 200 $\mu\text{g/ml}$, respectively. At a dose of 200 $\mu\text{g/ml}$, apoptosis in bone marrow cells and peripheral blood leukocytes from patients with acute lymphoblastic leukemia was statistically significantly increased ($p < 0.05$), when compared to peripheral blood leukocytes from healthy controls. A *Scutellaria baicalensis* root extract (aqueous extract) did not induce apoptosis of control peripheral blood leukocytes. Pro-apoptotic activity of a *Scutellaria baicalensis* root extract (aqueous extract) in the NALM-6 cell line was also reported (details relating to results not included). The authors noted that the observation of a *Scutellaria baicalensis* root extract (aqueous extract)-induced apoptosis in peripheral blood leukocytes from leukemia patients, but not from healthy controls, may be related to the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). They stated that TRAIL induces apoptosis in various cancer cells in vitro and in vivo, with little or no toxicity in normal cells.

The cytotoxicity of a *Scutellaria baicalensis* root extract (aqueous ethanol extract) was evaluated using human keratinocytes (HaCaT) that were cultured with the extract for 24 h.⁴ The extract tested was nontoxic at concentrations up to 30 $\mu\text{g/ml}$. However, statistically significant ($p < 0.05$) cytotoxicity was observed at concentrations of 100 $\mu\text{g/ml}$ and 1000 $\mu\text{g/ml}$.

Estrogenic Activity

Scutellaria Baicalensis Root Extract

A *Scutellaria baicalensis* root extract (ethanol extract) was assayed for estrogenic activity in vitro using a recombinant yeast system with both a human estrogen receptor expression plasmid and a reporter plasmid.²⁹ The extract (in dimethyl sulfoxide) was added to the culture, reaching final concentrations between 0.1 and 1000 $\mu\text{g/ml}$, and incubated for 2 h. β -Galactosidase activity, which is dependent on binding of the ligand to the estrogen receptor, was then assayed. The activity of β -galactosidase resulted in a color reaction, which was measured absorbance at 420 nm. 17 β -Estradiol served as the positive control. EC₅₀ (concentration of test material at half-maximum β -galactosidase activity) values were determined. The estrogenic relative potency (RP) of the test material was computed by dividing the EC₅₀ of 17 β -estradiol by the EC₅₀ of the test material, and then multiplying this value by 100. The EC₅₀ for 17 β -estradiol was 0.205 \pm 0.025 ng/ml (RP = 100). The EC₅₀ for this *Scutellaria baicalensis* root extract was 262.3 $\mu\text{g/ml}$ (RP = 8.77 $\times 10^{-5}$). This *Scutellaria baicalensis* root extract was classified as negative for estrogenic activity.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

Scutellaria Baicalensis Root Extract

The skin irritation/corrosion potential of a *Scutellaria baicalensis* root extract (aqueous extract) was evaluated in accordance with OECD TG 404, using 6 New Zealand white rabbits.³⁰ The dried powder (spray dried extract) test article comprised in part: baicalin (6.45%), wogonoside (3.37%), baicalein (2.07%), and wogonin (0.48%). Distilled water (negative control) was also applied to the 6 rabbits. Reactions were scored using the Draize scale, and the primary irritation index (PII) was calculated using the mean score at 24, 48, and 72 h. There were no significant body weight changes, clinical signs, or mortality following topical application of the test substance. Slight erythema with edema (score of 1) was observed

in 1 of 6 rabbits at 1 h after patch removal. By 24 h post-application, the reactions had resolved. The extract was classified as a non-irritant (PII = 0). The distilled water control also produced negative results.

Human

Scutellaria Baicalensis Root Extract

Results from a human patch test on a 10% Scutellaria Baicalensis Root Extract trade name mixture (butylene glycol extract; dose not stated) involving 12 subjects were negative for skin irritation.⁵ Details relating to the test protocol and results were not included.

Sensitization

Animal

Scutellaria Baicalensis Root Extract

The skin sensitization potential of a *Scutellaria baicalensis* root extract (aqueous extract) was evaluated in accordance with OECD TG 404 (Buehler method) using the following groups of Hartley guinea pigs: 10 test animals, 20 negative control animals, and 10 positive control animals.³⁰ The dried powder (spray dried extract), applied to the skin using an occlusive patch, was defined as a *Scutellaria baicalensis* root extract (aqueous extract) with the following components: baicalin (6.45%), wogonoside (3.37%), baicalein (2.07%), and wogonin (0.48%). DNCB (1%) and distilled water served as positive and negative controls, respectively. Skin reactions were scored at 24 h and 48 h after patch removal according to the Magnusson and Kligman grading scale. Results were expressed as mean \pm standard error of the mean. There were no significant body weight changes, clinical signs, or mortality following topical application of the test substance. Treatment with the test substance was not associated with any changes on the skin surface, including erythema and edema at 24 and 48 h following patch removal. The test material was classified as a non-sensitizer (Buehler score = 0). Skin sensitization was observed in the positive control group. The average skin response scores in the DNCB-treated group were 0.6 and 0.4 at 24 and 48 h, respectively. Reactions were not observed in the distilled water, negative control group.

Human

Scutellaria Baicalensis Root Extract

The skin sensitization potential of an undiluted leave-on product containing 0.001% Scutellaria Baicalensis Root Extract was evaluated in a human repeated insult patch test (HRIPT) involving 220 subjects.³¹ The product (0.2 g, under semi-occlusive patch) was applied undiluted to the skin for 24 h. The location and area of the application site were not stated. Nine induction patch applications were made during a 3-wk induction period, followed by a 2-wk non-treatment period. A challenge patch was then applied to a new test site (location not stated), and reactions were scored at 24, 48, 72, and 96 h according to the International Contact Dermatitis Research Group (ICDRG) reading scale: 0 (no visible reaction) to 4 (severe reaction with erythema, induration, vesicles, and pustules (may be weeping)). A low-level reaction was associated with a score of 0 or 1, and a high-level reaction was associated with a score of 2 and above. Three subjects had a low-level reaction during induction. A low-level reaction was also observed in 1 subject during the challenge phase. Whether or not the subject with the low-level reaction during challenge was among the 3 with a low-level induction reaction was not stated. None of the subjects had a high-level reaction. The product did not induce an allergic response, and the authors commented that the product did not induce dermal sensitization in any of the subjects tested.

Results from an HRIPT on a 10% Scutellaria Baicalensis Root Extract trade name mixture (butylene glycol extract; dose per cm² not stated) involving 49 subjects were negative for skin sensitization.⁵ Details relating to the test protocol and results were not included. In another HRIPT involving 54 subjects patch tested with an undiluted Scutellaria Baicalensis Root Extract trade name mixture (30% ethanol extract; dose per cm² not stated), test results were also negative for skin sensitization. Details relating to the test protocol and results were not included.

Phototoxicity

In Vitro

Scutellaria Baicalensis Root Extract

The phototoxicity of a trade name mixture containing 33.33% Scutellaria Baicalensis Root Extract (aqueous extract) was evaluated in the 3T3 neutral red uptake in vitro phototoxicity assay (equivalent to OECD Guideline for Testing Chemicals – In Vitro 3T3 NRU phototoxicity test) using Balb/c 3T3 cells at a density of 1×10^4 cells per well.⁶ The maximum test concentration of the trade name mixture was 1000 μ g/ml. Untreated cells served as the negative control, and the positive control was chlorpromazine. An appropriate continuous dose-response curve (model, x-axis = cell concentration and y-axis = cell viability) was used. This model was consistent with the European Union instructions (EU 67/548/EEC Appendix VB.41 “3T3 Neutral Red Uptake (NRU) in Vitro Phototoxicity Test Methods). A photo-irritation factor (PIF) was calculated. A PIF of 1 was calculated for the trade name mixture, and was interpreted as a prediction of no phototoxicity.

OCULAR IRRITATION STUDIES

Data on the ocular irritation potential of *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

CLINICAL STUDIES

Case Report

Scutellaria Baicalensis Extract

A normal female developed facial eczema after using a resveratrol skin cream containing *Scutellaria Baicalensis* Extract (concentration not stated) for several weeks.³² Repeated open application testing of the product twice daily on the antecubital flexures yielded a positive reaction within 2 d. Patch testing of the undiluted cream yielded a 1+ reaction on days 1 and 2. In other patch tests 0.5% aqueous *Scutellaria Baicalensis* Extract yielded a 1+ reaction on days 2 and 3, and weaker 1+ reactions to resveratrol (1% in petrolatum) on days 2 and 3 were also observed. Positive reactions were not observed when 15 control patients were patch tested with *Scutellaria Baicalensis* Extract or resveratrol. The case authors concluded that the patient was sensitized to *Scutellaria Baicalensis* Extract, with possible co-sensitization to resveratrol.

Another case report involves a male lupus patient with facial eczema who had applied a sunscreen containing *Scutellaria Baicalensis* Extract several times per day while on a 10-d vacation and afterwards.³³ The eczema occurred only after he returned home and he noted that the more the sunscreen was applied, the eczema became progressively worse. The results of a photopatch test on the sunscreen product were positive at the irradiated site (+ reaction) and non-irradiated site (+++) on day 2. Subsequent photopatch tests on ingredients of the sunscreen product yielded a positive reaction on only one of the ingredients, *Scutellaria Baicalensis* Extract. This ingredient was tested at a concentration of 0.2% in 50/50 water/alcohol, and a ++ reaction was observed at the non-irradiated site on day 2. A reaction at the irradiated site was not observed.

Scutellaria Baicalensis Root Extract

A female non-atopic patient had a 2-yr history of pruritic, erythematous scaly plaques involving both eyelids and periorbital skin.³⁴ The patient was patch tested, according to European Society of Cosmetic Dermatitis guidelines, with a sunscreen containing *Scutellaria Baicalensis* Root Extract that was being used. Reactions were scored on days 2, 4, and 7. Positive reactions to the sunscreen (-/+ /++) and 0.2% 50/50 *Scutellaria Baicalensis* Root Extract (?+ /++) were reported.

In a second case report, a female patient with a history of mild atopic dermatitis (antecubital flexures and face) presented with facial eczema that she had experienced for 1 yr.³⁵ She had slowly developed recalcitrant facial eczema, and, during the 1-yr period, a retinoic acid-containing cream and sunscreens had been applied to treat both the acne and solar brown spots. Both patch test and photopatch test results for one of the sunscreens (contained *Scutellaria Baicalensis* Root Extract) used were positive on day 2 (+ reaction) and day 3 (++) reaction). The reaction to the sunscreen was not photoaggravated, and was identical at UV-exposed and non-exposed sites. Furthermore, reaction to the sunscreen was confirmed by a positive repeated open application test result after 2 d of application. Patch and photopatch tests on ingredients of the sunscreen were also performed. In both tests, a positive reaction to *Scutellaria Baicalensis* Root Extract (0.2% aqueous/ethanol) was reported on day 2 (+ reaction) and day 3 (++) reaction), with no photoaggravation. The patch testing of 10 control subjects with *Scutellaria Baicalensis* Root Extract (0.2% aqueous/ethanol) yielded negative results.

SUMMARY

The safety of the following 4 *Scutellaria baicalensis*-derived ingredients, as used in cosmetics, is reviewed in this safety assessment: *Scutellaria Baicalensis* Extract, *Scutellaria Baicalensis* Root Extract, *Scutellaria Baicalensis* Root Powder, and *Scutellaria Baicalensis* Sprout Extract. These ingredients, collectively, have the following functions in cosmetics, although none of the ingredients has the same reported functions: antimicrobial agent, skin conditioning agent, abrasive, fragrance ingredient, skin protectant, and antioxidant.

Method of manufacture data on *Scutellaria Baicalensis* Root Extract (root extracted with ethanol, butylene glycol extract, or water) were received from the Council. The extractants used in 2 methods of manufacture are 90% ethanol (one method) and 30% ethanol (another method). In both methods, the starting material is dried raw material (root) that is extracted, subsequently concentrated, and then filtered prior to packaging. The only real difference between these 2 methods is the addition of squalene after the concentration step in the method involving extraction with 30% ethanol. The same methodology is used when butylene glycol (50% 1,3-butylene glycolic solution) is the extractant; squalene is not added. Regarding the method of manufacture of *Scutellaria Baicalensis* Root Extract (aqueous extract), the starting botanical raw material (root) is extracted and then concentrated and spray-dried.

A *Scutellaria Baicalensis* Root Extract trade name mixture (30% ethanol extract) contains flavonoid compounds. Another *Scutellaria Baicalensis* Root Extract trade name mixture (90% ethanol and butylene glycol extracts) contains tannin and flavonoid compounds. A *Scutellaria Baicalensis* Root Extract trade name mixture (90% ethanol and butylene glycol extracts) is reported to contain not more than 20 ppm heavy metals and not more than 2 ppm arsenic. Phytochemical analyses have detected and quantified the flavonoids baicalin, baicalein, scutellarin, wogonin, and the human neurohormones,

melatonin and serotonin, in leaf and stem tissues from *Scutellaria baicalensis*. Additionally, a *Scutellaria baicalensis* root (dried root) contains a variety of flavones, phenylethanoids, amino acids, sterols, and essential oils.

According to 2020 VCRP data, *Scutellaria Baicalensis* Root Extract is reported to be used in 514 cosmetic products (419 leave-on products, 95 rinse-off products). Of the *Scutellaria baicalensis*-derived ingredients reviewed in this safety assessment, this is the greatest reported use frequency. The results of concentration of use surveys conducted by the Council in 2018 and 2019 indicate that the maximum leave-on use concentration in this ingredient group is 0.5% *Scutellaria Baicalensis* Root Extract is in moisturizing products (not spray). According to VCRP and Council survey data, *Scutellaria Baicalensis* Root Powder is not currently in use in cosmetic products.

Scutellaria baicalensis Georgi is one of the 50 fundamental herbs of traditional Chinese medicine.

After a *Scutellaria baicalensis* extract (ethanol extract) was administered orally to rats, the tissue distribution and excretion (in urine and feces) of 2 major flavone constituents was reported. A *Scutellaria baicalensis* root extract (aqueous extract) was also administered orally to rats. After dosing, components of the extract, as well as their metabolites, were detected in the urine, feces, or bile: sulfate and glucuronide conjugates and hydroxylated, methylated, acetylated, and deoxygenated products. When a *Scutellaria baicalensis* root extract (suspended in an aqueous carboxymethyl cellulose sodium salt solution) was administered orally to rats, the 6 major flavonoid components detected in the plasma were rapidly absorbed. A human study was performed to investigate the urinary pharmacokinetics of flavone constituents of a commercial *Scutellaria baicalensis* root powder. The renal excretion of sulfate and glucuronide conjugates was reported.

The teratogenicity of a *Scutellaria baicalensis* root extract (aqueous extract) was evaluated using groups of 30 pregnant Sprague-Dawley female rats. The test substance was administered by gavage to 3 groups, at doses of 0.25, 12.49, and 24.98 g/kg/d, on gestation days 7 to 17. A statistically significant ($p < 0.05$), dose-dependent increase in the incidence of skeletal variations (presence of lumbar ribs) was observed. A dose-dependent increase in the frequency of dilatation of the ureter was also reported. In another study, the effect of a *Scutellaria baicalensis* root extract (aqueous extract) on embryonic development was studied using groups of 18 pregnant ICR mice that received oral doses of 2, 8, or 32 g/kg/d on gestation days 6 to 15. Oral administration of a *Scutellaria baicalensis* root extract (aqueous extract) at or below a dose of 32 g/kg/d during organogenesis did not cause statistically significant fetal external or skeletal malformations. A *Scutellaria baicalensis* root extract (aqueous extract) was also administered orally to 20 pregnant rats. The aqueous extract, in saline (15 g in 750 ml), was administered slowly (186 mg/kg body weight) from day 7 to day 17 of gestation. Fetal lumbar rib incidence was increased on gestational day 20, and then decreased on postnatal day 50. The results of this study suggest that the appearance of lumbar rib is a transient fetal variation rather than teratogenicity or maternal toxicity.

The genotoxicity of a trade name mixture containing 33.33% *Scutellaria Baicalensis* Root Extract (aqueous extract) was evaluated in the Ames test using the following *S. typhimurium* strains with and without metabolic activation: TA97a, TA98, TA100, TA102, and TA1535. Doses up to 5 μ l/dish were tested, and results were classified as negative in all strains tested. The genotoxicity of a *Scutellaria baicalensis* root extract (methanol extract and aqueous extract, 0.1 ml) was also evaluated in the Ames test using *S. typhimurium* strains TA98 and TA 100 with and without metabolic activation. Results for the aqueous extract were positive in strain TA100 with, but not without, metabolic activation. All strain TA98 results for the aqueous extract were negative. Results were negative for the methanol extract, with or without metabolic activation, in both bacterial strains.

The genotoxicity of a *Scutellaria baicalensis* root extract (methanol extract and aqueous extract, 100 mg/ml (60 μ l)) was evaluated in the *B. subtilis* rec-assay using strains H17 Rec⁺ and M45 Rec⁻ without metabolic activation. Results for the methanol extract and aqueous extract were positive and negative, respectively.

A *Scutellaria baicalensis* root extract (ethanol extract) had a strong inhibitory effect on melanogenesis in B16F10 melanoma cells. Incubation with a *Scutellaria baicalensis* root extract (ethanol extract) for 24 h resulted in a statistically significant ($p < 0.01$) decrease in melanin levels in a dose-dependent manner at concentrations between 35 μ g/ml and 70 μ g/ml.

In a study evaluating the antiallergic effects of a *Scutellaria baicalensis* extract (ethanol extract), groups of 6 Sprague-Dawley (SD) rats included rats sensitized with anti-DNP IgE and rats sensitized with anti-DNP IgE and treated with a *Scutellaria baicalensis* extract (28 mg/100 g body weight). Treatment with a *Scutellaria baicalensis* extract inhibited the passive cutaneous anaphylaxis reaction, when compared to the control group. In a study involving groups of 5 female BALB/c mice, a topically applied *Scutellaria baicalensis* root extract (aqueous extract, 0.1%) attenuated the epidermal thickness and mast cell infiltration into the skin in DNCB-induced contact dermatitis.

A *Scutellaria baicalensis* root extract (aqueous extract, 100 and 200 μ g/ml) induced apoptosis in peripheral blood leukocytes from leukemia patients, but not from healthy controls. The cytotoxicity of a *Scutellaria baicalensis* root extract (aqueous ethanol extract) was evaluated using HaCaT human keratinocytes. The extract was nontoxic at concentrations up to 30 μ g/ml, but statistically significant ($p < 0.05$) cytotoxicity was observed at concentrations of 100 μ g/ml and 1000 μ g/ml.

A *Scutellaria baicalensis* root extract (ethanol extract) was assayed for estrogenic activity in vitro using a recombinant yeast system with both a human estrogen receptor expression plasmid and a reporter plasmid. The extract was classified as negative for estrogenic activity at concentrations between 0.1 and 1000 μ g/ml.

A *Scutellaria baicalensis* root extract (aqueous extract) (comprised in part of baicalin (6.45%), wogonoside (3.37%), baicalein (2.07%), and wogonin (0.48%)) was classified as a non-irritant in 6 rabbits. This test substance was also classified as a non-sensitizer in a test involving 10 guinea pigs.

The skin sensitization potential of an undiluted leave-on product containing 0.001% *Scutellaria Baicalensis* Root Extract was evaluated in an HRIPT involving 220 subjects. The product (0.2 g, under semi-occlusive patch) was applied (24 h) repeatedly to the skin. A low-level reaction was observed in 3 subjects during induction and in 1 subject during challenge. The authors commented that the product did not induce dermal sensitization in any of the subjects tested. A 10% *Scutellaria Baicalensis* trade name mixture (butylene glycol extract) was not irritating in a patch test involving 12 subjects and was not a sensitizer in an HRIPT (dose per cm² not stated) involving 49 subjects. In another HRIPT involving 54 subjects patch tested with an undiluted *Scutellaria Baicalensis* trade name mixture (30% ethanol extract; dose per cm² not stated), test results were also negative for skin sensitization.

The phototoxicity of a trade name mixture containing 33.33% *Scutellaria Baicalensis* Root Extract (aqueous extract) was evaluated in the 3T3 neutral red uptake in vitro phototoxicity assay. The maximum test concentration of the trade name mixture was 1000 µg/ml. A PIF of 1 was calculated for the trade name mixture, and was interpreted as a prediction of no phototoxicity.

Skin sensitization was observed in a patient after patch testing with 0.5% aqueous *Scutellaria Baicalensis* Extract. The individual developed facial eczema after using a product that contained the extract. The extract is an ingredient of a skin cream that had been used over a period of several weeks. Positive reactions were not observed when 15 control patients were patch tested with *Scutellaria Baicalensis* Extract. Another eczema patient photo-patch tested with 0.2% *Scutellaria Baicalensis* Extract (in 50/50 water/alcohol) had a positive reaction at the non-irradiated site and no reaction at the irradiated site. A patient with pruritic erythematous plaques was patch tested with 0.2% *Scutellaria Baicalensis* Root Extract (in 50/50 water/alcohol). Reactions classified as ?+, +, and ++ were observed on days 2, 4, and 7, respectively. In another case report, an eczema patient was patch tested and photo-patch tested with *Scutellaria Baicalensis* Root Extract (0.2% aqueous/ethanol). In both tests, a positive reaction was reported on day 2 (+ reaction) and day 3 (++ reaction). The patch testing of 10 control subjects in this case report yielded negative results.

DISCUSSION

All of these ingredients are derived from the same species, i.e., *Scutellaria baicalensis*. The toxicities and composition of these plant extracts are dependent upon which solvent is used to prepare the extract.

The Panel initially expressed concern over the increased incidence or a statistically significant, dose-dependent increase in the incidence of skeletal variations (presence of lumbar ribs) in developmental and reproductive toxicity studies on *Scutellaria baicalensis* root extract (aqueous extract) involving Sprague-Dawley rats. However, after further review of the data, the Panel agreed that the study results suggest that the appearance of lumbar ribs induced by the test material was a transient fetal variation rather than teratogenicity or maternal toxicity.

The genotoxicity of *Scutellaria baicalensis* root extracts (methanol extract and aqueous extract) was evaluated in the *Bacillus subtilis* rec-assay using strains H17 Rec⁺ and M45 Rec⁻ without metabolic activation. Results were positive for the methanol extract and negative for the aqueous extract. However, in Ames tests, results were positive for the aqueous extract and negative for the methanol extract. The Panel noted that, given these mixed results, a repeat of these assays and the addition of another assay (mammalian system) would be needed in order to develop a weight of evidence approach for evaluating the genotoxicity of *Scutellaria baicalensis* root extract. Subsequently, negative Ames test results on a trade name mixture containing 33.33% *Scutellaria Baicalensis* Root Extract (aqueous extract) were received, and the Panel agreed that these data support the safety of *Scutellaria Baicalensis* Root Extract in cosmetic products.

In vitro studies indicated that ethanol and methanol extracts (but not n-hexane, ethyl acetate, and water extracts) could have an inhibitory effect on melanogenesis. However, the Panel noted that skin lightening is considered to be a drug effect and should not occur during the use of cosmetic products. Because of that caveat, and based on the low concentrations of use of *Scutellaria Baicalensis* Root Extract in cosmetic products, the results of these in vitro experiments on *Scutellaria baicalensis* root extract, and clinical experience, concern for this effect in cosmetics was mitigated. Nevertheless, the Panel noted that cosmetic formulators should only use *Scutellaria Baicalensis* Root Extract in products in a manner that does not cause depigmentation.

After considering that *Scutellaria Baicalensis* Root Extract is being used in suntan products and the in vitro data on the potential inhibitory effect of *Scutellaria baicalensis* root extract on melanogenesis, the Panel noted that phototoxicity data on *Scutellaria Baicalensis* Root Extract and other *Scutellaria baicalensis*-derived ingredients may be needed. In response to this concern, negative in vitro phototoxicity data on a trade name mixture containing 33.33% *Scutellaria Baicalensis* Root Extract (aqueous extract) were received.

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

Finally, although the Panel found the available data sufficient to support the safety of *Scutellaria Baicalensis* Root Extract and *Scutellaria Baicalensis* Root Powder, the Panel determined that available data are insufficient to conclude on the safety of *Scutellaria Baicalensis* Extract and *Scutellaria Baicalensis* Sprout Extract. The following data are needed to determine safety of these two *Scutellaria baicalensis* ingredients:

Scutellaria Baicalensis Extract and *Scutellaria Baicalensis* Sprout Extract

- genotoxicity (in vitro and mammalian); for ingredient extracts, methanol and aqueous extracts should be tested
- phototoxicity
- skin irritation and sensitization

Scutellaria Baicalensis Extract

- 28-day dermal toxicity; if dermal absorption occurs, additional data may be needed

Scutellaria Baicalensis Sprout Extract

- method of manufacture
- composition
- impurities
- dermal absorption; if dermal absorption occurs, additional data may be needed

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that *Scutellaria Baicalensis* Root Extract and *Scutellaria Baicalensis* Root Powder* are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also concluded that the available data are insufficient to make a determination that *Scutellaria Baicalensis* Extract and *Scutellaria Baicalensis* Sprout Extract are safe under the intended conditions of use in cosmetic formulations.

** Not reported to be in current use. Were this ingredient not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to the root extract.*

TABLES**Table 1.** Definitions and reported functions of the ingredients in this safety assessment.¹

Ingredient CAS No.	Definition	Function(s)
Scutellaria Baicalensis Extract 94279-99-9	Scutellaria Baicalensis Extract is the extract of the whole plant, <i>Scutellaria baicalensis</i> .	Antimicrobial Agents
Scutellaria Baicalensis Root Extract 94279-99-9	Scutellaria Baicalensis Root Extract is the extract of the roots of <i>Scutellaria baicalensis</i> .	Skin-Conditioning Agents – Humectant
Scutellaria Baicalensis Root Powder 94279-99-9	Scutellaria Baicalensis Root Powder is the powder obtained from the dried, ground roots of <i>Scutellaria baicalensis</i> .	Abrasives; Fragrance Ingredients; Skin Protectants

Table 2. Components of Scutellaria Baicalensis Extract (ethanol extract).¹⁰

5,7,6'-trihydroxyflavone 2'-O-β-D-glucopyranoside
(2R,3R)-3,5,7,2',6'-pentahydroxyflavanone
3,5,7,2',6'-pentahydroxyflavone
Viscidulin III 6-O-β-D-glucopyranoside
Chrysin 6-C-α-L-arabinopyranoside-8-C-β-D-glucopyranoside
Acteoside
5,6'-dihydroxy-7,8-dimethoxyflavone 2'-O-β-D-glucopyranoside
Chrysin 6-C-β-D-glucopyranoside-8-C-α-L-arabinopyranoside
Chrysin 8-C-β-D-glucopyranoside
5,2'-dihydroxy-6-methoxyflavone 7-O-β-D-glucuronopyranoside
(2S)-5,7,2',6'-tetrahydroxyflavanone
Baicalin
Baicalein 7-O-β-D-glucopyranoside
Norwogonin 7-O-β-D-glucuronopyranoside
Wogonin 5-O-β-D-glucopyranoside
Cistanoside D
Chrysin 7-O-β-D-glucuronopyranoside
Oroxylin A 7-O-β-D-glucuronopyranoside
Oroxylin A 7-O-β-D-glucopyranoside
Wogonoside
5,7,6'-trihydroxy-8,2'-dimethoxyflavone
Baicalein
Wogonin
Chrysin
5,6'-dihydroxy-6,7,8,2'-tetramethoxyflavone
Oroxylin A
(2S)-5,7,6'-trihydroxyflavanone 2'-O-β-D-glucopyranoside
(2S)-5-hydroxy-6-methoxyflavanone 7-O-β-D-glucuronopyranoside
Aschrysin 6-C-β-L-arabinopyranosyl-8-C-β-D-glucopyranoside
Chrysin 6-C-β-D-glucopyranosyl-8-C-β-L-arabinopyranoside

Table 3. Frequency (2020) and concentration (2018-2019) of use according to duration and type of exposure.¹⁴⁻¹⁶

	Scutellaria Baicalensis Extract		Scutellaria Baicalensis Root Extract		Scutellaria Baicalensis Sprout Extract	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals*/Conc. Range	109	0.000027-0.03	514	0.00001-0.5	NR	0.0002-0.0005
Duration of Use						
<i>Leave-On</i>	93	0.000027-0.03	419	0.0002-0.5	NR	0.00025-0.0005
<i>Rinse off</i>	16	NR	95	0.00001-0.002	NR	0.0002
<i>Diluted for (bath) Use</i>	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	9	NR	30	0.07	NR	NR
Incidental Ingestion	NR	NR	1	0.0045	NR	NR
Incidental Inhalation- Sprays	32 ^a ;31 ^b	0.03 ^a	163 ^a ;151 ^b	0.002 ^a	NR	NR
Incidental Inhalation- Powders	31 ^b	NR	151 ^b ;8 ^c	0.0002-0.35 ^c	NR	0.00025-0.0005 ^c
Dermal Contact	106	0.000027	473	0.00001-0.5	NR	0.0002-0.0005
Deodorant (underarm)	NR	NR	2 ^a	NR	NR	NR
Hair - Non-Coloring	1	0.03	25	0.002	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	15	0.0002-0.0045	NR	0.0002
Baby Products	3	NR	10	NR	NR	NR

NR = Not Reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

^aIt is possible that these products may be sprays, but it is not specified whether the reported uses are sprays^bNot specified these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories^cIt is possible that these products may be powders, but it is not specified whether the reported uses are powders**Table 4.** *Scutellaria baicalensis* root extract metabolites in the rat.⁸

Metabolite Type*	Formula	Source	Parent Compound**
glucuronide conjugation	C ₂₇ H ₂₆ O ₁₇	urine and bile	baicalin
glucuronide conjugation	C ₂₂ H ₂₈ O ₁₇	urine and bile	wogonoside
hydroxylation + sulfation	C ₁₆ H ₁₂ O ₉ S	urine	wogonin
sulfate conjugation	C ₁₅ H ₁₀ O ₈ S	urine	baicalein
sulfate conjugation	C ₁₆ H ₁₂ O ₈ S	urine	wogonin
2 x hydroxylation	C ₂₂ H ₂₆ O ₁₉	urine	wogonoside
loss of oxygen	C ₂₁ H ₁₈ O ₁₀	urine	baicalin
2 x hydroxylation	C ₁₅ H ₁₀ O ₇	urine and feces	baicalein
acetylation	C ₂₄ H ₂₂ O ₁₂	urine	wogonoside
reduction	C ₁₆ H ₁₄ O ₅	urine	wogonin
hydroxylation + methylation	C ₂₂ H ₂₀ O ₁₂	urine	baicalin
loss of oxygen	C ₁₅ H ₁₀ O ₄	urine and feces	baicalein
hydroxylation	C ₁₆ H ₁₂ O ₆	feces	wogonin
deglycuronide	C ₁₅ H ₁₀ O ₅	feces	baicalin
deglycuronide	C ₁₆ H ₂₀ O ₅	feces	wogonoside

*Metabolite of parent compound

**Component of *Scutellaria baicalensis* root

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2020 FDA VCRP Data**Scutellaria Baicalensis Extract**

1A-Baby Shampoos	1
1C-Other Baby Products	2
3D-Eye Lotion	5
3G-Other Eye Makeup Preparations	4
7C-Foundations	1
7F-Makeup Bases	1
7I-Other Makeup Preparations	1
10E-Other Personal Cleanliness Products	2
12A-Cleansing	9
12C-Face and Neck (exc shave)	31
12D-Body and Hand (exc shave)	10
12F-Moisturizing	25
12G-Night	3
12H-Paste Masks (mud packs)	4
12I-Skin Fresheners	1
12J-Other Skin Care Preps	6
13A-Suntan Gels, Creams, and Liquids	3
Total	109

Scutellaria Baicalensis Root Extract

1B-Baby Lotions, Oils, Powders, and Creams	8
1C-Other Baby Products	2
3A-Eyebrow Pencil	1
3B-Eyeliners	2
3D-Eye Lotion	13
3E-Eye Makeup Remover	1
3G-Other Eye Makeup Preparations	13
5A-Hair Conditioner	3
5E-Rinses (non-coloring)	3
5F-Shampoos (non-coloring)	9
5G-Tonics, Dressings, and Other Hair Grooming Aids	7
5I-Other Hair Preparations	3
7B-Face Powders	2
7C-Foundations	11
7F-Makeup Bases	3
7I-Other Makeup Preparations	6
9A-Dentifrices	1
10A-Bath Soaps and Detergents	4
10B-Deodorants (underarm)	2
10C-Douches	2
10E-Other Personal Cleanliness Products	8
11A-Aftershave Lotion	2
11E-Shaving Cream	1
12A-Cleansing	41
12C-Face and Neck (exc shave)	114

12D-Body and Hand (exc shave)	18
12F-Moisturizing	133
12G-Night	15
12H-Paste Masks (mud packs)	22
12I-Skin Fresheners	7
12J-Other Skin Care Preps	54
13A-Suntan Gels, Creams, and Liquids	1
13B-Indoor Tanning Preparations	2
Total	514

Scutellaria Baicalensis Root Powder - No FDA Data

Scutellaria Baicalensis Sprout Extract - No FDA Data



Memorandum

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

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

DATE: June 1, 2020

SUBJECT: Draft Tentative Report: Safety Assessment of *Scutellaria baicalensis*-Derived Ingredients as Used in Cosmetics (draft prepared for the June 8-9, 2020 CIR Expert Panel meeting)

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

Cytotoxicity - Please revised the following sentence as it incorrectly suggests that the NALM-6 cell line came from 26 children with acute lymphoblastic leukemia. "A *Scutellaria baicalensis* root extract (aqueous extract) was tested in apoptosis experiments involving the following cell types from 26 children with acute lymphoblastic leukemia: the NALM-6 cell line (human peripheral blood leukemia pre-B cells), peripheral blood leukocytes, and bone marrow cells."



Memorandum

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

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

DATE: July 9, 2020

SUBJECT: Tentative Report: Safety Assessment of *Scutellaria baicalensis*-Derived Ingredients as Used in Cosmetics (Release Date June 19, 2020)

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

Introduction; Definition - As a single species always shares the same genus, it is not necessary to state "from the same genus and species" in both the Introduction and Definition sections. It would be sufficient just to state that all of the ingredients in the report are derived from the same species.

Composition - In the Composition section, it would be helpful to state the relationship of baicalin, wogonin and oroxylin 7-O- β -D-glucuronide to baicalein, wogonin and oroxylin A (aglycones), respectively. If the relationship is not stated in the Composition section, it would be helpful to rearrange the ADME section so that the study from reference 7 where this relationship is described, is presented first. This would help clarify the additional ADME studies.

Cytotoxicity - Please revise the following sentence: "Peripheral blood leukocytes were isolated from the blood and bone marrow of 26 children with acute lymphoblastic leukemia." By definition, peripheral blood leukocytes are from the blood, and once they are found in the blood, cells from the bone marrow are no longer bone marrow cells. This should likely state: "Peripheral blood leukocytes and bone marrow cells were isolated from 26 children with acute lymphoblastic leukemia."

Summary - Please correct: "was not an irritant in a patch test..."

Discussion - It would also be helpful to note that in addition to toxicities, the composition of the plant extracts vary by solvent.

In the discussion of phototoxicity, it would be helpful to mention the case reports that did not see any evidence of phototoxicity in cases sensitized to a *Scutellaria baicalensis*-derived ingredient used in sunscreen products.

Table 4 - Baicalin (also called baicalein 7-O-glucuronide) and Baicalein 7-O- β -D-glucopyranoside appear to be two names for the same compound.