
Safety Assessment of *Helianthus annuus* (Sunflower)-Derived Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
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The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: September 2, 2016

Subject: *Helianthus annuus* (Sunflower)-Derived Ingredients as Used in Cosmetics

Attached is the Draft Final Report of 12 *Helianthus annuus* (sunflower)-derived ingredients as used in cosmetics. [*Helian092016Rep*] All of these ingredients are derived from parts of the *Helianthus annuus* (sunflower) plant. The Panel concluded that it was not appropriate to include Ozonized Sunflower Seed Oil in this group of ingredients, so it was removed from the report.

In March, 2016, the Panel issued a tentative report with a safe as used conclusion for the seed- and flower-derived ingredients and an insufficient data conclusion for the rest of the plant-derived ingredients. The data needs were:

- Method of manufacture
- Composition of these ingredients, especially protein content (including 2S albumins)
- Impurities

Dr. Stefano Luccioli, Senior Medical Advisor in the Food and Drug Administration's (FDA) Office of Food Additive Safety (OFAS), provided comments on 2S albumins in *Helianthus annuus* (sunflower)-derived cosmetic ingredients and their potential to induce sensitization. Dr. Luccioli stated that, in his clinical opinion, there is no need for a warning label for seed or tree nut allergic individuals. He indicated that labelling cosmetic products as containing *Helianthus annuus* (sunflower) seed-derived ingredients would likely satisfy any pertinent condition of safety for these ingredients. Dr. Luccioli's statement is included in this packet. [*helian092016Data_1*] Also included is Dr. Boyer's summary of information on 2S albumins. [*Helian092016Data_2*]

The Council submitted a clarifying statement about the source of a *Helianthus annuus* (sunflower)-derived ingredient that was reported to be derived from "bark". This product was derived from the seeds. Since the information from the "bark" product now appears to be from a product that is no longer available, the data on this product had been removed from the report. [*helian092016Data_3*]

Council comments have been addressed. [*helian092016PCPC1,2*]

After reviewing the additional information, the Panel is asked to consider whether adding a warning to the Conclusion is warranted to address the potential for *Helianthus annuus*-derived ingredients to elicit hypersensitivity reactions in sensitized individuals. The Panel is also asked to decide whether to include additional information on 2S albumin (from Dr. Boyer's summary) to this report.

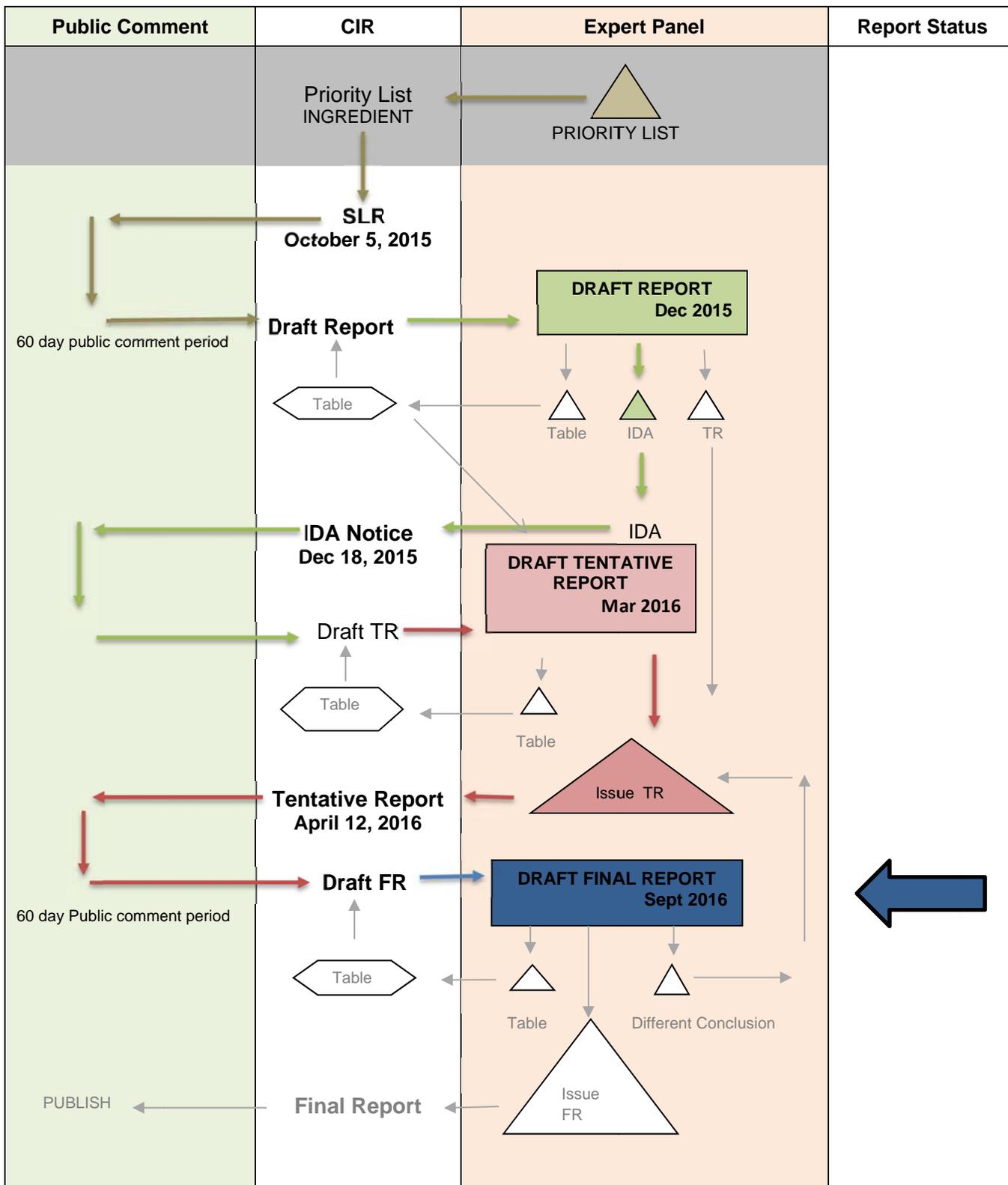
The Panel should discuss whether it is necessary to revisit the safety assessments of other ingredients likely to contain 2S albumins similar to those of sunflower seed. This should affect the progress of this report.

If the information from Dr. Luccioli warrants significant changes to the safety assessment, the Panel is to issue a Revised Tentative Report and provide the basis for changes to the Discussion and Conclusion. If there are no significant changes, then the Panel is to examine the Abstract, Discussion, and Conclusion in this Draft Final Report to make sure that they adequately address the Panel's concerns, and, if so, issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Helianthus annuus (sunflower)-derived ingredients

MEETING Sept 2016



History – *Helianthus annuus* (Sunflower)-Derived Ingredients

2014 – Added to the priority list

October, 2015 – SLR was posted with the following data requests:

- Characterization of constituents of each of these ingredients
- Method of manufacture for cosmetics for each of these ingredients including methods for removing constituents of concern
- Dermal and inhalation toxicity data for each of these ingredients at or above the reported concentrations of use
- Reproductive and developmental toxicity, genotoxicity, and carcinogenicity data for each of these ingredients at or above the reported concentrations of use
- Dermal and ocular irritation data for each of these ingredients at or above the reported concentrations of use
- Irritation and sensitization data of each of these ingredients at or above the reported concentrations of use

December, 2015 – The Panel issued an Insufficient Data Announcement for these ingredients. The ingredient needs are:

- HRIPT of hydrogenated sunflower seed extract at least 1%
- Method of manufacture including clarification of the source material (whole plant vs “bark”) of *helianthus annuus* (sunflower) extract
- Composition of these ingredients, especially protein content (including 2S albumin)
- Impurities

The Panel was not clear as to whether or not they were removing Ozonized Sunflower Seed Oil

March, 2016 – The Panel reviewed the information on 2S albumins and decided that they were probably not a problem. Ozonized Sunflower Seed Oil was removed from the report.

The Panel issued a Tentative Report with a conclusion that nine seed- and flower-derived ingredients are safe as used in cosmetics in the present practices of use and concentration described in this safety assessment. The data are insufficient to evaluate the safety of three ingredients that are derived from other plant parts. The data needs are:

- Method of manufacture
- Composition of these ingredients, especially protein content (including 2S albumin)
- Impurities

The Panel also explored the possibility of further discussing 2S albumins with an expert.

September, 2016 – The Panel is to review the new information on 2S albumins, the report (the Abstract, Discussion, and Conclusion in particular) and issue a Final Report.

H. annuus-Derived Ingredients Data Profile for **September, 2016**. Writer - Lillian Becker

	ADME		Acute toxicity			Repeated dose toxicity			Irritation			Sensitization		Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
	Dermal Penetration	Log K _{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal				
Helianthus annuus (sunflower) extract			X										X				
Helianthus annuus (sunflower) flower extract			X														
Helianthus annuus (sunflower) leaf/stem extract																	
Helianthus annuus (sunflower) sprout extract																	
Helianthus annuus (sunflower) seed			X														
Helianthus annuus (sunflower) seed butter																	
Helianthus annuus (sunflower) seedcake			X														
Helianthus annuus (sunflower) seed extract			X						X	X	X	X	X				
Helianthus annuus (sunflower) seed flour																	
Hydrolyzed sunflower seed wax			X														
Hydrogenated sunflower seed extract																	
Helianthus annuus (sunflower) seed wax			X								X		X				

Search Strategy – Sunflower

SciFinder

“Sunflower toxicity” – 682 hits. Remove patents, 559 hits. English, 386 hits. 13 possibly useful.
“sunflower” AND “dermal”; “genotox*”; “irritation”; “sensiti*”; “repro*”; “terato*”; “adverse event”
“Helianthus annuus” AND “dermal”; “genotox*”; “irritation”; “sensiti*”; “repro*”; “terato*”; “adverse event”

NTP

“sunflower” and “Helianthus annuus” – 1 hit. Not useful.

Google – National Sunflower Association

PubMed

("HELIANTHUS ANNUUS (SUNFLOWER)"[TW] OR "HELIANTHUS ANNUUS (SUNFLOWER)"[TW] OR "HELIANTHUS ANNUUS"[TW] OR "HELIANTHUS ANNUUS (SUNFLOWER)"[TW] OR "HELIANTHUS ANNUUS"[TW] OR "SUNFLOWER"[TW]) – 5948 hits; culled with toxic* - 121 hits, none useful.

"HELIANTHUS ANNUUS" AND toxic* - 76 hits, none useful.

“dermal”; “genotox*”; “irritation”; “sensiti*”; “repro*”; “terato*”; “adverse event”
“Helianthus annuus” AND “dermal”; “genotox*”; “irritation”; “sensiti*”; “repro*”; “terato*”; “adverse event”

Sunflower OR Helianthus annuus AND “2S albumin”

ECHA

Helianthus Annuus, Helianthus Annuus extract, and Helianthus Annuus, ext. are preregistered substances that have no data available yet.

GOOGLE

Data from Purdue, FDA, and Feedipedia.

**Transcripts – *Helianthus annuus* (Sunflower)-Derived Ingredients
April, 2016**

Dr. Marks' Team

DR. MARKS: Okay, next two, sunflower, *Helianthus annuus*. And we have a tentative report of these 13 sunflower- derived ingredients. At the December meeting the Panel issued an insufficient data announcement. And tomorrow our team will be making a second. And when I looked at it I thought we still -- insufficient data for the hydrogenated seed extract. I was concerned about -- even though --

DR. EISENMANN: One question. There's no uses report of that ingredient. So I mean it's okay if it goes insufficient --

DR. MARKS: Okay.

DR. EISENMANN: -- but I'm not sure why you had a data need for it --

DR. MARKS: Not used --

DR. EISENMANN: -- because there are no uses. And I --

DR. MARKS: But I can't (inaudible)

DR. EISENMANN: Especially at one percent.

DR. MARKS: Well --

DR. EISENMANN: We've got the -- we've got data on the --

DR. MARKS: The hydrogenated --

DR. EISENMANN: -- sunflower seed extract data.

DR. MARKS: It -- no uses. I thought there were --

DR. EISENMANN: Because of hydronated --

DR. MARKS: -- 400.

DR. EISENMANN: -- hydrogenated --

DR. MARKS: Yeah.

DR. EISENMANN: -- sunflower seed extract, no. Of the sunflower seed extract, yes.

DR. MARKS: Okay, let me --

DR. EISENMANN: That's what -- why I was very confused when I saw the data needs because --

DR. MARKS: Which is the use tables? What page is that, Carol? Because I must have looked at that incorrectly. Because I thought it was used like 400 times.

DR. EISENMANN: Sunflower seed extract itself is 389 uses.

DR. MARKS: What page are you on?

DR. EISENMANN: I'm -- I don't have a PDF file in front of me. I'm on Table 12.

MS. BECKER: 34.

DR. SHANK: Page 31. Here you go.

MS. BECKER: Yeah, 38, sorry.

DR. SHANK: Yeah.

DR. MARKS: See (inaudible).

DR. EISENMANN: So I interpreted it to mean that you wanted data on sunflower seed extract itself because that's the ingredient which had use --

DR. MARKS: One percent.

DR. EISENMANN: -- and so that's what we got.

DR. MARKS: Yes, okay.

DR. HILL: While were there on that table just because we're there and it's convenient, on the duration of use you've got leave on one percent up at that top, but five percent down there for mucus membrane. And five percent doesn't appear anywhere else up at the top. Do we know which one is correct?

MS. BECKER: Where are we?

DR. HILL: Yeah in -- it says the seed extract. That's why I only brought it up now even though it's off topic. We can just look into that --

MS. BECKER: Yeah.

DR. HILL: -- and go back to where you were.

DR. MARKS: Thank you, Carol. I misinterpreted that. I -- somewhere I had much -- I must have read the use table incorrectly and you're absolutely -- the seed extract we have a sensitization at 10 percent. So well above the use concentration. So, Tom, Rons', do we have the method of manufacture composition okay? And then we also have to talk about the 2S albumin in page 26. And then Ivan -- no, Lillian Becker again as the writer remove the ozonized seed oil. That's what we recommended. And our team felt we could -- in the previous we could say we wanted that removed. So let's take it one at a time.

Remove the ozonized seed oil. Again we didn't want it because it looked -- it was different than the other ingredients. And I forget who was the one. Ron Shank, were you the one that wanted that removed?

DR. SHANK: I agreed with it being removed.

DR. MARKS: Yeah.

DR. SHANK: I don't think I brought it up.

DR. MARKS: So you would still want that removed?

DR. SHANK: Mm-hmm.

DR. MARKS: Yes, okay. Who was it that wanted it removed? You agreed with it because it just was different than the other ingredients.

DR. SHANK: Right.

DR. MARKS: Yep. How about the method of manufacture composition? Are we okay with that now?

DR. SHANK: Yes.

DR. SLAGA: Yes.

DR. MARKS: And then let's move on to the 2S albumin in page 26. Concerns about that?

DR. SLAGA: Well I have no concerns. I think we should add a section to the report.

DR. MARKS: Ron Shank or Ron Hill?

DR. HILL: Okay, so what ingredients are we now saying everything's okay? Are we thinking that's all of them at this point --

DR. MARKS: I --

DR. HILL: -- except the seed oil? Because it's --

DR. MARKS: It's which?

DR. HILL: Because what we got in terms of new data here was aqueous extract of -- was it whole plant? I think these are all aqueous extracts of the whole plant. Is that correct? I'm fearing I have this crossed up with another one in my head, so that's why.

DR. EISENMANN: I think predominantly of information on the seed.

DR. HILL: Seed extract, right? Okay.

DR. MARKS: Right.

DR. HILL: Okay, so how is it that that covers all the rest of them? How do we cover the wax? Is that -- okay, go back to the use table -- read across table.

DR. MARKS: And while you're looking at that, Ron Hill, I wanted to ask Tom. Are you okay about benzopyrene in page 26? That didn't raise any concerns for you?

DR. SLAGA: It's a contaminant. It's not produced by the plant.

DR. MARKS: Is that clearly --

DR. SLAGA: I don't know of any plant that would produce it.

DR. MARKS: So it can -- so is that clearly stated in there that's --

DR. SLAGA: Well we discussed that last time. I think it comes across in the report.

DR. MARKS: Okay.

DR. SHANK: Where is this in the report?

DR. MARKS: Page 26. I think it's 26. I don't have it highlighted here, Tom. Yeah, there it is. It's constituents of concern. It's the second paragraph. A carcinogen benzopyrene has been detected in unrefined seed oil. And then under impurities in page 26, the -- one, two, three, fourth paragraph, the carcinogen benzopyrene has been detected in unrefined -- in cooking seed oil from sunflower.

DR. SHANK: I think it's wrong to consider it as a constituent.

DR. SLAGA: Yeah.

DR. SHANK: I think it's a contaminant.

DR. SLAGA: Yeah, it's only a contaminant.

DR. SHANK: It's not part -- a natural part of the (inaudible).

DR. SLAGA: In the next sentence it should -- it's not endogenous and it should be a contaminant.

DR. MARKS: Yeah, so it says -- yeah, the next sentence it says while the source may be endogenous synthesis, you're saying that can't be the case?

DR. SLAGA: Mm-hmm.

DR. MARKS: So that needs to be changed.

DR. HILL: I did flag the possibility of the cooking step and the manufacturer is possibly generating that. But that --

DR. SLAGA: Yeah.

DR. HILL: It's not an endogenous constituent at all. I agree.

DR. SLAGA: Yeah, the cooking could cause it, but that creates a little contaminant.

DR. MARKS: So should that be -- do you think in the discussion that -- now -- just make it clear in the impurities and above that this is a contaminant and not a -- not part of the plant ingredient?

DR. SHANK: Correct.

DR. MARKS: Okay, is -- so for Lillian, can you just make -- emphasize that somewhere in there that it's a contaminant? Okay, that answers my concerns with it. Ron Hill, I kind of -- while you were looking something up, I was -- I had switched over the benzopyrene. So we don't need to make any comment tomorrow in the -- when we have a discussion about the benzopyrene, correct Tom?

DR. SLAGA: Right.

DR. MARKS: I'll remove that.

DR. HILL: It was made at one of the ozonized oil out. That was really a pragmatic thinking that it relates more to the oils and that we didn't have any direct data.

DR. MARKS: Okay, so getting back, I think, Ron Hill, you asked are we going to second attempt a report safe for all the ingredients removing the ozonized seed oil? And the answer is yes. Safe for all.

DR. HILL: So let me see if I can reiterate our logic because I remember we had a pretty robust discussion and I was sort of trying to wiz back through the transcript here.

Our idea was that the constituents that are there in the seed extract -- and we do have sensitization on the wax, but we have a lot of data on the seed extract that we are able to read that over to the whole plant because our characterization suggested that we were capturing everything in the seed that might otherwise come from whatever the bark of a sunflower is; the root, all of that. Do we have a root ingredient here? Because I know my comfort level was good for the seed extract and for the wax because we have the sensitization and we know what waxes are like and nothing else. But then I think everybody argued that, well, we have constituent characterizations and that made everybody else comfortable.

DR. MARKS: Yeah, we had the -- I have in my original notes here, we had the extract, presumably the whole plant at the HRIPT. It's okay on that. It used concentration. The seed cake at .4 percent, HRIPT, is okay on that. We have this -- even though it's not used, the seed extract, we have at 10 percent, okay. And then we add the seed wax. I have four percent as okay. So we actually have a lot of sensitization data. Some of it -- in fact, all of it is human.

DR. HILL: Just because it all pertain to the seed, but then we only have --

DR. MARKS: Well we have the whole extract. We have the seed cake. We have the seed wax.

DR. HILL: I remember what the deal on the whole extract was is we didn't have any information, good information, about how that was -- exactly how that was created or characterization on what it was that we're being tested at. Okay.

DR. MARKS: Yeah, and we aren't going to get anything on the flower, leaf, stem, or the sprout because -- or I'm --

DR. HILL: Not safe.

DR. MARKS: -- should say the leaf, stem, and the sprout. Presumably that's in the extract. That's what I interpreted it. That you cover that, but they're being used. So I was okay with the seed situation.

DR. HILL: Yeah, and after that I got more interested in the 2S albumin and forgot about it, so.

DR. MARKS: Okay, any -- and then as far as the 2S albumin, that's okay? The discussion on page 26.

MR. BEST: I have a quick question on that. So I mean, it was a little unclear to me. I'm so --

DR. MARKS: Good.

MR. BEST: So its presence of a universal allergen. I mean does this mean that if you have some other kind of nut allergen that a product like this might not be safe for you to use?

DR. HILL: My impression was that that's not the case.

MR. BEST: That's not the case, okay.

DR. HILL: Except for the attempts at genetic engineering where they were actually using a protein from a species that somebody might cross-react. And in general we won't cross-react one to another.

DR. BOYER: It's basically, if you're looking for an allergen in an ingredient or a food stuff that's derived from a seed or a nut and you're seeing people reacting to it in some way, then one of the things you want to look at is the 2S fraction to see whether or not the protein that's causing the problem is in that fraction because it just may be.

MR. BEST: Okay.

DR. BERGFELD: Jim, in your conclusion, can you read your conclusion in its entirety, please?

DR. MARKS: This is going to be a tentative report. It'll be -- let me see. I didn't count it up. It's either 13 or 12. I think it's 12 since we removed the ozonized seed oil. That these 12 ingredients are safe in the present practice and use, our standard conclusion.

DR. BERGFELD: And you don't feel the need to put should be formulated to be non-sensitizing?

DR. MARKS: I think --

DR. BERGFELD: Well you have it in the discussion. You covered a little bit there.

DR. MARKS: Yeah, I think there and, again, actually there's a fair amount of sensitization data here.

DR. BERGFELD: Okay.

DR. MARKS: So I was comfortable with it. We'll see. Let me see. I'm seconding it tomorrow, so we'll see what the Belsito team has. I have no problems putting that in the conclusion with a botanical, but then it almost becomes -- as I said before, you know, if you put formulated to be non-sensitizing that means, obviously, you can put a sensitizer in there. It's just got to be the -- below the threshold of causing allergic contact dermatitis. So, I like it safe for all in the present practice and use. Yeah.

Ron, Ron, and Tom, sound good to you?

DR. SHANK: Agree.

DR. MARKS: I want to represent the team well.

DR. HILL: Okay, what -- clarify one more time. How about the ozonized seed oil?

DR. MARKS: That's where we're moving at.

DR. HILL: Okay, yeah, because I see --

DR. MARKS: So I think -- does that -- right. Lillian, it'll be 12 ingredients?

MS. BECKER: Yes, 12 is correct.

DR. MARKS: Yeah.

MS. BECKER: And how much more than what's already in the report do you want to talk about the 2S albumin?

DR. MARKS: I guess, getting back to your comments, when you have a paragraph in -- this allergen is -- it doesn't give me -- when I read it I didn't have a sense of, okay, real world. It contains an allergen, but what does this mean? All these plants contain it. And then I always go after that. And if it were like the -- as I recall the wheat protein in the Japanese product. I think it was a soap or -- soap where there was a lot of type 1 allergy, that raises a red flag. With this there wasn't like an epidemic of sunflower ingredient that was causing type 1 allergy. And I presume that's the allergy we're talking about with this. Not a type 1 delayed type hypersensitivity.

DR. BOYER: That's correct. And in fact cases of allergy, you know, to the -- to sunflower seeds are rare. There are very few (inaudible).

DR. MARKS: So I wonder if that might -- a sentence in -- might be worthwhile putting in that paragraph even though it contains it. Reports of allergy are rare. Yes, Linda.

DR. KATZ: I'm not really sure it's all that rare that there are a lot of people who have nut allergies who have cross-sensitization with seeds including sunflower seed allergies. And so that -- I wouldn't say necessarily it's that's rare. I'm not sure if it's a type 1 or a type 4, but it does happen.

DR. MARKS: Hmm.

DR. KATZ: And so I wouldn't just write it off. And most people who do have a nut allergy who are -- also have a cross-sensitization with seeds are aware of it. And if they know the seed is present they will avoid it because they have the allergy itself.

DR. BOYER: Okay, and at the last meeting there was some discussion about including a warning kind of statement in the discussion and that's probably what we ought to do.

DR. HILL: I mean what spoke to me the most, really of all of that, was the data from the processing workers where they were processing sunflower seeds. And I think they determined that people there were there 14 years or longer than that, quite a significant number of them did develop allergy and then they went on to trace down which component was causing it and it turned out to be the shell I think or something like that, but. Just suggest if you used it every day, those people like that, for 20 years might become sensitive, I guess.

DR. BOYER: Yeah, and what complicates things also is that often -- or you get sunflower pollen associated with the seeds and that's actually --

DR. HILL: I think -- was that -- I think (inaudible)

DR. BOYER: That was in the --

DR. HILL: -- that was the conclusion.

DR. MARKS: Yeah, we're at page 31. I'm reading clinical use here. And Linda this just reinforces what you said. The first sentence says there are multiple cases of reports. Multiple case reports of children and adults who are allergic. So I guess -- so contact by dermal, oral, and inhalation. And then, Ron Hill, your reference to the workers in the animal feed processing plant. How do we translate the concern there in the 2S albumin that we aren't concerned about it in cosmetic use with these ingredients? That's where I -- that's -- I think that's where I want to be reassured if I were a consumer. You bring this up but then why do you say it's safe?

MR. BEST: Yeah, absolutely. And -- I mean -- and -- I mean you said that maybe a warning is appropriate. It seems like -- that feels strongly to me. I mean reading this it was really sort of an eye opener. I was like, wow, I had no idea. I think if I had some kind of an allergy and -- you know, I would see this as totally unrelated. I mean I guess some people are aware, but I mean it seems like -- it seems like a real disconnect to me. Some kind of warning or (inaudible) would be appropriate.

DR. BOYER: Yeah, so atopic individuals are at risk. People who have broad allergies to a number of different nuts and seeds and so forth, they're certainly at risk. And so I think that probably warrants a warning.

DR. MARKS: Yeah, so actually, Lillian you addressed that to us and I have -- I've ignored it up to this point because I knew it would extend the discussion. On page 33, the first paragraph, consequently the 2S albumin proteins in Helianthus annuus seed are potential allergens. And then you have in brackets, to be further developed by the Panel. So team, how do you want to further develop individuals with known allergies to sunflower ingredients should avoid if they -- you know, this is -- it's --

MR. BEST: I guess I'm still confused. I feel like -- Ivan you were actually just saying that. It isn't just individuals with sunflower allergies, right? That there are -- that you have other allergies that you're also at risk to the sunflower, right?

DR. BOYER: Yeah, mm-hmm.

DR. MARKS: I almost want an allergist to weigh in on this really because I -- I've -- none of you are -- in a sentence it said dermal exposure, but was that dermal exposure to cosmetics?

MS. BECKER: It must be in the table.

DR. MARKS: Yeah, who --

DR. MATZ: It may be worthwhile to get an allergists opinion because I don't know if by processing that the way that the seeds themselves will be processed in the cosmetic if you denaturize the protein enough that it's no longer an allergen. And it might be something to -- worthwhile to get an opinion from an allergist just to make sure that whatever advice and recommendations you're giving are actually correct in the finished product.

DR. MARKS: Okay, Lillian points out dermal exposure, but that looks like that was allergic contact dermatitis. Patch test with European standard and an (inaudible) positive or reserved for. So that's a patch test. That's -- and I'm not concerned about. There're going to be individual case reports of positivity of patch test. I'm concerned about type 1 allergy where you're getting bronchospasm and potential shock as a consequence of exposure.

Lillian Gill, how would we engage it? I mean I could go back to Hershey and ask my allergist about this. Is that the way you'd like to proceed? Perhaps we could ask several different allergist or would you formally want to -- is -- does the CIR have an allergist on retainer quote unquote? Type 1 -- (Laughter)

DR. GILL: We don't have --

DR. MARKS: Type 1 --

DR. GILL: -- any on retainer. I could certainly have Ivan look into this, develop sort of a draft statement, get it to you and to the panel, consult with an external allergist; an expert to see what we could come up with a statement on and pass it around. It is a tentative report. You would see it again --

DR. MARKS: Right, that's -- that the next thing.

DR. GILL: -- with the next version.

DR. HILL: And I strongly suspect most of what you need is probably in that write-up about the 2S albumin or in a couple of the cross-references, but I'm not sure. I think most of what you're looking for is probably in there. Figure out how to carve it out and convert it to something we would warn about.

DR. BERGFELD: I don't think all allergist are equal.

DR. MARKS: What's that last page?

DR. BERGFELD: So it would be --

DR. MARKS: (inaudible) on 28 --

DR. BERGFELD: -- be very careful of the selection of a consultant.

DR. MARKS: Yeah, it's said to be further down -- not the table. In -- was it the discussion?

Yeah.

DR. GILL: Page 33.

DR. MARKS: Thirty-three, okay. Okay, so I'm going to -- hmm. So tomorrow I'm going to presumably second a tentative report with the conclusion 12 -- that the 12 ingredients are -- all 12 ingredients are safe and the -- we are going to expand upon the issue of type 1 allergy to sunflower-derived ingredients. Specifically, the 2S albumin. And that will be pending, I think. We can still move forward with a tentative report with a conclusion as safe. And we can always go retract that if there're concerns. Does that sound reasonable? I'm sure we'll have a robust discussion tomorrow. And we're removing the ozonized seed oil. Okay.

DR. BERGFELD: Do you guys need a break?

DR. MARKS: Yeah. You guys need a break?

RESPONSE: Yes. Okay, we will re-adjourn at 10:30. It's 10:19 now.

(Recess)

DR. BERGFELD: "Re-adjourn?"

DR. MARKS: "Re-adjourn"? 10:36? So, we restart. We're --

SPEAKER: We will land at whatever gauge, you know. We have to go through wind chill three, four times.

SPEAKER: Twice a week?

Dr. Belsito's Team

DR. SYNDER: So we have the sunflowers.

DR. BELSITO: Then again Kurt wants to remind this is the state flower of Kansas and we need to be kind to it. So at the December meeting we issued an insufficient data announcement for the thirteen ingredients in the report, the highest concentration 10 percent rinse off, 4 percent leave on, we discussed the lack of clarity about the composition, the extracts of a whole plants, leaves, stem and sprout. We discussed the reports that indicated hypersensitivity reactions with constituents of flower and seed cake, specifically and here is where I had real difficulty in this report because we are talking about allergy and it is important that we differentiate the two different types of allergy we are talking about. IGE mediated which really concerns us because you don't want someone dying from a cosmetic product versus contact delayed type hypersensitivity and throughout the report I went back in and said IGE mediated and delayed type hypersensitivity (allergic contact dermatitis) so it was quite clear what kind of hypersensitivity we are talking about here. So that is just an aside.

We did get data on this in Wave 2, and let's take a look.

DR. SNYDER: We got sensitization data, we got method manufacturing data, and we got composition data.

DR. BELSITO: Right. So the first issue, I think before we go on, is I thought, who was the writer for those? Okay. I thought we made it clear we wanted the ozonized sunflower seed oil removed from this report.

MS. BECKER: Well, we went back to the transcripts and the audio when we did the final statement of the motion it was not included so we couldn't include it.

DR. BELSITO: Okay, so do we want the ozonized sunflower seed oil, which has no reported uses, no concentrations given, removed?

DR. LIEBLER: Yes. I read through the transcript and I noticed it just got lost in the sauce of the discussion there. I think Jim Marks reported on this.

MS. BECKER: Correct.

DR. LIEBLER: And their motion was to take out the ozonized oil, which I'm fine with taking it out, and then we got on to other subjects and then when we restated the list of things that somehow got left off of things to be excluded. But I agree that we can exclude that.

DR. BELSITO: As we move on one of the things that we had asked for was an HRIPT MI hydrogenated seed extract and we have HRIPTs but not any of the hydrogenated seed extract.

DR. SNYDER: Seed.

MS. BECKER: It was determined that there was a misstatement by Dr. Marks and he actually did need the seed extracts. So we're good.

DR. BELSITO: Okay. So, I thought overall the seed ingredients were safe with a caveat on the flower and seed cape and patients with potential sunflower seed allergy and I didn't know if we wanted to use the same type of language that we used in the wheat report about people who no known IGE mediated sun sensitivity to wheat and for the full extract leaf, stem and the sprouts the data was still insufficient for composition depending upon that other data and points that we needed. That's all I have here.

DR. LIEBLER: I agree. We're still insufficient on leaf, stem and sprout. I did have a question about whether the first two ingredients, the sunflower extract and flower extract, are actually the same thing? They have two different names.

DR. BELSITO: No, I think that the sunflower extract is the whole plant.

DR. LIEBLER: Yes. But again, it's always context. I don't know if it is sufficiently defined as whole plant that should be something that we know and can refer to but if it's not whole plant it might just be the sunflower extract in which case it is the same as the flower extract and then we are a little redundant in the name. I would like to know if it is possible to know that.

DR. BELSITO: What does the dictionary define sunflower extract as?

DR. LIEBLER: I think Carol has a statement and I don't seem to have a copy of it right here.

MS. BECKER: The definition as in Table 1 is the definition in the dictionary. All the distinctions are from that.

DR. LIEBLER: Take another quick look at Table 1 then. Oh, it says definition is of the whole plant. Okay, never mind.

DR. BELSITO: Good?

DR. LIEBLER: Yes.

DR. BELSITO: What is exactly is meant by sprout? Is that like when it first comes out of the ground and they harvest it and do something? What is the sunflower sprout?

MS. BECKER: When you talk about it in food it's sprouted in water or nutrient water and as soon as you've got the first two leaves come up it is considered sprouted.

DR. BELSITO: Right, so it's a very juvenile plant?

MS. BECKER: Yes.

DR. BOYER: Like the bean sprouts.

DR. BELSITO: I know.

DR. LIEBLER: On a salad it's a sprout.

DR. BELSITO: Yes, I guess.

DR. SNYDER: So we're insufficient for four? Leaf stem extract, the seed sprout, the seed extract, the seed and the hydrogenated seed extract. Is that right?

DR. BELSITO: The seed ingredients are safe.

DR. SNYDER: All the seed ingredients.

DR. BELSITO: So we are insufficient for the full extract, the leaf, the stem and the sprouts? So, whole plant, the leaf, the stem and the sprouts are insufficient?

We are removing the ozonized sunflower seed oil and then the discussion about the different types of sensitivity is important. The only issue I had, and I don't know enough about this, is when you look at a figure where they have, on PDF page 27, where they have the production of the Helianthus seeds. So they do solvent extraction and they remove the solvent and then they have enzymatic or chemical treatment. The question I have is would that not destroy the 2S proteins that are thought to cause the issues with mediate hypersensitivity? If you are enzymatically treating them? But I don't know, I guess it depends upon what type of enzyme you are using, right?

DR. LIEBLER: It does.

DR. BELSITO: So then do these 2S proteins even become an issue for cosmetic ingredients?

DR. LIEBLER: It depends. An enzymatic chemical treatment is unfortunately vague. What we know is that these (inaudible) proteins are really stable.

DR. BELSITO: Okay.

DR. LIEBLER: That is one of the points raised in the report, they are very stable.

DR. BOYER: One of the issues for ingesting these proteins and allergies is they are very, very stable. They can be absorbed through the gastrointestinal tract.

DR. LIEBLER: So they are a combination of stability and relatively small size for proteins.

DR. BELSITO: So the manufacturing doesn't help us, we still need to have that in the discussion and I would suggest it be among the same lines as we dealt with wheat.

DR. SNYDER: Under the impurity section it is the third paragraph.

DR. BELSITO: Okay. Any idea what?

DR. LIEBLER: PDF 26, bottom of the page.

DR. BELSITO: Aflatoxins?

DR. SNYDER: No, it's the third paragraph where it says further analysis shows allergens are less than parts per (inaudible) did they say what specific allergens they tested for? It just says allergens.

MS. BECKER: That is unpublished data submitted by the Counsel so they probably did not.

DR. BELSITO: Again, allergens could be the succaterrmium bactim, could be the (inaudible) proteins. You need to be very careful in this report to always specify what type of allergy you are looking at.

DR. SNYDER: Because if that data was done before they knew about the 2S we can't assume there was no allergen.

MS. BECKER: That would have been new data since the meeting because it's got the bars on either side.

DR. BELSITO: I understand.

MS. BECKER: I'm trying to find the source.

DR. LIEBLER: It must clarify as to the nature of the allergens. That shouldn't be repeated here in this report.

DR. SNYDER: But we can't take it in any other --

DR. LIEBLER: Because all-inclusive it can be misinterpreted in the context.

DR. BELSITO: So we are definitely removing the ozonized. The seed ingredients are safe with the caveats and the full extract leaves, stem and sprouts are insufficient for composition at this point depending upon composition and perhaps other data.

DR. SNYDER: Solubility. Where they are absorbed or not.

DR. ANSELL: So we are putting sprouts in with the insufficient?

DR. BELSITO: Yeah, basically. Why?

DR. ANSELL: I thought we agreed they were baby plants.

DR. BELSITO: Some babies are pretty toxic.

DR. ANSELL: Oh, okay.

DR. LIEBLER: We'll see if they have sunflower sprouts at lunch today.

DR. ANSWELL: We'll see who actually takes some of them. (Laughter)

DR. LIEBLER: You first Jay.

DR. BELSITO: Speaking of lunch, it's 12:06. It's time to break.

(Recess)

Day Two

DR. BERGFELD: So we are moving forward then. Now the next group of reports are those advancing to the next level and the next set is first hit off by Dr. Belsito, sunflower.

DR. BELSITO: Okay, so this is helianthus annuus and Curt wants to remind us this is the state flower of Kansas which is hurting economically because of the price of oil and other things I guess. I don't know, the governor or whatever. Anyway, the December 2015 meeting, the Panel issued an insufficient data announcement for the 13 ingredients in this report.

The highest reported maximum concentration has 10 percent rinse off, four percent leave on. We discussed really the lack of clarity about the composition of the extracts of the whole plant, the leaf, the stem and the sprout. We discussed reports that indicated the potential for hypersensitivity reactions associated with constituents of the flower and seed cake and in this report, one of the things that we pointed out in editing is there were two types of hypersensitivity here. There are cespurpurian [sesquiterpene?] lactones that cause delayed type T-cell mediated hypersensitivity and then there are S2 proteins that cause the immediate type of hypersensitivity IGE mediated that can cause anaphylaxis so we are looking at two very different types of hypersensitivity here than we normally would look at in a cosmetic product and that needs to be made clear throughout the context of this report as to what kind of hypersensitivity we are talking about and we did extensive editorial work there so anyway, the data that we requested was an HRIPT on the sunflower seed extract at one percent or greater method of manufacture, clarification of the source of the material, will plant with or without bark, the helianthus sunflower extract composition data.

Additional information on the 2S albumen fraction of the sunflower seed, that's the fraction that is thought to cause the type one IG mediated hypersensitivity. So with all of those data requests, we thought that we had largely got them -- there was a ripple to it, not a wave to it. It was a rather small amount this time, certainly not a tsunami and we were okay, I believe. Why can't I find it?

The seed ingredients, all of the seed ingredients were safe with a caveat on the flower and seed cake and potential sunflower seed allergies, similar to what we have done with the wheat ingredient and for the full extract, the leaf the stem and the sprouts, it was still in sufficient [insufficient] for all of the information we had originally requested. Oh and the ozonide [ozonized] was going out, yes.

DR. BERGFELD: And that's a motion? Can you restate the motion?

DR. BELSITO: So all of the various seed ingredients are safe with a caveat on the flower [flour?] and seed cake as potential source of allergy and that would be similar to what we did with wheat and for the full extract, the leaf, the stem and the sprouts are insufficient so flower and seed cake, okay, the others are insufficient.

MS. BECKER: Because we have homonyms here, specify flour and flower because we have flour powder and we have flower of the plant in the ingredients. I just want to make sure we are clear on which one we are talking about.

DR. BELSITO: We are talking about all the components of the flower so I don't understand --

MS. BECKER: Well we have --

DR. BELSITO: F-L-O-W-E-R.

MS. BECKER: We have F-L-O-U-R and F-L-O-W-E-R so it's --

DR. BELSITO: We have both the flower and flour that is extracted from the seed so the components of the flower, F- L-O-W-E-R and the components of the seed are okay but the full extract, the stem, the sprouts are insufficient.

DR. BERGFELD: Does the Marks team want to comment or second?

DR. MARKS: Yeah, we had a little different conclusion, actually, a significantly different conclusion. We thought we could go safer. All 12, we agreed with removing those in ozonized seed oil. We had difficulty, and we will come back to working out. Obviously there is a tentative report so we can go out with the insufficient and then see what we can get and then look at that more. We just felt that we could probably go -- not probably, we could go with safe with the data we have now.

We had difficulty with the 2S albumen type I allergy to sunflower, just what you were talking about there, Don, and so I was interested in hearing how your team would deal with that issue. We actually wanted to consult an allergist and get a better sense of what this is about because it talks about this

allergy being frequent, although I don't think it is frequent from cosmetic exposure but you would deal with the same way as the wheat protein and the soap, that if it's a molecular weight of such and such, then you wouldn't be concerned about it bindingly.

DR. BELSITO: No, this is different. This is a 2S protein so this is slightly different but we had the similar situation with not the hydrolyzed wheat, which is where we put the restriction on molecular weight but when we did wheat protein, you need to look at that document as to how we dealt with it.

A note that individuals who are allergic to wheat, they want to avoid this product; I forget exactly how that was but there was a cautionary statement on the product but quite honestly, you know, comparatively speaking, to peanuts and soy and seafood, this is not an allergy that I see patients reporting often on my medical questionnaires.

DR. MARKS: Yes, I agree. When you read though, in the text, it says "frequent" so we maybe need to change that and actually in our consultation, my team, we are going to second your motion since this is a tentative report and then we can sort out the insufficiencies just to let you know that we thought we were okay at this point with all of them removing the ozonized seed oil but we'll second your motion.

DR. LIEBLER: Can I ask a question, how did you get comfortable with the whole plant -- the method of manufacturing impurities for the whole plant, the sprout and the lead stem. Was there something we missed or did you -- because I thought that was just plain not there. Anything with the flower and seed stuff were good but we have lots of method of manufacturing impurities. There are a couple of descriptions of the bark extract but I wasn't sure if that really is an adequate surrogate for whole plant. It was even a revelation to me that sunflowers had bark. I guess you would need it if you are living in Kansas.

DR. KLASSEN: Or at least tough skin.

DR. LIEBLER: Anyway, I don't know if I missed something, we can come back to that later.

DR. MARKS: Dan, I suspect not. I suspect you are focused on method of manufacture with this meeting and our bar is a lot lower than yours.

DR. BERGFELD: Ron Hill, do you wish to comment?

DR. HILL: Yeah, I think our discussion in September was along the lines of we had constituents concern characterizations but yet I don't like the absence of data so it sure would be nice to see more.

DR. BERGFELD: So the motion is on the table?

DR. HILL: The other thing I wanted to point out is to make sure is I don't think we want to put the molecular weight restriction. We're not, right? We weren't proposing to do that because we have actually in the way of two memos, there was an incorrect statement that said. 4 percent of the proteins were greater than 2,000 but that's not correct if you look at the data. We had. 7 percent 2,000 to 3,500 and. 4 percent between 3,500 and 10,000 so that would be in a problematic molecular weight range if we had the situation like we did with hydrolyzed wheat but that's not what's going on here so we don't have that situation best I can tell because the problem there came from doing the hydrolysis under conditions that changed up the amino acids so anyway, I just want to make sure, because the writers are here, that we didn't go overboard on the molecular weight thing. I don't think we have a problem with --

DR. BELSITO: The IG mediated is not due to molecular weight; it's the 2S.

DR. HILL: Yeah in this case it's the 2S and some of that can fall on that molecular weight range so that's the point.

DR. BERGFELD: Mike?

MR. BEST: Thank you. So just one other piece that we talked about on our team yesterday that I was curious where we are standing at is while there may not be a high instance of allergic reactions to sunflower in and of itself, there was some discussion on how other nut allergies could be activated by this albumen in the sunflower and that maybe a warning label was appropriate and that had been discussed and I just wasn't sure where we were on that because I hadn't heard either term.

DR. BELSITO: Other nut allergies also were mediated by reactions to 2S protein. I don't know that they can be activated. I mean --

DR. BERGFELD: A cross reaction --

DR. BELSITO: Right.

MR. BEST: I am certainly not an expert; that came up yesterday when we were discussing it, when Ivan was talking about this issue.

DR. BELSITO: Do you want to clarify what you said, Ivan?

MR. BEST: Sorry to put you on the spot.

DR. BOYER: Actually the potential for cross reactivity is not great with this particular group of proteins from the various seeds and nuts. What we did try to emphasize yesterday is that people who are allergic to many different proteins and other allergens and people who are exposed to sunflower pollen and so forth because it can be difficult to separate the pollen from the seed and so on, they would be at greater risk. That was, I think the main point.

MR. BEST: Okay thanks and in some previous conversation you indicated about maybe a warning label being appropriate because of that and --

DR. BOYER: The warning would be for that at great risk population.

MR. BEST: Okay, great.

DR. BOYER: Primarily.

MR. BEST: Thank you. I just wanted to know where we stood on that because I had heard it mentioned, that's all.

DR. BERGFELD: I think I heard that Don was addressing that by citing the wheat protein.

MR. BEST: Okay, thank you, I didn't understand that.

DR. BERGFELD: Can you restate your motion that we are going to ask people to vote on? Because you had two were sufficient and the rest insufficient.

DR. BELSITO: Yeah, so all of the components of the seed, everything that is derived from the seed and everything that is derived from the flower, F-L-O-W-E-R are safe as used. All of the other components of the plant, including the whole plant are insufficient for all of the data that we originally requested.

DR. BERGFELD: Thank you. Any other discussion otherwise I'll call the question. All those in favor of this conclusion, raise your hands. Thank you, unanimous.

(Motion passed unanimously)

DR. BERGFELD: Good discussion, thank you.

**Transcripts – *Helianthus annuus* (Sunflower)-Derived Ingredients
December, 2015**

Dr. Marks' Team

DR. MARKS: ...This is the safety assessment of *Helianthus annuus* or sunflower ingredients. This is our first review, and so the first thing would be are the 13 ingredients in this review as presented okay? I particularly want to ask Ron and Ron and Tom, would you included the ozonai [ozonized] seed oil also in this? And then what needs do we have? So I will open it to Ron, Ron, and Tom.

DR. SHANK: (Inaudible) wave 2; right?

DR. HILL: A good bit of wave 2 on this one, too.

MS. BECKER: Yes.

DR. SLAGA: No.

DR. MARKS: I don't know. (Inaudible).

DR. HILL: Yeah, we did. Wave 2 starting page 42.

DR. SLAGA: Okay.

DR. MARKS: Let's see.

DR. HILL: Which I just closed.

DR. MARKS: Wave 2. I have in wave 2 some HRIPTs and a study with the ozonized oil, sunflower oil. But --

DR. SHANK: Okay. Well, with wave 2, we got sensitization data on the whole plant extract. If we can use that to cover flower extract, leaf stem extract, and sprout extract, that should be safe as used.

DR. MARKS: I -- so what I -- the first question I had is what is the extract, and Lillian, maybe you can help me with that because is it from the bark or is it from the whole plant? And on page 11, it implies it's from the bark, and page 16, it applies that it's the plant. So I want to know what is the extract, and if it's the whole plant, then we would use that -- we would use the reasoning that Ron Shank suggested. However, the hydrogenated seed extract is used at 1 percent, and what we have of the HRIPT is 0.05 percent. So I would like to see an HRIPT at a much higher concentration.

So let's get back first to the extract because I -- I didn't actually know what it was.

MS. BECKER: They are two different material safety data sheets that gave that information from the same company. One said bark and one said whole plant. I would assume they're two different versions of the same thing, but being one a subpart of the other, so as long as the one of the whole plant is okay with using the bark should be okay because it's the part.

DR. MARKS: Yes.

MS. BECKER: Although technically, sunflowers don't have bark, but it is a Chinese company and I imagine there's a translation issue.

DR. HILL: Well, we need to get that resolved so we know what we're really dealing with.

MS. BECKER: I just envision they're just peeling off the top layer and using that, which would be a subset of taking the whole plant, chewing it up, and soaking it in whatever.

DR. HILL: The top layer of the stem?

MS. BECKER: Yeah, I mean, that's what I envisioned was that if they were just doing the outside, there must be something special about it and they'll pulling that off. But it would be part of the other. I know.

DR. MARKS: So it sounds like we're going to clarify what the bark is for the next rendition of the report. I don't know if that can be clarified other than in the discussion we assume that the extract refers to an extract of the whole plant.

Now, can -- so I don't know that we'll move on to the conclusion in a minute.

I also, the hydrogenated seed extract is used at 1 percent. There are 380 uses, so it has

a lot of uses, and I didn't see an HRIPT with that. We have one with the seed wax at 4 percent, and that was fine. It wasn't a sensitizer. I'm not sure we can say the seed extract. It seems to me a wax would be a subset of the extract. So going into the next, I'd like to find out what the HRIPT for the hydrogenated seed extract is at 1 percent. Other HRIPTs were small concentrations, like I said, with the extract.05, and with the seed cake it was.4 percent. Now, those, the HRIPTs, it wasn't an issue of sensitivity. It's just could I compare that with the seed extract and feel comfortable that the seed extract is a nonsensitizer at 1 percent.

So my way I would move is that we put an insufficient data notice. The needs are to clarify what the extract is and see if we can't get an HRIPT of the hydrogenated seed extract at 1 percent. That was the way I was leaning. Ron, Ron, and Tom, you didn't have any data needs otherwise?

DR. HILL: Wait a minute. I'm getting there. Hang on. I'm sorry.

DR. MARKS: Any ozonized seed oil? That's fine. You know, it's interesting because we have seed oil in another report.

SPEAKER: It was safe.

DR. MARKS: It was safe. So I was wondering, you know, which is fine. I didn't include it here. I just -- I guess I don't know why it wasn't in the other report. Was it because it was ozonized and just not included in that since it was an oil report?

MS. BECKER: We have our oils expert just came in. Did we include any ozonized oils?

DR. BURNETT: We did not at the time.

MS. BECKER: Okay. And then --

DR. BURNETT: The Panel did not feel comfortable with it.

DR. MARKS: Oh, didn't feel comfortable with it. Hmm.

MS. BECKER: There are several ozonized. I checked, so we can include it here or you can (inaudible) their own report.

DR. ANSELL: There is also safety data on the ozonized material.

DR. HILL: So what do we have about how they actually do that and what actually results though?

DR. MARKS: Let me see. I thought wave 2 had some of that in there.

DR. HILL: That's what I'm trying to remember because I --

DR. MARKS: Bubbling ozone gas in the water bath at room temperature until solidified. Do you see that in wave 2, Ron?

DR. HILL: I'm looking. I'm not finding it.

DR. MARKS: It's at the bottom of the first page in a memo.

DR. SHANK: I haven't been able to find wave 2.

DR. MARKS: There you go.

SPEAKER: Bubbling ozone gas. It's page 44 (inaudible).

DR. MARKS: You have to go on the Internet to find it.

SPEAKER: Page 44.

DR. HILL: Yeah, that left some -- that left some loose ends. So what I was trying to figure out is whether they're actually carrying out ozonolysis or partial ozonolysis of the double bonds and those unsaturated fatty acids, or putting hydroxyl groups in here and there, so it's not clear to me what they're making. So we do have data. What data do we have? HRIPTs.

DR. MARKS: No, we don't have -- we don't have any data on the (inaudible). Yeah, that's right.

DR. HILL: I'm looking to see what --

DR. MARKS: Human dermal irritation but not -- and that's not used, so you're not going to find much data on the ozonized sunflower seed oil if it's not being used.

DR. HILL: Okay, it is not? Do we know that?

DR. MARKS: My notes are it's not being used. But Lillian, would you confirm that?

MS. BECKER: No. It is not -- there is no record of it being used.

DR. HILL: Okay. In which case --

DR. MARKS: I guess always in the conclusion, if not being used, we expect it will conform with the other ingredients.

MS. BECKER: Correct.

DR. MARKS: So I think that would address any tox issues.

DR. HILL: No. No, I don't think -- not knowing exactly what goes on there, I don't think we read across the natural oil to whatever happens with the ozonized without having some better idea and some data to back it up, in my humble opinion.

DR. MARKS: So would you like it in this report?

DR. HILL: Because if you do ozonolysis of double bonds, you generate aldehydes and that raises all kinds of consequences.

DR. MARKS: Would you want to -- it's not being used. Would you want to just delete it from this report?

DR. HILL: I would think that that's a reasonable course of action.

DR. MARKS: Tom? Ron?

DR. SLAGA: If we can do it, that would be good.

MS. BECKER: You may say it doesn't belong here. Yes.

DR. SLAGA: We can"

DR. SHANK: Either take it out of the report or say it's insufficient data.

DR. HILL: I mean, I'm good either way, but if we keep it in, I think it ought to be insufficient.

DR. MARKS: Well, why don't we make the -- I think we've come to a final conclusion. This one we're never going to resolve as insufficient, so just remove it. What's your feeling, Jay? You're nonverbally communicating.

DR. HILL: I was purposefully not looking over there at that juncture.

DR. ANSELL: I have an issue with the formation of families, that if the other material in here which is so different than everything else, that none of the data is relevant, then it should not be in the same family. We can have multiple families in a report, but you know, this is the type of thing which suggests that the ozonides are unique -- so unique that they should not be included in the family of oils.

DR. MARKS: Okay. So tomorrow I'm going to move that we issue an insufficient data notice. The needs are clarify what the extract is of what. We assume the whole plant but let's clarify that. HRIPT of the hydrogenated seed extract, let's see how the Belsito team reacts to that at 1 percent, and remove the ozonized seed oil from the report.

DR. HILL: I also wanted to compliment this particular writer. The very last sentence of the introduction says, "When we are referring to the plant from which these ingredients are derived, standard scientific practice whereas were written, we'll write them" -- let's see -- "if they are an ingredient without italics and without abbreviations." I love that because it makes it much more clear as you're going through what we're actually talking about. I know it's hard for the writers who are -- I would say anal retentive about such things, but yet in terms of actually reading and knowing what we're dealing with, it's wonderful.

DR. MARKS: Okay. Any other comments?

DR. SHANK: Nope.

DR. MARKS: Okay. Apple.

MS. BECKER: Just to make sure, are we just insufficient for the hydrolyzed seed oil?

DR. MARKS: Yes.

MS. BECKER: And everything else is --

DR. MARKS: Yeah, the others were fine. There were a lot of the extracts, seed extract, seed cakes, seed wax were okay from an irritation and sensitization. Really, that was the main thing with

this.

MS. BECKER: Right. Right.

DR. MARKS: Is what's the irritation sensitization.

MS. BECKER: So safe, no qualifications.

DR. MARKS: So I felt they were fine. The whole plant, we need to clarify what that is.

DR. HILL: You know, my initial take on this is why are we mixing leaf and stem and sprout with seed stuff, but then I couldn't come up with a good enough justification to split it.

DR. SLAGA: Well (inaudible) in a few reports.

DR. MARKS: Yeah, I think it's because in contrast to citrus where we have a huge number of ingredients, this one is a small number.

DR. HILL: That was the conclusion I eventually came to.

DR. MARKS: Yeah. So yes, Lillian, the answer is we'll see what the needs are after our meeting tomorrow, but from my vantage point, I'd like to see an HRIPT for the hydrogenated seed oil extract at 1 percent since it has so many uses and that concentration is not replicated by the extract, whatever the extract is.

DR. BECKER: Okay. Thank you.

DR. MARKS: You're welcome. Okay.

Dr. Belsito's Team

DR. BELSITO: ...Okaydoke, so last one, wow. Okay, sunflower. We end with a botanical. This is helianthus annuus. So the good news here at least is we're dealing largely with seed, but then there are a few things like sunflower extract, leaf stem extract, sprout extract that may or may not be different, and we don't have data on anything other than the seeds.

The only thing we have other than seed data is an HRIPT on an extract, so I guess I was fine with all the seed-derived ingredients although I know that we've had issues in the past about some concerns when we hydrogenated and hydrolyzed and ozonized stuff, and there's hydrogenated sunflower seed extract, hydrolyzed sunflower seed wax and ozonized sunflower seed oil and didn't know how you guys felt about those, and also as a matter of point about the sprout, leaf stem, and whole extract, flower extract, and extract.

DR. LIEBLER: So I didn't really know what the sunflower extract was.

DR. BELSITO: It says extract of sunflowers, right, if I remember.

DR. HELDRETH: Extract of the whole thing?

DR. BELSITO: Extract of the whole plant, yes.

DR. HELDRETH: The whole plant.

DR. BELSITO: Including the roots.

DR. LIEBLER: God, I wish people wouldn't do that.

(Laughter)

SPEAKER: (Inaudible).

DR. LIEBLER: I know. Well, that's the thing. In light of the citrus discussion we had, I don't even know if that's really real or if that's really sunflower -- just the flowers extract.

DR. BELSITO: Well, it seems like most of the sunflower they use are the seeds.

DR. LIEBLER: Right.

DR. BELSITO: So when you -- and they have a good method of manufacture for the seeds and how everything gets divided up, and we have a -- I think all of the seed components, unless you have a problem with ozonized seed, are -- I'm happy with.

It's the whole plant, the leaf, the stem, the flower, and then when you go in and -- we don't have any information on the ingredients. We've got physical forms, but we don't know what's in them. We've got crude protein fat, fiber, but it's the oil content in the seed we have the fatty acid components. Again, seeds for the phytosterols, vitamins in the seeds, amino acid in seed flower. I mean

everything we have is really based on the seed, and yet there are 91 reported uses of sunflower extract, and no reported uses of flower -- well, 5 reported uses of flower extract and that's it. Otherwise the leaf stem has no reported uses, so with the exception of the whole plant extract and the flower extract, everything else is a seed use and I'm fine with that, but I don't know what's in the flower, what's in the stem, what's in the leaf.

DR. LIEBLER: Right, so I'm in the same place as you are. All the seed related ingredients I think we're fine with. I'm fine with -- I'm also fine with the ozonized sunflower seed oil because they do have that study, the topical application study on humans and no adverse reactions, and -- but the sunflower extract does not specify what it entails. The flower extract and leaf stem, we don't really have anything on, or the sprout for that matter. We don't have anything on those, so I'm inclined to say we're insufficient on those.

DR. BELSITO: That was my conclusion. All of the seed- derived ingredients are safe as used. All of the other components are insufficient based upon composition, and depending upon composition other toxicity end-points may be needed is what I phrased.

MS. BECKER: Dr. Belsito, just want to make sure you saw the HRIPTs in Wave 2.

DR. BELSITO: Yes, but we have an HRIPT for the whole extract.

DR. BECKER: Right.

DR. BELSITO: Right, so that gives us sensitization data, and that was clean. But --

DR. LIEBLER: The.05 -- was the use.

DR. BELSITO: Right, but it doesn't necessarily mean -- I don't know if there's anything toxic in the whole plant that you wouldn't pick up in a sensitization study. We don't know what's in there. I mean, that's the only other bit of information we have is Wave 2. We have sensitization and irritation for the whole plant extract. I don't know. Does that give you any comfort, Dan? It didn't for me.

DR. LIEBLER: No.

DR. BELSITO: Okay, so we're going to go sufficient for all the seeds, insufficient for the others. The insufficiency is we'd like to know what the others consist of and then depending upon that other toxicologic end-points may be needed.

MS. BECKER: Okay.

DR. KLAASSEN: I guess some seeds are grass [GRAS]?

DR. BELSITO: No, they're seeds. Yes, they are grass[GRAS].

DR. KLAASSEN: It doesn't say that in here, does it?

DR. BELSITO: I don't remember.

DR. KLAASSEN: I don't remember seeing it.

DR. BECKER: I don't think they're in there as grass[GRAS], but they're in there as a historic food, and the plants as historic feed.

DR. KLAASSEN: I thought historic food kind of automatically became grass[GRAS]. Now, you have to realize that the sunflower is the flower of the State of Kansas, so you've got to be careful there.

DR. LIEBLER: So that's what they've been chewing on.

(Laughter)

DR. BELSITO: I don't know.

DR. LIEBLER: Smoking that stuff too? (Laughter)

DR. BELSITO: Colorado made a new state flower. Now all the Kansans are moving over there. Okay, so, anything else? We are done.

MS. BECKER: I have a question. Is there any comment on Table 14 with --

DR. BELSITO: Table 14, PDF?

MS. BECKER: PDF 21.

DR. LIEBLER: Case reports of children and adults.

DR. BELSITO: Case reports -- I mean -- I see you had some individuals who had an

IGE-mediated reaction to sunflower seed, but --

DR. SNYDER: Most of them have tree and seed allergies.

DR. BELSITO: Mm-hmm.

DR. SNYDER: Which is pretty common.

DR. BERGFELD: It goes to show you if you eat one seed and are allergic to it, you shouldn't eat another, huh? (Laughter) Must be some common components.

DR. BELSITO: I mean how did we deal with -- well, first of all, I think we can go back to things like the wheat and oat and other things where you have IGE-mediated allergies, and then the real issue would come down to the hydrolyzed products, right? And do we know the molecular weight range of the hydrolyzed product? We do not.

DR. EISENMANN: Flower might be the problem. I don't think it's used.

DR. SNYDER: Flower extract.

DR. EISENMANN: No, it's not even extract. It's flower [flour?], so ground up.

DR. SNYDER: What's wrong with it on the (inaudible)?

DR. EISENMANN: The seed flower [flour?].

DR. BELSITO: Because hydrolyzed seed would --

DR. EISENMANN: Make it smaller.

DR. BELSITO: -- would be --

DR. EISENMANN: Hydrolyzes seed wax, so that (inaudible).

DR. BELSITO: Right. That's going to mainly oils, yeah.

DR. EISENMANN: So you have seed cake and seed flower. I guess cake is what -- this is how the dictionary uses what's left over after the oil is removed.

DR. BELSITO: Right.

DR. EISENMANN: But we have HRIPT data on those (inaudible)?

DR. SNYDER: Yes, .405 percent.

DR. EISENMANN: That's all the higher that have been used.

DR. SNYDER: Yes.

DR. LIEBLER: So what the question? Keep Table 14? Exclude Table 14?

DR. BELSITO: No, but I guess how do we deal with the reports of type 1 hypersensitivity particularly in light of the fact that the seed cake has incidental inhalation 10?

DR. BERGFELD: Isn't that a discussion point that you can go in at those -- with known allergies? Looks like most of these had other responses to other allergens to be cautioned about.

DR. SNYDER: Was there (inaudible) Stand-alone? I thought they were all nut and seed.

DR. BELSITO: Confirmed peanut allergy.

DR. SNYDER: Yes, there's poppy seed, pumpkin seed.

DR. BELSITO: Good point, Lillian. I didn't really think of it. I saw it, but I --

DR. BERGFELD: You didn't think the case report showed other allergies? I thought there was a whole list of them.

DR. BELSITO: No, I -- sunflower seed. It's just not one of those things that you see very common as a food allergen.

DR. BERGFELD: Or recognize.

DR. BELSITO: No, I know, but when you think of food allergens, you know, I mean soy, nuts, berries, fish, but -- shellfish -- but they're clearly -- this is probably the world's body of literature on type-1 reactions to sunflower seeds, but it's there. I don't know.

DR. LIEBLER: I think we can handle it in the discussion, don't you?

DR. BELSITO: How? Since the seed cake is used in a product that could be aerosolized?

DR. BERGFELD: Well, I mean, if you have a person who is allergic and has known

allergies, they may be more commonly sensitized to a topical product containing a seed. I mean, multiple allergies, people have -- they cross over a little bit. Especially, a lot of these are not in --

DR. BELSITO: I understand that but --

DR. SNYDER: Yeah, but I think Don's point is the inhalation exposure. It could be life threatening as opposed to a --

DR. BELSITO: Right, as opposed to an itchy rash.

DR. BERGFELD: Yes.

MS. BECKER: And there are a couple case reports of dermal exposure; five on page 22.

DR. BERGFELD: I know there was only one anaphylaxis.

DR. LIEBLER: So you can't say something along the lines of individuals who have a history of allergic responses to nuts -- seeds and nuts should avoid using products that contain sunflower seed cake?

DR. BERGFELD: Be cautioned maybe.

DR. BELSITO: Well, I mean, you actually do see that, but I'm trying to think if it's -- they're only drugs because I know like there's a product called Derma Smooth and it's a prescription topical steroid that contains peanut oil, and it has a disclaimer on there even though it's oil and not protein, but it's not advised for people with peanut allergies, but I don't know if they have those kind of -- they don't have disclaimers like that on cosmetic products that I know of.

DR. KATZ: Not uniformly. In other countries they do. And this is something that we're looking at from the agency perspective because there are so many more allergic individuals than there were years ago, and there's cross sensitization which is known as in this case as you mentioned between nuts and the seeds themselves, so that people who have tree nuts probably shouldn't use the product because they may have a cross sensitization depending upon what kind of reaction they had. It could be something that you could consider to suggest that there might be necessity for a warning. Right now the agency doesn't require one, but that's not to say that in the future we might not.

DR. BOYER: Also I think the Panel has at least one conclusion in which they've said, for example, in this case it would be analogous to saying people who have known allergies to sunflower should avoid products that contain these ingredients. I don't remember exactly what ingredient or ingredient group that report was, but I'm pretty sure we have an example.

DR. SNYDER: We have data in here that suggests that it's a 2S albumen allergen in the report, so we could ask for a concentration (inaudible).

DR. BELSITO: How would that happen though?

DR. SNYDER: Well, you see if it's in there -- in the seed cake or the seed wax after it's been --

DR. BELSITO: So whether -- what the chemical composition of the seed flower and the seed cake is. Is that what you're asking for?

DR. SNYDER: That's what -- yeah, it says we have data on -- underneath the chemical (inaudible).

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

DR. SNYDER: It's the last paragraph of the constituents and components. It says the 2S albumen protein is present in other seeds and (inaudible).

DR. BELSITO: Page 9 PDF. It says electrophoresis showed that protein bands were similar among three helianthus seeds strain samples. There were three polypeptide groups of helianthine fraction detected. Of these two were acidic and one was basic. The molecular weight of the 28 albumen proteins ranged from da-da- da-da-da-da. They are rich in globulins, albumens. So, how does that help you, Paul? It doesn't really tell us anything specific, right?

DR. SNYDER: Well, then we -- it appears to be they've identified what the allergen is.

DR. BELSITO: Oh, where do you get that?

DR. SNYDER: The last paragraph -- of that section right above method of manufacture.

Helianthus annuus seeds have been found to contain an allergen 2S albumen.

DR. BELSITO: I'm not where you are.

DR. SNYDER: It's PDF 10.

DR. BELSITO: Okay, PDF 10.

DR. LIEBLER: So, Paul, are you saying this sets you up to say that the 2S albumen analogous to other allergenic albumens in other beans and seeds, the Panel noted that and --

DR. SNYDER: I think we need to know whether it's present in the seed cake and the seed wax.

DR. BELSITO: Not the wax. Flower [flour?].

DR. SNYDER: Flower [flour].

DR. BELSITO: So then, we're going sufficient for all of the seed ingredients except for the seed cake and seed flower [four?], and for those we want to know the potential IGE- mediated allergenicity or the composition of this 2S albumen. Is that right?

And then for all of the others we want to know method of manufacturing, impurities, and composition, and depending upon those, additional data may be needed. So, all the seed ingredients except cake and flower [flour?] are fine. Cake and flower, 2S albumen --

DR. SNYDER: Please excuse me. Cake and flower [flour] are the two that (inaudible)?

DR. BELSITO: Right.

DR. SNYDER: No others have inhalation?

DR. BELSITO: Well, the others we're not concerned about. They wouldn't contain protein. They're seed oils like wax, oil.

DR. BERGFELD: You have on page 10, I believe, the method of manufacturing. You want something else?

DR. BELSITO: That's for --

DR. BERGFELD: The oil, the flower, the protein, the meal.

DR. SNYDER: I guess what we really want is the protein composition.

DR. BERGFELD: Right.

DR. BELSITO: Well, how is the protein composition going to help you?

DR. SNYDER: To see if it has any protein or any other protein (inaudible) That's been associated with (inaudible). I wasn't aware of it. (inaudible).

DR. BELSITO: So are you asking for protein composition or specifically for 2S album? Or as Linda suggested can we just say cautionary statements should be labeled that this contains helianthus annuus seeds or put in parentheses sunflower; caution should be used in individuals with known allergies to sunflower?

DR. BERGFELD: To allergic individuals, right? I think you have to -- would be sunflower plus allergic individuals because your case report's allergic to other things, multiple.

DR. SNYDER: Not to seed allergies, but no (inaudible).

DR. BELSITO: Individuals with nut, seed allergies.

DR. SNYDER: If we've done it -- have we done it before -- that report?

DR. BERGFELD: Evidently.

DR. SNYDER: If we find out that wording before tomorrow --

DR. BOYER: We'll look it up.

DR. BELSITO: Okay, otherwise we're just going to ask for a little more information on the protein content, so we've got two possibilities. A cautionary statement on the label, in which case all the seed ingredients go through and the whole plant, stem, ya-da ya-da need method of manufacture, impurities, and composition, or if we can agree with a cautionary language for the statement we want more information on the seed cake and flower as to its content of 2S albumen and other proteins, right?

DR. SNYDER: Correct.

DR. BELSITO: Okay. Thank you. Now are we done?

DR. KLAASSEN: I have a question. If 2S protein is so important, how come we never ran into this on any of our other seed, et cetera? That's a pretty strong statement that short paragraph that we have there, you know, like it's really a well-known phenomenon, but we never heard about it before. Should that have been included in a lot of our other reports or is it being over-emphasized here? I guess --

DR. SNYDER: We also have -- I just noticed we also have a statement in the last paragraph of the summary in which it also says that seeds, possibly from inhalation of the pollen, from seeds and possibly inhalation of pollen from the flower.

DR. BELSITO: So where are you going with that, Paul?

DR. SNYDER: No, I'm just saying it's just. So we don't have a table like we did before with known allergens? In this report?

DR. BELSITO: Well, the known allergens table was the 26 fragrance ingredients that Europe required labeling. That's what we're seeing there.

DR. LIEBLER: So to Curt's point, the reference cited in that paragraph is this paper in the journal, allergy from 2000 says 2S methionine-rich protein SSA from sunflower seed is an IGE-binding protein, so it may be involved in IGE-mediated allergy. The statement that the 2S albumens from others are involved in IGE-mediated allergies is not supported by any citation in the text as it currently stands, right?

MS. BECKER: Say that part again. I'm sorry.

DR. LIEBLER: So, reference 37 is just about a sunflower seed; IGE-binding protein is 2S. The rest of the statement that Curt was referring to is a strong statement which I'm paging up to -- constituents of concern -- oh, come on. The statement on PDF page 10, in the last paragraph before method of manufacture, the first sentence is supported by reference 37; the one I just mentioned. That reference is just about that protein in sunflower seeds. The remaining sentence -- the next sentence -- 2S albumen proteins and other seeds such as rape seed, castor beans, et cetera have been associated with allergenicity. I don't know much about that. We haven't seen it. There's no citation, so maybe if we have that (inaudible).

MS. BECKER: That's all from 37. The entire paragraph's from 37.

DR. LIEBLER: So, 37 has to be citing other work, so that other work should be cited if we're going to talk about the role of that albumen -- that type -- those albumen proteins with those others. There may be a review that could be cited or there may be a couple of papers that could be cited. If we're going to bring that point out, we should cite it with an appropriate reference. Even though the authors of reference 27 mentioned it, I assume that they cited other work.

DR. KLAASSEN: I pulled it up on PubMed and the overall conclusion is what's written in our document, and it says here that sunflower seed contains 2S albumen and in other crops have been associated with allergenicity, and so there must -- if you read the introduction paper it must give you some references. The sunflower seed methionine-rich 2S albumen may be an IGE-binding protein responsible for anaphylactic reactions in some sunflower-seed sensitive subjects, and then they conclude that SSA is an IGE-binding protein and subjects allergic to sunflower seed is IGE binds to SSA are at risk of developing allergic reactions if they consume SSA. So I think that needs to be -- as just mentioned we need to get more information about what is known about these proteins and allergenicity in addition to what's known about sunflower. It's an interesting phenomenon that -- this paper was 10 years ago, 15 years ago, and all this other work with the other plants and nuts was known before that, and --

DR. BELSITO: Okay, so right now sufficient for all the seed ingredients except seed cake and flower [flour?] for which we need to dig further about the allergenicity of this 2S molecule or consider a cautionary statement on the label, and insufficient for all the other ingredients for method of manufacture, impurities, and composition, and depending upon those potentially other toxicity data. Fair?

DR. BERGFELD: Great.

DR. BELSITO: And unfortunately I can't -- I should be able to pull up that allergy article

because I think Columbia has access to it, but I don't have Internet access right now.

MS. BECKER: I do here.

DR. BELSITO: Actually what it says here, Curt, is that sunflower seed-allergic subjects have IGE-binding sights to different proteins including regents of the SSA; however, this 2S sunflower seed protein has not been characterized and now they characterize it as another binding site, so it's not just the 2S that binds IGE. There's this SSA site as well. And then in the discussion they say one of the limitations of the study is the lack of enough sunflower seed-sensitive subjects to determine more adequately whether SSA is the major allergen. So, it is a pretty rare allergy, but --

DR. SNYDER: Well, here's an article that says the 2S albumen is a major allergen (inaudible) Soybean-allergic children, 2013.

DR. BELSITO: What?

DR. SNYDER: There's a 2013 paper talking about that same protein being associated with soybean-allergic children, so the point is that if they're -- it's not just where they're allergic to sunflowers. If they have seed allergies then they're going to be --

DR. BELSITO: SSA you mean? Yeah. Yeah, so I mean that's all it -- all it says it doesn't really go into other -- at least I don't see it mentioning other -- in their introduction it talks about -- references 5 to 11. It says the nature of sunflower seed allergen -- it's not known because the seed contains 2S albumen proteins that other seeds such as rape seed, castor, cotton, Brazil, walnut, have been associated with allergenicity, and then they reference those references -- six references. So they didn't look at it. They just made reference of it and then specifically looked at this SSA 2S protein. And you're saying, Paul, that that was the protein responsible for allergy in soy and other --

DR. SNYDER: And there's another sunflower 2S albumen paper published in 2013, in food and chemical which has a lot of references, so I think we need to learn more about it.

DR. BELSITO: Okay, so either a cautionary statement or learn much more about sunflower seed protein allergy, okay? I think --

DR. KLAASSEN: I think, you know --

DR. BELSITO: -- we need to discuss it tomorrow.

DR. KLAASSEN: And we need to be cognizant of this whole phenomenon for future products -- natural products that we haven't been aware of previously.

DR. BELSITO: Okay. Any other comments?

DR. BERGFELD: I think in following this what we did with wheat was identifying the antigen, that this is very appropriate to do now.

DR. KLAASSEN: Okay.

DR. BELSITO: Anything else? So, Wilma, are you suggesting that we forgo the idea of a cautionary statement and say insufficient?

DR. BERGFELD: No, no. I'm just making an overview that we're in the process of trying to identify, you know --

DR. BELSITO: Wow, 4:36.

Day Two

DR. BERGFELD: ...Moving on to the next ingredient then, which is our sunflower-derived ingredients. And Dr. Marks, you're up.

DR. MARKS: This is the first review of these ingredients, a draft review, or I should say the ones presented in this report of *Helianthus annuus*, or sunflower, and there are 13 ingredients. The sunflower seed oils were reviewed in the vegetable oil report, so they are not included here.

After looking at what we have in this report, our team felt we should move with an insufficient data announcement. We wanted to clarify what actually was the sunflower extract. And page 11, it talks about the bark and we had the discussion as to whether sunflowers actually have bark or not.

And then on page 16, it indicated the whole plant was the extract, so we'd like that clarified.

I felt that we needed an HRIPT of the hydrogenated seed extract. That 1 percent, that's the highest use concentration. It has a lot of uses, 380.

And then we felt we should remove the ozonized seed oil from this report. We didn't feel that ingredient fit in with the rest of the ingredients.

So, again, I move for an insufficient data announcement with those points.

DR. BERGFELD: Dr. Belsito's team?

DR. BELSITO: Okay. Well, we, of course, had a slightly different take. First of all, we felt that all of the seed oil ingredients, seed and seed oil ingredients, were safe. We had a little bit of a pause with the flower and seedcake given the reports, although rare, of immediate hypersensitivity and, in that regard, looked back to our wheat report where we had the same issue with some immediate hypersensitivity. And in our discussion simply said the Panel recommends that people with known allergies to wheat proteins avoid using personal care products that contain these ingredients and maybe, incidentally, inhaled during use, and we felt that same type of language could be used to clear the flower and the seedcake. However, as with the Marks team, we felt that the data were insufficient for the extract of the whole plant, for the leaf, stem, and sprout. And for those, we needed composition, manufacturing impurities, and possibly depending upon these other toxicologic end points.

So basically, the seed ingredients, safe with a caveat on the flower and seedcake and potential sunflower seed allergy. And for the full extract, the leaf, stem, and the sprouts, insufficient.

And Curt would like to point out that this is the state flower of Kansas. (Laughter)

DR. BERGFELD: Marks team, any comment?

DR. MARKS: No, I guess since you have insufficient needs, also, it would be an insufficient data announcement rather than move forward with a tentative report.

DR. BERGFELD: And you had a motion?

DR. MARKS: Yes.

DR. BERGFELD: It was not seconded. We have to have another motion.

DR. BELSITO: I mean, you know, as Jim said, it's insufficient.

DR. BERGFELD: Right.

DR. BELSITO: This is the first time we're seeing it, so it's going to go out insufficient regardless of --

DR. BERGFELD: Right.

DR. BELSITO: -- whether we go with our request or Jim's request. So I'm fine with going out with asking for everything that the Marks team wants. I don't think we need it, but let's do it.

DR. BERGFELD: Okay. So you're seconding it?

DR. BELSITO: Sure. Well --

DR. BERGFELD: Well, you're seconding it.

DR. MARKS: And then you had some insufficients, too, Don, that you mentioned.

DR. BERGFELD: We'll insufficient.

DR. BELSITO: I think they were the same as yours basically.

DR. MARKS: Yeah.

DR. BELSITO: Composition, manufacturing impurities, and possibly more depending upon what we find for the leaf, stem, sprout, and whole plant extract.

DR. MARKS: Yeah.

DR. BERGFELD: And so we're going to call the question for an insufficient data announcement. All those in favor, please indicate by raising your hands. And we have recorded the needs. Everyone clear on those? Okay.

Safety Assessment of *Helianthus annuus* (Sunflower)-Derived Ingredients as Used in Cosmetics

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The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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ABSTRACT

This is a review of the scientific literature and unpublished data that are relevant for assessing the safety of 12 *Helianthus annuus* (sunflower)-derived ingredients as used in cosmetics. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid levels that may be hazardous to consumers. *Helianthus annuus* (sunflower)-derived ingredients may contain allergens, including 2S albumins and sesquiterpene lactones. Industry should use good manufacturing practices to limit impurities and constituents of concern. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded that nine *Helianthus annuus* (sunflower) seed- and flower-derived ingredients are safe as used in cosmetics in the present practices of use and concentration described in this safety assessment. The data are insufficient to evaluate the safety of three ingredients that are derived from other plant parts.

INTRODUCTION

This is a review of the scientific literature and unpublished data that are relevant for assessing the safety of *Helianthus annuus* (sunflower)-derived ingredients as used in cosmetics. According to the *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)*, the functions of these ingredients include skin-conditioning agent – miscellaneous, abrasive, and absorbent (Table 1).¹ The 12 ingredients in this safety assessment are:

Helianthus Annuus (Sunflower) Extract	Helianthus Annuus (Sunflower) Seed Butter
Helianthus Annuus (Sunflower) Flower Extract	Helianthus Annuus (Sunflower) Seedcake
Helianthus Annuus (Sunflower) Leaf/Stem Extract	Helianthus Annuus (Sunflower) Seed Flour
Helianthus Annuus (Sunflower) Sprout Extract	Helianthus Annuus (Sunflower) Seed Wax
Helianthus Annuus (Sunflower) Seed Extract	Hydrogenated Sunflower Seed Extract
Helianthus Annuus (Sunflower) Seed	Hydrolyzed Sunflower Seed Wax

The ingredients in this report are grouped together because they are extracts, waxes, or powders (flour) derived from plant parts of *Helianthus annuus*, commonly called the sunflower. Helianthus Annuus (Sunflower) Seed Oil, and other *Helianthus annuus* (sunflower)-derived seed oils, were included in the CIR safety assessment of plant-derived oils and are therefore not included in this review.²

In the safety assessment of plant-derived oils, the CIR Panel concluded that Helianthus Annuus (Sunflower) Seed Oil, Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables, Hydrogenated Sunflower Seed Oil, and Sunflower Seed Acid are safe as used.² The Panel has also reviewed the safety of phytosterols, plant-derived sterols that include Phytosteryl Sunflower Seedate, and concluded that they are also safe as used in cosmetics.³

The seeds of *Helianthus annuus* (sunflower), both raw and roasted, are consumed by humans on a regular basis. The rest of the plant, as well as the seeds, are fed to farm animals and pets. Because the rates of absorption and metabolism of these ingredients in the skin are expected to be negligible compared to the corresponding rates in the digestive tract, exposure from food use is expected to result in much greater systemic exposures than those from use in cosmetic products. Additionally, there are only a few reported cases of food allergies to the seeds and of inhalation allergies to the pollen.^{4,12} Although oral data may be included in this safety assessment, the primary focus is on the potential for irritation and sensitization from dermal and inhalation exposure, and the systemic toxicity potential of *Helianthus annuus* (sunflower)-derived ingredients via oral exposure is not addressed further in this report.

In this assessment, CIR is reviewing information available to evaluate the potential toxicity of each of the *Helianthus annuus* (sunflower)-derived ingredients as a whole, complex substance. Except for specific constituents of concern, CIR is not reviewing information that may be available to assess the potential toxicity of the individual constituents derived from *Helianthus annuus* (sunflower). Botanical cosmetic ingredients, such as *Helianthus annuus* (sunflower)-derived ingredients, contain hundreds of constituents, some of which have the potential to cause toxic effects. For example, sesquiterpene lactones may cause Type IV allergic reactions (cell-mediated, delayed-type hypersensitivity) and toxicity when present in sufficient amounts, and 2S albumins may cause Type I allergic reactions (IgE-mediated, immediate hypersensitivity).¹³⁻¹⁵ It is noted that *Helianthus annuus* (sunflower) is a member of the *Asteraceae* family; members of this family are well known to contain sensitizing constituents.^{6,10,15-17}

The ingredient names, according to the *Dictionary*, are written as listed above, capitalized without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the taxonomic practice of using italics will be followed (e.g., *Helianthus annuus*).

CHEMISTRY AND CHARACTERIZATION

Definition

The definitions and functions of the *Helianthus annuus* (sunflower)-derived cosmetic ingredients included in this report are provided in Table 1. In some cases, the definition provides insight on the method(s) of manufacture.

The ingredients in this report are related to each other by source, because each is a derivative of a part, or parts, of the *Helianthus annuus* (sunflower) plant. The identities and concentrations of the constituents of botanical ingredients typically vary widely from plant part to plant part, by extraction method, and many other factors. Although some information on the exact constituents and their concentrations can be found in the literature, the actual manufacture and characterization of these ingredients, and their use in cosmetic formulations are best determined from composition information provided by Industry.

Plant Identification

Helianthus annuus is an annual plant in the family *Asteraceae* (synonym *Compositae*), daisy or sunflower family, subfamily *Asteroideae*.¹⁸⁻²¹ The plant is a dicot ranging in height range from 0.7 to 3.5 m.²¹ *Helianthus annuus* (sunflower) leaves are rough, broad, coarsely toothed, and mostly alternate. What is often called the "flower" of the *Helianthus annuus* (sunflower) is actually a "flower head" called a pseudanthium or capitulum, which is made up of numerous small individual five-petaled flowers ("florets"). The outer flowers, which resemble petals, are called ray flowers. These ray flowers consist of a ligule composed of fused petals in an asymmetrical pattern. They are sexually sterile and may be yellow, red, orange, or other colors. The flowers in the center of the head are called disk flowers, and these are arranged spirally. If pollinated, usually by insects, the flowers mature into fruit (seeds). The taproot is strong, penetrates to a depth of 3 m, and has large lateral spread of surface roots. Wild *Helianthus annuus* (sunflower) is a widely branched annual plant with multiple flower heads that mature sequentially.

Helianthus annuus (sunflower) seeds are achenes (or fruits) each of which consists of a kernel (true seed) and a pericarp (hull); the pericarp is four-sided and flat.^{20,22} The seeds are approximately 0.6 cm long and 0.3 cm wide. *Helianthus annuus* (sunflower) oil seeds (seeds having high oleic acid content; oil content >40% and 35%-38% protein) usually have a black seed coat; seeds grown for consumption (oil content approximately 30%) usually have a hull that is dark brown or white. The kernel consists of an embryo, endosperm, and seed coat. The pericarp (maternal tissue) consists of several layers: cuticle (external layer), epidermis, hypodermis, phytomelanin layer, fibrose tissue, and parenchymal layers adjacent to the kernel.

The pseudanthium (flower head) may contain 1000–4000 florets, with the potential of as many seeds.²³ The average yield of seeds in a pseudanthium is 1200-1500.²² The average yield of seeds ranges from 900–1575 kg/ha; yields of over 3375 kg/ha have been reported.

Helianthus annuus (sunflower) is native to western North America.²¹ The plant was introduced to Europe and Russia in the 16th century and has spread to tropical and temperate countries, including Argentina, China, India, Turkey, and South Africa, as well as Russia and the combined European Union.²⁴ Hybridization and selective breeding has increased oil production. Breeding resulted in the development of strains with high oleic acid content, referred to as oil-seed.²⁵

Physical and Chemical Properties

Helianthus Annuus (Sunflower) Flower Extract is a solid powder, and Hydrolyzed Sunflower Seed Wax is a yellow or white wax (Table 2).²⁶

The color of *Helianthus Annuus* (Sunflower) Seed Flour changes with pH.²⁷ From pH 2-7, the color is cream white. At a pH of 8, it is grey; at pH of 9 it is yellowish grey, at pH of 10 it is light brown, and at pH of 10.5 it is dark brown.

Method of Manufacture

A scheme of the general manufacturing process of *Helianthus annuus* (sunflower) oil, flour/protein, and meal is depicted in Figure 1. A scheme of the method of manufacture for *Helianthus Annuus* (Sunflower) Seedcake is depicted in Figure 2. A scheme of the method of manufacture for *Helianthus Annuus* (Sunflower) Seed Wax is depicted in Figure 3.

Several methods of manufacture of *Helianthus Annuus* (Sunflower) Seed Extract have been reported. One supplier reported that *Helianthus Annuus* (Sunflower) Seed Extract is a methanolic extract of *Helianthus annuus* seeds, followed by filtration, purification, and drying.²⁸

Another supplier reported that *Helianthus Annuus* (Sunflower) Seed Extract is manufactured from the fresh or dry seed, which is extracted with a specified eluent under appropriate temperature conditions (not specified) to yield a concentrate.²⁹ The concentrate, containing phytochemical constituents, is then blended with a diluent and preservatives to produce the final product. Each batch is analyzed for compliance to specifications, contaminants, and physiochemical properties.

A third supplier reported that *Helianthus Annuus* (Sunflower) Seed Extract is manufactured by aqueous extraction of the *Helianthus Annuus* (Sunflower) Seedcake produced by the method depicted in Figure 2.³⁰ Soluble and insoluble phases are separated by filtration and then the extract is sterilized. The final product consists of water (97.25%-98.15%), *Helianthus Annuus* (Sunflower) Seed Extract (1.4%-2.2%), and preservatives (0.45%-0.55%).

Composition

Helianthus annuus Plants

The *Helianthus annuus* (sunflower) plant has a high amount of moisture at maturity.³¹ The composition of the *Helianthus annuus* (sunflower) plant (minus the pseudanthium) varies with maturity level (Table 3).

Helianthus annuus (sunflower) leaves are known to contain high levels of saponins, but they have not been quantified.³¹

The fatty acid profile of *Helianthus annuus* (sunflower) varies with selective breeding; a specific example is provided in Table 4.³¹ Overall, oleic acid (C18:1) may be present as low as 14% to 39.4% in wild/conventional (edible) plant seeds and as high as 75% to 90.7% in selectively bred plant (oil) seeds; palmitic acid (C16:0) may be present as low as 2.6% to 5.0% in high oleic acid oil seeds or as high as 5.0% to 7.6% in low oleic acid oil seeds. The phytosterols and tocopherols also vary with the oleic acid content in the seeds of wild and cultivated plants (Table 5).

The hulls are difficult to remove from the oilseed strains of *Helianthus annuus* (sunflower) seed and thus, the data on oilseed includes the hulls (Table 4, Table 5, and Table 6). Hulls are easily separated from the non-oilseed strains of *Helianthus annuus* (sunflower), and thus, the non-oilseed data does not include the hull.

The amino acid content profile of *Helianthus annuus* (Sunflower) Seed Flour includes phenylalanine + tyrosine (8.2 g/100 g crude protein) and leucine (6.5 g/100 g crude protein; Table 7).³¹ The fatty acids in *Helianthus annuus* (Sunflower) Seed Flour were palmitate (12.04% of detected fatty acids), stearate (8.26%), oleate (31.14%), and linoleate (48.56%).²⁷ The unheated flour is reported to be made up of 6.80% moisture, 45.50% protein, 4.40% crude fat, and 2.00% crude fiber; the heated flour is reported to be made up of 8.56% moisture, 42.37% protein, 9.20% crude fat, and 1.90% crude fiber. Ash content is 7.70%.

The composition (e.g., crude protein, fiber, and fat) of *Helianthus annuus* (sunflower) seed meal (possible precursor to *Helianthus annuus* seed extract and seed cake) may vary with the source and depending on whether or not the seed hull is included or the seeds are partially dehulled (Table 8).³¹ This also applies to amino acids and crude protein contained in the meal (Table 9).

Electrophoresis showed that protein bands were similar among 3 *Helianthus annuus* (sunflower) seed strain samples.³² There were 3 polypeptides groups of helianthinin fraction detected. Of these, 2 were acidic (α , MW=36,800 to 42,900 Da and α' , MW=31,000 to 35,300 Da), and one was basic (β , MW=21,000 to 29,600 Da). The molecular weight of the 2S albumin proteins ranged from 11,500 to 20,100 Da. Another analysis characterized the 2S albumin fractions from inbred lines and cultivars as single chain proteins with relative molecular masses between 10,000 and 18,000 Da, some with intra-chain disulphide bonds.³³ *Helianthus annuus* (sunflower) proteins are rich in globulins (55% to 60%), albumins (17% to 23%), and glutelins (11% to 17%).³⁴

Helianthus Annuus (Sunflower) Seed Wax mainly contains: esters of C16-24 fatty acids and C26-32 alcohols (approximately 90%), free alcohols (approximately 1% to 5%), and hydrocarbons (approximately 1%) with no glycerol and other polyalcohol esters.³⁵

Helianthus Annuus (Sunflower) Seed Wax is a complex mixture consisting of long-chain non-glyceride esters, and a small amount of free fatty alcohols and free fatty acids.²⁶ The seed hull contains most of the wax found in a seed (Table 10).³⁶

Constituents of Concern

Helianthus annuus (sunflower) plants are reported to contain sesquiterpene lactones, which may cause dermal Type IV (delayed-type) hypersensitivity reactions following dermal exposure (i.e., allergic contact dermatitis).^{13,15}

Helianthus annuus (sunflower) petals were reported to contain saponins, and helianthosides A, B, and C derived from echinocystic acid.³⁷

A 14-amino-acid, backbone-cyclized peptide (SFTI-12) has been reported in the seeds of *Helianthus annuus* (sunflower); it is a potent trypsin inhibitor and a relatively weak inhibitor of thrombin and other proteases.³⁸

Helianthus annuus (sunflower) kernels and hulls contain phenolic compounds, which include chlorogenic and caffeic acids; these are readily oxidized during common processing causing green to brown discoloration in protein isolates or concentrates.^{39,40} These compounds have been studied both for their additive/synergistic effect on carcinogenesis and their anti-carcinogenic properties, with no definitive result.⁴¹

Helianthus annuus (sunflower) seeds contain a 2S-protein fraction that, in other seeds and nuts, includes albumins known to induce IgE-mediated allergies.^{14,42} The characteristics of 2S albumins include low molecular weight, high solubility in water, and high nitrogen and cysteine contents.⁴³⁻⁴⁶ *Helianthus annuus* (sunflower) seeds have been reported to cause anaphylactic reactions after ingestion and rhinitis and asthmatic reactions after occupational exposure to the seed dust in susceptible people.^{14,42} Clinical reports indicated that exposure to *Helianthus annuus* (sunflower) seeds can cause allergic reactions in *Helianthus annuus* (sunflower) seed-sensitized individuals.³² Some of the 2S albumins from sunflower seeds were first suspected to be allergens based on their degree of homology (34%) with the allergenic mature 2S albumins of Brazil nuts.^{14,42} 2S albumins in *Helianthus annuus* (sunflower), sesame, and mustard seeds are considered major allergens.⁴⁷ Other seeds, nuts, grains, and cereals contain related allergens, including peas, soy beans, castor beans, rapeseeds, cotton seeds, Brazil nuts, walnuts and peanuts.^{42,47,48} Thus, the 2S albumin seed-storage proteins have been described as “universal allergens” and “inherently allergenic” or “intrinsically allergenic” proteins in seeds in which they occur.⁴⁷⁻⁵⁰ However, not all the 2S albumins should be considered major allergens,⁴⁵ and those that are allergenic are not necessarily cross reactive.^{45,48,50} In fact, cross-reactivity seems to be uncommon in this protein family.^{45,49} This view is consistent with observations that, in general, proteins with a similar fold are not necessarily cross-reactive.^{48,51} On the other hand, the compactness and rigidity of 2S albumins, resulting from their disulfide bond arrangement and electrostatic interactions, confers high stability against thermal or surfactant-induced denaturation and digestion by proteolytic enzymes.^{45,48,49} Resistance to denaturation and digestion is a key factor for the allergenicity of food components. This property would allow 2S albumins to reach the gastrointestinal tract almost intact.⁴⁸ The resistance of allergenic 2S proteins to food processing, cooking, and proteolytic attack may help explain their potential to cause severe food allergies.^{45,48}

Impurities

Analysis of three product mixtures that contained *Helianthus Annuus* (Sunflower) Seed Extract showed that heavy metal, pesticide, and other impurity content (i.e., formaldehyde) were below the limits of detection (Table 11).^{29,30,52}

The protein content was approximately 0.52% in a product mixture that contained *Helianthus Annuus* (Sunflower) Seed Extract (10%).²⁹ Analysis of a product mixture that contained *Helianthus Annuus* (Sunflower) Seed Extract (1.4% to 2.2%) showed that a total of 87.0% of the proteins were <243 Da (1.35 g/L).³⁰ This product mixture was reported to be mainly composed of peptides with a molecular weight lower than 2000 Da (99% of total proteins); 0.4% of the proteins were >2000 Da and there were no proteins >10,000 Da (Table 12).

The carcinogen benzo[a]pyrene (3,4-benzopyrene) has been detected as a contaminant in unrefined and cooking seed oil from *Helianthus annuus* (sunflower).^{53,54} While the source may be endogenous synthesis, atmospheric pollution, or contamination from the soil, there is also evidence that levels of benzo[a]pyrene increase in plant products as a result of processing.

Commercial *Helianthus annuus* (sunflower) seeds that have not been shelled were shown to be contaminated with pollen, a potential allergen.¹⁰

Aflatoxins or molds that produce aflatoxins have been detected in some dried *Helianthus annuus* (sunflower) seed samples.⁵⁵⁻⁵⁷ Not all samples were contaminated.⁵⁸

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated based on the data the Panel receives from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected cosmetic use of ingredients. The data from the FDA are those it collects from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). Those received from the cosmetic industry are submitted in response to a survey conducted by the Personal Care Products Council (Council) of the maximum reported use concentrations by category.

According to 2016 VCRP data, *Helianthus Annuus* (Sunflower) Seed Extract had the highest number of reported uses in this safety assessment at 389 formulations (Table 13).⁵⁹ *Helianthus Annuus* (Sunflower) Extract had the next highest number of reported uses in 96 formulations. All other in-use ingredients are reported to be used in 76 or fewer formulations.

The concentration of use survey conducted by the Council in 2015 indicate that Hydrolyzed Sunflower Seed Wax had the highest reported maximum concentration of use; it is used at up to 10% in rinse-off skin cleansing formulations.^{60,61} The highest maximum concentration of use reported for leave-on products is 4% in *Helianthus Annuus* (Sunflower) Seed Wax in mascara and 4% Hydrolyzed Sunflower Seed Wax in lipstick.

The ingredients not in use according to the VCRP and industry survey are listed in Table 14.

In some cases, reports of uses were received in the VCRP, but no concentration-of-use data were provided. For example, *Helianthus Annuus* (Sunflower) Flower Extract is reported to be used in 5 formulations, but no use concentration

data were provided. In other cases, no reported uses were received in the VCRP, but use concentrations were provided in the industry survey. For example, *Helianthus Annuus* (Sunflower) Seed was not reported in the VCRP to be in use, but the industry survey indicated that it is used in 2 types of hair products and a suntan product; it should be presumed that *Helianthus Annuus* (Sunflower) Seed is used in at least one cosmetic formulation in each use category for which a concentration of use is reported.

These ingredients are reported to be used in products used near the eye (e.g., 4% *Helianthus Annuus* (Sunflower) Seed Wax in mascara), in products that may be ingested (e.g., 4% Hydrolyzed Sunflower Seed Wax in lipstick) and in products that may come in contact with mucus membranes (e.g., 5% *Helianthus Annuus* (Sunflower) Seed Extract in bath soaps and detergents). Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Additionally, some of the *Helianthus annuus* (sunflower)-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, *Helianthus Annuus* (Sunflower) Seed Extract is reported to be used at up to 0.05% in hair sprays and *Helianthus Annuus* (Sunflower) Seedcake is reported to be used at up to 0.0012% in spray face and neck products. In practice, 95%-99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles <10 µm compared with pump sprays.^{62,63} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{64,65} *Helianthus Annuus* (Sunflower) Extract is reported to be used in powders (concentration not reported). Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400- to 1000-fold less than protective regulatory and guidance limits for inert airborne particles in the workplace.⁶⁶⁻⁶⁸

None of the *Helianthus annuus* (sunflower)-derived ingredients named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union (EU).⁶⁹

Non-Cosmetic

Helianthus annuus (sunflower) is cultivated primarily for the seeds which yield the world's second most common source of edible oil.²¹ Hulled seed press-cake is used as a high protein feed for livestock. The raw kernels are used as feed for poultry and cage birds. The stalks and leaves are used for fodder, silage and as a green-manure crop.^{70,71} The seed hulls are used for filler in livestock feed and bedding. A yellow dye is extracted from the flowers.

Non-oilseed seeds are used for confectionary purposes.³¹ De-hulled seeds (kernels) are eaten roasted and salted alone or in other foods (e.g., salads and cakes). Whole *Helianthus annuus* (sunflower) seeds (with hulls) are also eaten as a snack food. Such seeds contain less oil.

Helianthus annuus (sunflower) seeds are not listed as a major allergen by the Food Allergen Labeling and Consumer Protection Act.⁷²

Helianthus annuus (sunflower) seeds are used to make an alternative to peanut butter.⁷³ In the EU, foods containing *Helianthus annuus* (sunflower) sunflowers and seeds are not required to be labelled as allergens.⁷⁴

In the EU, the flowers and seed oil from the seeds of *Helianthus annuus* (sunflower) were on the market as food or food ingredients and were consumed to a significant degree before 15 May 1997.⁷⁵ Thus its access to the market is not subject to the Novel Food Regulation (EC) No. 258/97. However, other specific legislation may regulate the placing on the market of this product as a food or food ingredient in some Member States.

Traditional medicinal uses of *Helianthus annuus* (sunflower) seeds are reported to be as a diuretic, expectorant, and to treat colds, coughs, throat, and lung ailments.²³ The flowers and seeds are reported to be used in folk remedies for cancer in Venezuela. The flowers and seeds are also reported to have multiple uses, including: antiseptic, aphrodisiac, bactericidal, diuretic, expectorant, and malaria preventative uses. *Helianthus annuus* (sunflower) plants have multiple uses in folk remedies, including: bronchitis, carbuncles, cold, colic, cough, diarrhea, eye ailments, fever, flu, inflammations, rheumatism, urogenital ailments, and wounds.

Native Americans have been reported to use *Helianthus annuus* (sunflower) in multiple ways.⁷⁶ The seed and root were used to ward off illness in neonates by feeding them to newly pregnant women. The ground seed flour was used for food; roasted and ground seeds were made into cakes and used to feed livestock. The flower head was used as a vegetable. The sap was chewed to ward off thirst.

The stalks have been used to make acoustic ceiling tiles, door cores (with flame suppressors, burn-resistant doors), deburring and polishing abrasives for metal, and plant starter material.⁷⁷

Helianthus annuus (sunflower) plants are used in phytoremediation to extract heavy metals and other toxic substances from the soil (e.g., lead, arsenic, and uranium).^{78,79} This plant is also used in rhizofiltration to neutralize radionuclides and other toxic substances and to remove harmful bacteria from water.⁸⁰

TOXICOKINETIC STUDIES

Data on the toxicokinetics of *Helianthus annuus* (sunflower)-derived ingredients would not be practical because these ingredients are complex mixtures. However, exposure to the components of these ingredients in cosmetics is expected to be lower than exposure resulting from dietary exposure since these ingredients are consumed as food and feed.

TOXICOLOGICAL STUDIES

As noted earlier, some of the ingredients reviewed in this safety assessment and various plant parts may be consumed as food and/or feed, and daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. Therefore, the systemic toxicity potential of those *Helianthus annuus* (sunflower)-derived ingredients which are normal components of the human and animal diet is not the focus of this safety assessment. The primary focus is the potential for irritation and sensitization reactions after topical exposure to these ingredients. Acute and repeated dose toxicity data on *Helianthus annuus* (sunflower)-derived ingredients were not found in the published literature and no unpublished data were submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Reproductive and developmental toxicity data on *Helianthus annuus* (sunflower)-derived ingredients were not found in the published literature and no unpublished data were submitted.

GENOTOXICITY STUDIES

Genotoxicity data on *Helianthus annuus* (sunflower)-derived ingredients were not found in the published literature and no unpublished data were submitted.

CARCINOGENICITY STUDIES

Carcinogenicity data on *Helianthus annuus* (sunflower)-derived ingredients were not found in the published literature and no unpublished data were submitted.

IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

A trade name mixture containing *Helianthus Annuus* (Sunflower) Seed Extract (1.4%-2.2%; maximum concentration of 2.2%) was administered neat to the undamaged skin of rabbits (n=3) under occlusion for 4 h.³⁰ There were no signs of cutaneous reactions at 1, 24, 48, and 72 h after removal of the patch. It was concluded that this mixture was not dermally irritating.

Human

Human irritation studies are summarized in Table 15.

In a 4-week use study of a moisturizer containing *Helianthus Annuus* (Sunflower) Seed Extract (0.0335%) in humans with sensitive skin and a 2-week use study of a lipstick containing *Helianthus Annuus* (Sunflower) Seed Wax (4%), there were no signs of the potential for dermal irritation.^{81,82} A trade name mixture containing *Helianthus Annuus* (Sunflower) Seed Extract (effective concentration 10%) was well tolerated in a 48-h patch test.²⁸

Sensitization

Animal

In a guinea pig sensitization study using the Buehler protocol, a trade name mixture containing *Helianthus Annuus* (Sunflower) Seed Extract (12%) was tested at 10% (in petrolatum).⁸³ The final concentration of *Helianthus Annuus* (Sunflower) Seed Extract was 1.2%. There were no skin reactions observed and the sensitization rate at 24 and 48 h after challenge was 0%. It was concluded that the mixture was not sensitizing at 10%.

In a guinea pig maximization test, a trade name mixture (12.5%, 25%, 50%, or 100%) containing *Helianthus Annuus* (Sunflower) Seed Extract (1.4%-2.2%; maximum concentration of 2.2%) was administered to albino guinea pigs (n not specified).³⁰ No significant reactions were observed at any concentration. There were no signs of a reaction under macroscopic examination during the challenge phase of the experiment. It was concluded that this trade name mixture was probably not sensitizing.

Human

Human sensitization studies are summarized in Table 15.

A human repeated insult patch test (HRIPT) of a face cream containing *Helianthus Annuus* (Sunflower) Seed Extract (0.238%) resulted in low-level reactions; it was concluded that it was not irritating and not sensitizing.⁸⁴ A trade name mixture containing 12% *Helianthus Annuus* (Sunflower) Seed Extract was not sensitizing to human subjects when tested at 10% (1.2% *Helianthus Annuus* (Sunflower) Seed Extract) in an HRIPT.⁸³ A trade name mixture containing 10% *Helianthus Annuus* (Sunflower) Seed Extract was not sensitizing to human subjects at 100% in an HRIPT.⁸⁵ In HRIPTs, a moisturizer containing *Helianthus Annuus* (Sunflower) Seed Extract (0.0335%) and 2 different lipsticks containing *Helianthus Annuus* Seed Wax (3.34% and 4%) were not irritating or sensitizing.⁸⁶⁻⁸⁸

OCULAR IRRITATION STUDIES

In a hen's egg chorion-allantoic membrane (HET-CAM) assay for predicting ocular irritation of a product mixture containing *Helianthus Annuus* (Sunflower) Seed Extract (effective concentration 10%), the mean irritation index was 3 and it was concluded that the product mixture was slightly irritating.²⁸

CLINICAL STUDIES

Retrospective and Multicenter Studies

Provocative Assays

Helianthus Annuus (Sunflower) Extract

A patch test of *Helianthus Annuus* (Sunflower) Extract (1%) was performed in subjects (n=9) that were known to have developed allergies to chrysanthemums (another member of the *Asteraceae* family).¹⁹ To make the extract, freshly cut *Helianthus annuus* (sunflower) plants were dipped whole into peroxide-free diethyl ether for 60 sec; the ether was then dried over sodium sulfate for 8 h to a dry residue. The residue was incorporated into white petrolatum. The test substance was administered using plaster strip and the test site was observed at 24, 48, and 72 h. Five of the subjects had positive reactions ranging from + to +++.

Helianthus Annuus (Sunflower) Seed Extract

Patch tests and IgE tests of *Helianthus Annuus* (Sunflower) Seed Extract (concentration not specified) were both performed in subjects (n=17) with established fruit, nut, and/or legume allergies, including 2 subjects with a confirmed *Helianthus annuus* (sunflower) seed allergy.⁸⁹ Negative and positive controls for skin testing were saline solution and histamine dihydrochloride, respectively. Seven (41%) of the subjects had a positive reaction in one or both of the allergy tests; it was not specified whether the 2 subjects with the *Helianthus annuus* (sunflower) seed allergy had positive results.

A *Helianthus annuus* (sunflower) seed extract (1:100 w/v) was used in skin prick tests in atopic subjects (n=84; each positive for a common allergen).⁹⁰ A commercial radioallergosorbent test (RAST) was also performed on these subjects. The *Helianthus annuus* (sunflower) seed extract was prepared from hulled seed after pressing with a hydraulic press to remove the oil. The pressed seeds were extracted with physiologic saline overnight and centrifuged. The supernatant was ultracentrifuged and the middle fraction extracted and sterilized. There were 18 positive reactions for the skin prick test, of these three were also positive for the RAST. The positive reactions strongly correlated to owning a cage bird and a history of at least one food allergy.

A skin prick test and food-specific IgE assays were conducted in subjects (n=65 adults) with various fruit and or seed allergies, including 2 subjects with allergies to *Helianthus annuus* (sunflower) seeds.⁸⁹ Seventeen of 65 subjects had a positive reaction to *Helianthus annuus* (sunflower) seeds in one or both of the assays; none of the subjects with positive reactions had a positive reaction to a double-blind placebo-controlled food challenge for *Helianthus annuus* (sunflower) seeds.

Case Reports

There are multiple case reports of children and adults who are allergic to *Helianthus annuus* (sunflower) seeds (Table 16).^{4-6,8-12,91} Contacts were by dermal, oral, and/or inhalation exposure.

Cases of food allergies to *Helianthus annuus* (sunflower) seeds have also been reported in the literature (Table 16).^{7,89,92-94} These allergies are confirmed with skin prick tests, RASTs, and/or double-blind, placebo-controlled food challenges. It has been shown that there is the possibility that during the harvesting process, the seeds are contaminated with pollen, which may be a cause of the allergic reaction.¹⁰

There are cases of people developing allergies to *Helianthus annuus* (sunflower) pollen.^{4,10,16,17,92,95-98} These tend to be people who live in areas where *Helianthus annuus* (sunflower) is grown or work in facilities that process these plants and

handle the plant material. Some perceived allergies to the seeds have been found to be allergies to the pollen (Table 16).^{10,95} For example, subjects who worked in an animal feed processing plant (n=35) were administered skin prick tests of aqueous preparations of the components of the feed (1:10 w/v dilution), which included *Helianthus annuus* (sunflower) seeds.⁹⁸ The subjects had worked in the plant an average of 14 years (3-30 years) and were exposed to feed “aerosols” 8 h per shift. Positive reactions to the *Helianthus annuus* (sunflower) seeds were observed in 19 (54.3%) of the exposed subjects. There was only 1 positive reaction to *Helianthus annuus* (sunflower) seeds in the control group of subjects who did not work in the plant (n=30).

SUMMARY

This is a review of the available scientific literature relevant to assessing the safety of *Helianthus annuus* (sunflower)-derived ingredients as used in cosmetics. The reported functions of these ingredients in cosmetics include skin-conditioning agents – miscellaneous, abrasives, and absorbents.

The ingredients in this report are grouped together because they are extracts, waxes, or powders derived from plant parts of *Helianthus annuus*, the sunflower plant.

The seeds of *Helianthus annuus* (sunflower) are consumed by humans, both raw and roasted, on a regular basis. The remaining parts of the plant, as well as the seeds, are fed to farm animals and pets. Exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. Therefore, the oral toxicity of these ingredients will not be the focus of this safety assessment. Instead, the primary focus of this safety assessment of *Helianthus annuus* (sunflower)-derived ingredients as used in cosmetics is on the potential for irritation and sensitization from topical exposure. *Helianthus annuus* (sunflower) is a member of the *Asteraceae* family; members of this family are known to comprise, in part, sensitizers.

In an analysis of a product mixture that contained *Helianthus Annuus* (Sunflower) Seed Extract (10%), the protein content was approximately 0.52%. In an analysis of a product mixture that contained *Helianthus Annuus* (Sunflower) Seed Extract (20%), the protein content was 0.02%.

In an analysis of a product mixture that contained *Helianthus Annuus* (Sunflower) Seed Extract (1.4% to 2.2%), a total of 87.0% of the proteins were <243 Da (1.35 g/L). This product is mainly composed of peptides with a molecular weight lower than 2000 Da (99% of total proteins); 0.4% of the proteins were >2000 Da and there were no proteins >10,000 Da.

According to the 2016 VCRP data, *Helianthus Annuus* (Sunflower) Seed Extract had the highest reported number of uses of the ingredients in this safety assessment; it is used in 389 formulations. *Helianthus Annuus* (Sunflower) Extract had the next highest number of reported uses (96) in formulations. All other in-use ingredients are reported to be used in 76 or fewer formulations.

In the 2015 Council survey, Hydrolyzed Sunflower Seed Wax had the highest reported maximum concentration of use at up to 10% in skin cleansing formulations. The highest maximum concentration of use reported for leave-on products is 4% *Helianthus Annuus* (Sunflower) Seed Wax in mascara and 4% Hydrolyzed Sunflower Seed Wax in lipstick.

A trade name mixture containing *Helianthus Annuus* (Sunflower) Seed Extract (1.4% to 2.2%) was not irritating to the undamaged skin of rabbits at 100%.

In a 4-week use study of a moisturizer containing *Helianthus Annuus* (Sunflower) Seed Extract at 0.0335% in humans with sensitive skin and a 2-week use study of a lipstick containing *Helianthus Annuus* (Sunflower) Seed Wax at 4%, there were no signs of dermal irritation. A trade name mixture containing *Helianthus Annuus* (Sunflower) Seed Extract at 10% was well tolerated in a patch test.

In a HET-CAM assay for predicting ocular irritation of a product mixture containing *Helianthus Annuus* (Sunflower) Seed Extract (10%), it was concluded that the product mixture was slightly irritating.

In a guinea pig sensitization study of a trade name mixture containing *Helianthus Annuus* (Sunflower) Seed Extract at 12% and tested at 10% (1.2% *Helianthus Annuus* (Sunflower) Seed Extract), there were no skin reactions observed and it was concluded that the mixture was not sensitizing at 10%. In a guinea pig maximization test, a trade name mixture containing *Helianthus Annuus* (Sunflower) Seed Extract (1.4% to 2.2%) was not sensitizing to albino guinea pigs at up to 100%.

An HRIPT of a face cream containing *Helianthus Annuus* (Sunflower) Seed Extract at 0.238% resulted in low-level reactions; it was concluded that it was not irritating and not sensitizing. A lipstick containing *Helianthus Annuus* (Sunflower) Seed Wax at 3.34% was non-sensitizing in a 2-week use study in subjects with sensitive skin. A trade name mixture containing *Helianthus Annuus* (Sunflower) Seed Extract at 10% was not sensitizing to human subjects at 100% in an HRIPT. In HRIPTs of cosmetic products, a moisturizer containing *Helianthus Annuus* (Sunflower) Seed Extract at 0.0335% and 2 lipsticks containing *Helianthus Annuus* Seed Wax at 3.34% and 4% were not irritating or sensitizing.

In a patch test of *Helianthus Annuus* (Sunflower) Extract in human subjects with known allergies to another member of the *Asteraceae* family, 5 of 9 subjects had positive reactions ranging from + to ++++. In test of human subjects with known

food allergies, 7 of 17 had positive reactions to *Helianthus Annuus* (Sunflower) Seed Extract in a patch test and/or an IgE test. The concentration was not specified. In a skin prick test of *Helianthus Annuus* (Sunflower) Seed Extract (1:100 w/v) in human subjects with a common allergy, 18 of 84 subjects had a positive result; 3 of these were also positive in a RAST.

There are multiple case reports of people with food allergies to *Helianthus annuus* (sunflower) seeds. These allergies were confirmed with skin prick tests, RASTs, and/or double-blind, placebo-controlled food challenges.

There are multiple cases of humans developing allergies to *Helianthus annuus* (sunflower) plants and/or seeds, possibly from inhalation of the pollen. For example, 19 of 35 subjects who work in a facility processing animal feed, including *Helianthus annuus* (sunflower), had positive reactions in a skin prick test for and aqueous extract (1:10 w/v) of the plant.

DISCUSSION

The Panel examined irritation and sensitization data on *Helianthus annuus* (sunflower)-derived ingredients. The Panel also considered data linking food allergies and 2S albumins, with the methods of manufacture and impurity data. *Helianthus annuus* (sunflower) seeds have been found to contain 2S albumins similar to those of other seeds. Some 2S albumins found in other seeds, such as rapeseed, castor beans, cottonseed, Brazil nuts, and walnuts, have been associated with allergenicity. Consequently, the 2S albumin proteins in *Helianthus annuus* (sunflower) seed are potential allergens. These proteins are generally known to be quite stable against enzymatic or chemical treatment. Two studies indicated that *Helianthus annuus* (sunflower) seeds are likely to be allergenic in some people and that the 2S proteins of *Helianthus annuus* (sunflower) seeds may be cross-reactive with the allergens in other foods, but the evidence does not indicate that a heightened level of public concern is warranted for the use of *Helianthus annuus* (sunflower) seed-derived ingredients in cosmetic products. Further, *Helianthus annuus* (sunflower) seeds are not considered a high risk by the EU and are not listed as a major allergen by the Food Allergen Labeling and Consumer Protection Act.

Type I immediate hypersensitivity reactions could possibly occur following exposure to a protein-derived ingredient. Traditional HRIPTs and related tests do not detect Type I reactions. The Panel noted that these ingredients may be used in aerosolized products, however, and incidental inhalation of allergenic peptides has the potential to cause Type I reactions in sensitized individuals. Thus, the Panel recommends that people with known allergies to *Helianthus annuus* seed proteins avoid using personal care products that contain these ingredients and may be incidentally inhaled during use (e.g., spray or loose powder products).

Because final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For *Helianthus annuus* (sunflower)-derived ingredients, the Panel was concerned about the presence of 2S albumin and sesquiterpene lactones, which could result in irritation and sensitization. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

The Expert Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. To address these concerns, the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

Aflatoxins have been detected in some samples of *Helianthus annuus* (sunflower) seeds. The Panel recognizes the United States Department of Agriculture (USDA) designation of ≤ 15 ppb as corresponding to “negative” aflatoxin content and believes that aflatoxins will not be present at levels of toxicological concern in *Helianthus annuus* (sunflower)-derived ingredients.

The Panel concluded that the data were sufficient to come to a conclusion of safe as used for all of the ingredients that are derived from the seeds and the flower. However, the data were insufficient for the ingredients that are derived from other plant parts. The additional data needed are:

- Method of manufacture
- Composition of these ingredients, especially protein content (including 2S albumins)
- Impurities

The Panel discussed the issue of incidental inhalation exposure from hair sprays, face and neck products, and face powders. There were no inhalation toxicity data available. These ingredients are reportedly used at concentrations up to 0.05% in cosmetic products that may be sprayed; there was no reported concentration of use for the face powder. The Panel noted that droplets/particles from spray and loose-powder cosmetic products would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for *Helianthus annuus* (sunflower)-derived ingredients to cause irritation and sensitization. They noted the lack of irritation and

the negative results in studies testing for the potential for these ingredients to induce sensitization. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

CONCLUSION

The CIR Expert Panel concluded that the following 9 *Helianthus annuus* (sunflower)-derived ingredients are safe as used in cosmetics in the present practices of use and concentration described in this safety assessment:

Helianthus Annuus (Sunflower) Seed Extract	Helianthus Annuus (Sunflower) Seed Flour*
Helianthus Annuus (Sunflower) Flower Extract	Helianthus Annuus (Sunflower) Seed Wax
Helianthus Annuus (Sunflower) Seed	Hydrogenated Sunflower Seed Extract*
Helianthus Annuus (Sunflower) Seed Butter*	Hydrolyzed Sunflower Seed Wax
Helianthus Annuus (Sunflower) Seedcake	

and that the data are insufficient to come to a conclusion of safety for the following 3 ingredients:

Helianthus Annuus (Sunflower) Extract
Helianthus Annuus (Sunflower) Leaf/Stem Extract*
Helianthus Annuus (Sunflower) Sprout Extract*

Persons with known allergies to nut or seed proteins should avoid using personal care products that contain these ingredients.

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

TABLES AND FIGURES**Table 1.** Definitions and functions of the *Helianthus annuus*-derived ingredients in this safety assessment.¹

Ingredient	Definition	Functions
Helianthus Annuus (Sunflower) Extract	Helianthus Annuus (Sunflower) Extract is the extract of the whole plant, <i>Helianthus annuus</i> .	Skin-conditioning agent – miscellaneous
Helianthus Annuus (Sunflower) Flower Extract	Helianthus Annuus (Sunflower) Flower Extract is the extract of the flowers of <i>Helianthus annuus</i> .	Skin-conditioning agent – miscellaneous
Helianthus Annuus (Sunflower) Leaf/Stem Extract	Helianthus Annuus (Sunflower) Leaf/Stem Extract is the extract of the leaves and stems of <i>Helianthus annuus</i> .	Skin-conditioning agent – miscellaneous
Helianthus Annuus (Sunflower) Sprout Extract	Helianthus Annuus (Sunflower) Sprout Extract is the extract of the sprouts of <i>Helianthus annuus</i> .	Skin-conditioning agent – miscellaneous
Helianthus Annuus (Sunflower) Seed	Helianthus Annuus (Sunflower) Seed is the seed of <i>Helianthus annuus</i> .	Abrasive; Skin-conditioning agent – miscellaneous
Helianthus Annuus (Sunflower) Seed Butter	Helianthus Annuus (Sunflower) Seed Butter is the fat obtained from the seeds of <i>Helianthus annuus</i> .	Skin-conditioning agent – emollient; skin-conditioning agent - occlusive
Helianthus Annuus (Sunflower) Seedcake	Helianthus Annuus (Sunflower) Seedcake is the residue from the expression of oil from the seeds of <i>Helianthus annuus</i> .	Abrasive; absorbent; bulking agent; Skin-conditioning agent – miscellaneous
Helianthus Annuus (Sunflower) Seed Extract	Helianthus Annuus (Sunflower) Seed Extract is the extract of the seeds of <i>Helianthus annuus</i> .	Skin-conditioning agent – miscellaneous; sunscreen agent
Helianthus Annuus (Sunflower) Seed Flour	Helianthus Annuus (Sunflower) Seed Flour is the flour obtained from the finely ground seeds of <i>Helianthus annuus</i> .	Abrasive; absorbent; bulking agent; viscosity increasing agent
Hydrolyzed Sunflower Seed Wax	Hydrolyzed Sunflower Seed Wax is the hydrolysate of Helianthus Annuus (Sunflower) Seed Wax derived by acid, enzyme or other method of hydrolysis.	Skin-conditioning agent – miscellaneous
Hydrogenated Sunflower Seed Extract	Hydrogenated Sunflower Seed Extract is the end-product obtained by the controlled hydrogenation of helianthus annuus (sunflower) seed extract	Skin-conditioning agent – miscellaneous
Helianthus Annuus (Sunflower) Seed Wax	Helianthus Annuus (Sunflower) Seed Wax is the wax obtained from the seed of the sunflower, <i>Helianthus annuus</i> .	Skin-conditioning agent – miscellaneous

Table 2. Chemical and physical properties of *Helianthus annuus* (sunflower)-derived ingredients.

Property	Value	Reference
Helianthus Annuus (Sunflower) Seed Extract		
Physical Form	Powder	26
Helianthus Annuus (Sunflower) Seed Extract		
Physical Form	Liquid	29
Color	Colorless or pale yellow	29
Odor	Characteristic	29
pH @ 25 °C	4.0-7.5	29
Specific Gravity @ 25°C	0.99-1.02	29
Water Solubility	Soluble	29
Helianthus Annuus (Sunflower) Seed Flour		
Color		
pH 20-7	Cream white	27
pH 8	Gray	27
pH 9	Yellowish gray	27
pH 10	Light brown	27
pH 10.5	Dark brown	27
Helianthus annuus (sunflower) seed wax		
Melting Point (°C)	74-80	35
Hydrolyzed sunflower seed wax		
Physical Form	Solid wax	26
Color	Yellow White ^a	26 99
Odor	Very low	26
Density/Specific Gravity @ 20°C	0.87-0.95	26
Melting Point (°C)	74-77 67-75 ^a	26 99
Boiling Point (°C)	>200	26
Water Solubility	Insoluble	26

^a Wax extracted from seed hulls**Table 3.** Composition of *Helianthus annuus* (sunflower) whole plant at different growth stages.³¹

	Mature		Before bloom	Beginning of bloom	In bloom	After bloom
	Source 1	Source 2	Source 3			
	g/100 g fresh weight					
Dry matter	-	30	12	20	14	15
	g/100 g dry matter					
Crude protein	11-12	12.5	19.3	13.9	14.7	14.0
Crude fat	10-12	10.7	2.7	4.4	2.4	2.8
Acid-detergent fiber	32.0	39	-	-	-	-
Lignin	10-16	12.3	-	-	-	-

- = No data

Table 4. Sample comparison of oil content (g/100 g dry seed material) in oilseed (high in oleic acid content) and non-oilseed strains *Helianthus annuus* (sunflower) seeds.³¹

Acid	Oilseed (includes hulls) ¹	Non-oilseed (no hulls)
Myristic acid (C14:0)	0.02	0.05
Palmitic acid (C16:0)	2.84	2.95
Palmitoleic acid (C16:1)	0.03	0.05
Stearic acid (C18:0)	2.12	2.33
Oleic acid (C18:1)	8.48	9.89
Linoleic acid (C18:2)	27.8	34.48
Linolenic acid (C18:3)	0.04	0.07
Arachidic acid (C20:1)	0.06	0.05

¹ The hulls are difficult to remove from the oilseed strains of *Helianthus annuus* (sunflower) seed, so the data on oilseed includes the hulls. Hulls are easily separated from the non-oilseed strains of *Helianthus annuus* (sunflower), and thus, the non-oilseed data does not include the hull.

Table 5. Composition of phytosterols and tocopherols as a function of oleic acid content in *Helianthus annuus* (sunflower) seeds.³¹

Sterol	Conventional/wild	Mid oleic acid	High oleic acid ^a
Total sterols	240-500 mg/g	ND	170-520 mg/g
β-Sitosterol ^b	50%-70%	56%-58%	42%-70%
Campesterol ^b	6.5%-13.0%	9.1%-9.6%	5%-13%
Stigmasterol ^b	6.0%-13.0%	9.0%-9.3%	4.5%-13%
Total tocopherols (mg/g)	44-152	50.9-74.1	45-112
α (vitamin E) (mg/g)	40.3-93.5	48.8-66.8	40-109
β (mg/g)	ND-4.5	1.9-5.2	1.0-3.5
γ (mg/g)	ND-3.4	0.2-1.9	0.3-3.0

ND=Not detected

^a The hulls are difficult to remove from the oilseed strains of *Helianthus annuus* (sunflower) seed, so the data on oilseed includes the hulls. Hulls are easily separated from the non-oilseed strains of *Helianthus annuus* (sunflower), and thus, the non-oilseed data does not include the hull.

^b Percent of total sterols

Table 6. The vitamin content of seeds of non-oilseed strains of *Helianthus annuus* (sunflower).³¹

Vitamin	Amount (/100 g dry materials) ¹
Vitamin C (mg)	1.48
Thiamine (mg)	2.42
Riboflavin (mg)	0.26
Niacin (mg)	4.75
Pantothenic acid (mg)	7.13
Vitamin B-6 (mg)	0.81
Folate (μg)	239.86
Vitamin A (IU)	52.84
Vitamin E (α tocopherol) (mg)	36.46
Vitamin K (μg)	2.85

¹ Hulls are easily separated from the non-oilseed strains of *Helianthus annuus* (sunflower), so the non-oilseed data does not include the hull.

Table 7. Amino acid content in *Helianthus annuus* (sunflower) seed flour.³¹

Amino acid	Amount (g/100 g of crude protein)
Isoleucine	3.7
Leucine	6.5
Lysine	3.4
Methionine + cysteine	4.1
Tryptophan	1.5
Phenylalanine + tyrosine	8.2
Valine	4.9
Threonine	3.3

Table 8. Composition of *Helianthus annuus* (sunflower) meal derived from whole and part-dehulled seeds from different sources.³¹

	Whole seed meal		Part-dehulled seed meal		Hulls
	Source 1 (mean±SD)	Source 2 (mean)	Source 1 (mean±SD)	Source 2 (mean)	Source 3 (mean (range))
g/100 g fresh weight					
Dry matter	88.7±1.4	-	89.7±1.2	92.0	87.8 (85.0-92.0)
g/100 g dry matter					
Crude protein	27.7±2.2	28.4	33.4±2.2	38.0	5.0 (3.5-9.0)
Crude fiber	25.5±2.6	-	21.2±2.0	20.0	45.0 (40.0-50.0)
Crude fat	2.0±0.8	1.4	6.7±0.5	8.0	3.0 (0.5-3.0)
Minerals (ash)	6.2±0.6	7.7	6.7±0.5	8.0	
Neutral-detergent fiber	41.1±3.7	40.0	35.9±3.6	36.0	70.0 (65.0-75.0)
Acid-detergent fiber	29.3±3.0	30.0	24.7±2.4	24.0	56.0 (50.0-63.0)
Lignin	10.1±1.4	-	8.2±1.2	-	
Ash	-	-	-	-	2.7 (2.0-3.0)
Calcium	-	-	-	-	0.30 (0.25-0.35)
Phosphorus	-	-	-	-	0.15 (0.10-0.20)
Magnesium	-	-	-	-	0.20 (0.15-0.25)

- = No data

sd = standard deviation

Table 9. Amino acid and protein content (g/100 g dry matter) of *Helianthus annuus* (sunflower) meal derived from whole and part-dehulled seeds from 3 sources.³¹

Amino acid	Non-dehulled <i>Helianthus annuus</i> meal			Dehulled <i>Helianthus annuus</i> meal	
	Source 1	Source 2	Source 3	Source 2	Source 3
Arginine	2.32	2.64	2.56	3.15	3.17
Histidine	0.74	0.73	0.61	0.99	0.97
Isoleucine	1.16	1.43	1.11	1.55	1.59
Leucine	1.82	2.07	1.78	2.48	2.47
Lysine	1.01	1.12	1.11	1.29	1.38
Methionine	0.65	0.66	0.56	0.88	0.89
Cystine	0.50	0.53	0.56	0.71	0.71
Phenylalanine	1.31	1.37	1.28	1.78	1.85
Threonine	1.06	1.16	1.17	1.43	1.44
Tryptophan	0.34	0.42	0.50	0.47	0.46
Valine	1.41	1.66	1.78	1.87	1.94
Glycine	-	-	-	-	2.26
Tyrosine	-	0.84	-	1.11	1.01
Serine	-	-	1.11	-	1.66
Crude protein	28.4	29.8	25.9	45.4	41.0

- = No data

Table 10. Wax distribution in the whole seed, hull, and dehulled seed of two samples of *Helianthus annuus* (sunflower) seeds.³⁶

Wax (carbon number)	Sample 1			Sample 2		
	Hull (wt%)	Whole seed (wt%)	Dehulled seed (wt%)	Hull (wt%)	Whole seed (wt%)	Dehulled seed (wt%)
36	2.7	8.5	14.5	1.5	11.6	16.1
37	1.7	7.0	11.1	0.6	8.5	11.2
38	1.9	2.9	4.6	0.7	3.4	4.9
39	0.8	2.6	4.2	0.2	3.0	4.2
40	3.6	10.0	16.5	2.3	12.5	18.0
41	2.2	11.5	19.4	0.8	13.7	18.8
42	10.0	7.1	6.6	7.7	7.0	6.3
43	1.9	3.5	5.3	1.1	4.3	4.9
44	24.4	14.1	3.4	26.6	10.9	1.9
45	2.5	2.3	1.8	2.2	2.0	1.7
46	26.6	15.9	4.6	30.0	11.9	3.1
48	23.9	14.6	8.0	26.3	11.2	8.9
Total wax content (mg/kg)	14,250	1254	759	14,955	1008	580

Table 11. Impurities in product mixtures that contain *Helianthus Annuus* (Sunflower) Seed Extract.^{29,30,52}

Impurity	<i>Helianthus Annuus</i> (Sunflower) Seed Extract at 10%	<i>Helianthus Annuus</i> (Sunflower) Seed Extract at 20%	<i>Helianthus Annuus</i> (Sunflower) Seed Extract at 1.4%-2.2%
Protein	Approximately 0.52%	0.02%	Detected
Allergens	<2 ppm ^a	None ^{a,b}	None ^b
Formaldehyde	<2.5 ppm ^a	NR	NR
Pesticides	<0.03 ppm	None	None
Methanol	<10 ppm ^a	NR	NR
Nonylphenol	<500 ppm ^a	NR	NR
Microbial count	NR	<100 organisms/g	NR
Heavy metals	<2.5 ppm	NR	NR
Antimony	NR	<0.25 mg/L ^a	NR
Arsenic	NR	<0.050 mg/L ^a	<1 ppm ^a
Cadmium	NR	<0.010 mg/L ^a	<1 ppm ^a
Chromium	NR	<0.050 mg/L ^a	None
Iron	NR	<5.0 mg/L ^a	NR
Lead	NR	<0.050 mg/L ^a	None
Mercury	NR	0.0040 mg/L ^a	None
Nickel	NR	0.050 mg/L ^a	<1 ppm ^a

^a = Limit of detection^b = None of the 26 allergens defined by the 7th Amendment to the EU Cosmetic Directive were detected (detection limit <10 ppm).

NR = Not reported

Table 13. Frequency of use according to duration and exposure of *Helianthus annuus* (sunflower)-derived ingredients.⁵⁹⁻⁶¹

Use type	Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)		Maximum Concentration (%)	
	Uses		Uses		Uses		Uses	
	Helianthus Annuus (Sunflower) Seedcake		Helianthus Annuus (Sunflower) Seed Wax		Hydrolyzed Sunflower Seed Wax			
Total/range	76	0.000015-0.41	28	0.0038-4	NR	3.3-10		
<i>Duration of use</i>								
Leave-on	65	0.000015-0.41	28	0.19-4	NR	3.3-4		
Rinse-off	11	0.000015-0.12	NR	0.0038	NR	10		
Diluted for (bath) use	NR	NR	NR	NR	NR	NR		
<i>Exposure type</i>								
Eye area	10	0.000015-0.41	2	3.6-4	NR	3.5		
Incidental ingestion	NR	0.00012	16	3.4	NR	3.3-4		
Incidental Inhalation-sprays	32 ^b ; 12 ^c	0.0012; 0.000015 ^b	4 ^b ; 2 ^c	0.19 ^b	NR	NR		
Incidental inhalation-powders	12 ^c	0.41 ^d	2 ^c	0.52-0.75 ^d	NR	NR		
Dermal contact	75	0.000015-0.41	11	0.19-3.6	NR	10		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair-noncoloring	1	NR	NR	0.0038	NR	NR		
Hair-coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	NR	NR	NR		
Mucous Membrane	NR	0.00012-0.12	16	3.9	NR	3.3-4		
Baby	NR	NR	NR	NR	NR	NR		

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

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

^a 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.

^b It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

^c Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^d It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 14. *Helianthus annuus* (sunflower)-derived ingredients with no reported uses.⁵⁹⁻⁶¹

Helianthus Annuus (Sunflower) Leaf/Stem Extract	Helianthus Annuus (Sunflower) Sprout Extract
Helianthus Annuus (Sunflower) Seed Butter	Helianthus Annuus (Sunflower) Seed Flour
Hydrogenated Sunflower Seed Extract	

Table 15. Human irritation and sensitization studies on products/mixtures containing *Helianthus annuus* (sunflower)-derived ingredients.

Ingredient	Product; concentration	Study; n	Results	Reference
Irritation				
Helianthus Annuus (Sunflower) Seed Extract	Moisturizer; 0.0335%	4-week use study; 34	No signs of the potential for dermal irritation	82
Helianthus Annuus (Sunflower) Seed Extract	Trade name mixture; 10%, 0.2 mL	Patch test in approximately 50 mm ² Finn chambers for 48 h. Examination 30 min after removal; 10	Very slight erythema in 2 subjects and clear erythema in 1 subject. Well tolerated.	28
Helianthus Annuus (Sunflower) Seed Wax	Lipstick; 3.34%	2-week use study in humans with sensitive skin; 26	Not irritating or sensitizing	81
Sensitization				
Helianthus Annuus (Sunflower) Seed Extract	Face cream; 0.238%	HRIPT; 53	2 + level reactions and 11 ? level reactions during induction. 2 + level reactions and 5 ? level reactions at 48, 72, and/or 96 h after challenge. Not irritating or sensitizing.	84
Helianthus Annuus (Sunflower) Seed Extract	Moisturizer; 0.0335%	HRIPT; 102	Not irritating or sensitizing	86
Helianthus Annuus (Sunflower) Seed Extract	12% in a trade name mixture tested at 10%, final concentration 1.2%	HRIPT; 50	1 marginal reaction during induction. Not irritating or sensitizing.	83
Helianthus Annuus (Sunflower) Seed Extract	10% in a trade name mixture, tested at 100%	HRIPT; 48	Not irritating or sensitizing.	85
Helianthus Annuus (Sunflower) Seed Wax	Lipstick; 4%	HRIPT; 114	There were no adverse events. It was concluded that this product was not a potential dermal irritant.	88
Helianthus Annuus (Sunflower) Seed Wax	Lipstick; 3.34%	HRIPT; 107	Not irritating or sensitizing	87

Table 16. Case reports of children and adults with oral, dermal, and inhalation allergic reactions to *Helianthus annuus* (sunflower) seeds and plants.

Case History	Testing	Reference
Oral Exposure		
3-year-old boy presented with oral discomfort that developed after eating <i>Helianthus annuus</i> (sunflower) seeds for the first time. Treatment with diphenhydramine and rest resolved the reaction. A few weeks later, he had a similar reaction to a snack bar made with <i>Helianthus annuus</i> (sunflower) seed "butter". He was not treated but observed by his parents. In a subsequent episode, the boy had a similar reaction to a bread roll with poppy seeds; this required epinephrine and an emergency room visit. This child had a history of mild infantile atopic dermatitis. There was an older sibling with a confirmed peanut allergy and the home had been peanut-free for	A SPT of a slurry of fresh <i>Helianthus annuus</i> (sunflower) seed resulted in a 1-mm wheal within 3-4 min and severe pruritus. A similar reaction was elicited from poppy seeds (>10 mm wheal) and a reaction to pumpkin seeds (8 mm wheal).	8

Table 16. Case reports of children and adults with oral, dermal, and inhalation allergic reactions to *Helianthus annuus* (sunflower) seeds and plants.

Case History	Testing	Reference
some time and alternatives, such as <i>Helianthus annuus</i> (sunflower) seed "butter" had been fed to the children.		
5-year-old girl with a diagnosed peanut allergy (at 18 months of age) presented with generalized urticaria and angioedema of the lips. She had just eaten a few bites of <i>Helianthus annuus</i> (sunflower) seed butter (reportedly from a facility that does not process peanuts).	SPT at 18 months were positive for peanuts (6 mm wheal) and negative for <i>Helianthus annuus</i> (sunflower) seed; at 5 years, the tests were positive for peanuts (21 mm wheal) and <i>Helianthus annuus</i> (sunflower) seed (16 mm wheal).	91
11-year-old boy who presented with generalized urticaria/angioedema and bronchospasm within 30 min of eating <i>Helianthus annuus</i> (sunflower) seeds. Epinephrine relieved the symptoms. He had eaten <i>Helianthus annuus</i> (sunflower) seeds at least once before without any reactions. He had a history of seasonal allergic rhinitis for the previous 2-3 years.	Scratch tests and RAST to <i>Helianthus annuus</i> (sunflower) seed extract were positive as well as tree molds and grasses.	9
A 22-year-old female, with a history of atopic dermatitis and Japanese cedar pollenosis, ate 5 pieces of <i>Helianthus annuus</i> (sunflower) seed chocolates. She experienced sudden nausea and dyspnea 5 min later, followed by development of wheals all over her body. In the emergency room, wheezing was heard in the region of her larynx. Her bulbar conjunctiva was hyperemic. She was treated with injections of epinephrine and corticosteroids. Later, although she again ate chocolate confections, no immediate allergic reactions occurred. She recalled having often eaten <i>Helianthus annuus</i> (sunflower) seeds as a snack during high school.	SPT, CAP assay, ELISA, the ImmunoCAP® inhibition assay, immunoblot and immunoblot inhibition assays, and N-terminal sequence analysis. SPT were performed with the native protein extract from <i>Helianthus annuus</i> (sunflower) seeds and 7 other extracts from the <i>Asteraceae</i> family. There were positive reactions to the extracts of <i>Helianthus annuus</i> (sunflower) seeds in SPTs but not in other extracts. The level of serum IgE antibody for <i>Helianthus annuus</i> (sunflower) seed was high (35.1 UA/ml, class 4). There was a high titer of IgE antibody specific for Japanese cedar pollen (27.2 IU/ml, class 4). Her serum was negative for specific IgE antibodies against mugwort, birch, ragweed, dandelion, latex, chocolate, cacao, peanuts, almonds, Brazil nuts, and gelatin. ELISA of the extract from <i>Helianthus annuus</i> (sunflower) seeds showed higher absorbance than the controls (P < 0.01). There were no reactions to the 4 kinds of nuts. The ImmunoCAP® inhibition assay of the extract from <i>Helianthus annuus</i> (sunflower) seeds showed suppression that depended on the concentration of the inhibitor (<i>Helianthus annuus</i> (sunflower) seed). The same test for Japanese cedar pollen with <i>Helianthus annuus</i> (sunflower) seeds showed no suppression. Several IgE-binding protein bands on the immunoblot assay using the extract from <i>Helianthus annuus</i> (sunflower) seeds were identified. These IgE-binding protein bands were almost undetectable when using control sera. On the inhibition immunoblot assay using the <i>Helianthus annuus</i> (sunflower) seed extract, the IgE-binding signal of one band (13 kDa) disappeared completely. The N-terminal amino acid sequence of the IgE-binding protein band (13 kDa) of <i>Helianthus annuus</i> (sunflower) seed closely matched LTP from <i>Helianthus annuus</i> (sunflower) seeds. The author concluded that LTP is able to induce severe and systemic symptoms and sensitization by the oral route in fruit allergic patients who do not have associated pollen allergy	12
A 22-year-old woman developed systemic allergic reactions comprising rhinitis, nasal congestion, tearing, and facial and generalized urticaria after eating shelled <i>Helianthus annuus</i> (sunflower) seeds. The symptoms resolved in a few hours. She had no history of allergy to seed that she shelled herself.	Skin prick test-positive for <i>Helianthus annuus</i> (sunflower) pollen and dust mites; negative for other pollens and foods. Open food challenge-positive for shelled <i>Helianthus annuus</i> (sunflower) seeds. Analysis showed that the shelled seeds were contaminated with pollen.	10
A 23-year-old man, with a history of rhinoconjunctivitis, asthma, and hypersensitivity to grass pollens presented with contact urticaria from dermal contact with peeled <i>Helianthus annuus</i> (sunflower) seeds. The symptoms (itching, erythema, and wheal-and-flare reactions) appeared 15 min after contact. He reported tolerating the consumption of <i>Helianthus annuus</i> (sunflower) seeds with occasional pruritus or the oral mucosa and mild obstruction of the pharynx after eating larger amounts of the seeds. He tolerated <i>Helianthus annuus</i> (sunflower) oil both dermally and orally.	Total serum IgE was 456 IU/mL (strongly positive). Local urticaria was observed after 30 min in a closed patch test of peeled <i>Helianthus annuus</i> (sunflower) seed; and open patch test showed only local erythema. An itchy wheal of 5 mm was observed in a prick test of <i>Helianthus annuus</i> (sunflower) seed.	5
A 37-year-old woman experienced anaphylaxis (diffuse pruritus, urticaria, angioedema, nausea and vomiting, chest tightness, and wheezing, followed by vascular collapse and loss of consciousness) within 20 min of ingesting <i>Helianthus annuus</i> (sunflower) seeds. She was treated with epinephrine, intravenous fluids, diphenhydramine and steroids. Over the next week, she had several episodes of lip and facial swelling in the morning on awakening. She had a history of eating <i>Helianthus annuus</i> (sunflower) seeds without incident and she	P-K test- Heated and unheated serum from the subject was used. After injections of the serums, skin sites were challenged with intradermal injections of commercial <i>Helianthus annuus</i> (sunflower) seed extracts (1:1000 w/v; 0.02 mL). The passive transfer recipient was strongly positive at the unheated serum site on challenge with <i>Helianthus annuus</i> (sunflower) seed extract. The heated serum site challenged with <i>Helianthus annuus</i> (sunflower) seed extract was negative.	7

Table 16. Case reports of children and adults with oral, dermal, and inhalation allergic reactions to *Helianthus annuus* (sunflower) seeds and plants.

Case History	Testing	Reference
had no prior allergic reactions to foods. She had a history of anaphylactic reactions to fire ant venom. Her general health was good, and she was taking no medications.	Skin Prick Test-commercial <i>Helianthus annuus</i> (sunflower) seed extract resulted in a 12x16 mm wheal; causative seed extract resulted in a 16x16 mm wheal; cold-pressed <i>Helianthus annuus</i> (sunflower) oil was negative. RAST-Commercial <i>Helianthus annuus</i> (sunflower) seed extract (1:20 w/v in 50% glycerin) and an extract prepared from the causative seeds (extracted in diluent saline, 1 gm/100 mL, filtered) resulted in a class 4 reaction (a moderate reaction). Open challenge to the inner upper lip and oral mucosa-refined and cold-pressed oil had no reaction.	
A 50-year-old woman who presented with generalized urticaria, facial angioedema, laryngeal edema, wheezing, and dyspnea about 2 h after ingesting several <i>Helianthus annuus</i> (sunflower) seeds. The symptoms were relieved by antihistamine. She had eaten these seeds in the past. She reported that when she handled <i>Helianthus annuus</i> (sunflower) seeds that she used to feed birds, she developed pruritus of her hands. She had no other history of food sensitivity; she had a history of allergic rhinitis and occasional mild bronchospasm since childhood, for which she was not taking medication.	Scratch tests and RAST titers to the <i>Helianthus annuus</i> (sunflower) seed extract were positive with mixed results to grass, ragweed, tree pollens walnut, and peanut	9
A 58-year-old man present with “tingling of his lips”, a generalized itching sensation, and laryngeal edema that began within 5 min of ingesting 3 <i>Helianthus annuus</i> (sunflower) seeds. He developed abdominal pain, generalized angioedema, and bronchospasm within 30 min of arriving at the hospital. Most of the symptoms were resolved with epinephrine, but he was hypotensive, so he was admitted for treatment with theophylline and steroids. He had a history of perennial rhinitis and reported sensitivity to walnuts. He had no known allergies to foods in the <i>Asteraceae</i> family.	Scratch tests and RASTs to a <i>Helianthus annuus</i> (sunflower) seed extract were positive along with June grass and ragweed. The <i>Helianthus annuus</i> (sunflower) seed extract was an aqueous paste made by emulsifying washed <i>Helianthus annuus</i> (sunflower) seeds in buffered saline.	9
Dermal Exposure		
A 62-year-old man presented with forehead dermatitis that had lasted for 2 months. It was resolved with topical corticosteroids but returned when treatment stopped. The man handled cattle fodder that was composed of <i>Helianthus annuus</i> (sunflower) plants.	Patch tested with European standard series and <i>Asteraceae</i> plant series. Positive results were observed for <i>Helianthus annuus</i> (sunflower) leaves and the cattle fodder.	6
Inhalation Exposure		
A 24-year-old man had developed rhinitis and conjunctivitis over 5 years of exposure to <i>Helianthus annuus</i> (sunflower) pollens and then developed asthma during the fifth year. All respiratory and ocular symptoms resolved when he discontinued exposure to <i>Helianthus annuus</i> (sunflower) plants and pollen. He later had a food allergic reaction while eating honey containing 30% <i>Helianthus annuus</i> (sunflower) pollen.	Skin prick tests and RAST to a <i>Helianthus annuus</i> (sunflower) pollen extract (1/20 w/v) showed that he had developed an occupational allergy; skin test results with <i>Helianthus annuus</i> (sunflower) seed were negative. Bronchial provocation tests were performed after a rest period away from exposure to <i>Helianthus annuus</i> (sunflower) pollens, but there was no nonspecific hyperactivity. It was found by RAST that <i>Helianthus annuus</i> (sunflower) pollen does not cross-react with other pollens from the <i>Asteraceae</i> family or with <i>Helianthus annuus</i> (sunflower) seed. The honey that elicited food intolerance was demonstrated to inhibit significantly <i>Helianthus annuus</i> (sunflower) pollen RAST.	4

Table 16. Case reports of children and adults with oral, dermal, and inhalation allergic reactions to *Helianthus annuus* (sunflower) seeds and plants.

Case History	Testing	Reference
<p>A 31-year-old man developed rhinoconjunctivitis and asthma when exposed to dried <i>Helianthus annuus</i> (sunflower) seeds. After working as a baker for approximately 9 years, he started working in a bakery that used <i>Helianthus annuus</i> (sunflower) seeds. After 3 months, he developed rhinoconjunctivitis and asthma, even when his coworkers were handling the <i>Helianthus annuus</i> (sunflower) seeds. He reported having experienced an anaphylactic reaction after eating approximately half a <i>Helianthus annuus</i> (sunflower) seed. The symptoms were increasing as he continued to work in the bakery. After changing jobs to another bakery, he still exhibited rhinitis and asthma at work and developed nocturnal asthma attacks. The subject stopped working at bakeries but still experienced symptoms, even with treatment of inhaled fluticasone propionate and salbutamol.</p>	<p>After 8 months without exposure to <i>Helianthus annuus</i> (sunflower) seeds, a baseline lung function test was conducted showing FEV₁=3.17 (72% of predicted value) and FEV₁/forced vital capacity ratio of 62%. The subject had a 20% decrease in these scores after tipping lactose powder back and forth between 2 trays, indicating a marked nonspecific bronchial hyper-responsiveness. The next day, the tray experiment was repeated with <i>Helianthus annuus</i> (sunflower) seeds for 5 min. There was a 39% decrease in FEV₁. The next day, the same types of exposure to flour (assumed wheat) for 75 min resulted in a 42% decrease in FEV₁. Skin prick test-positive reactions to dust mites but not extracts of wheat, barley, rye, and oats. An extract of <i>Helianthus annuus</i> (sunflower) seed dust was prepared by stirring the dust in phosphate-buffered saline (20% w/v) for 10 min; a 1/10 dilution of the seed extract was used, there was a 10-mm wheal reaction. Skin prick tests of <i>Helianthus annuus</i> (sunflower) and other <i>Asteraceae</i> pollen were negative. <i>Helianthus annuus</i> (sunflower) seed dust elicited positive reactions in inhalation challenges and immunologic tests (details not provided). The author suggested that the continued respiratory symptoms, even after months of avoidance, showed a probable sensitization to α-amylase and that sensitization can develop from the inhalation of <i>Helianthus annuus</i> (sunflower) seed dust.</p>	11

CAP - cell-based antioxidant protection; ELISA - enzyme-linked immunosorbent assay; FEV - forced expiratory volume; K-P test - Prausnitz-Küstner; LTP - lipid transfer protein; RAST - radioallergosorbent test; SPT - skin prick test

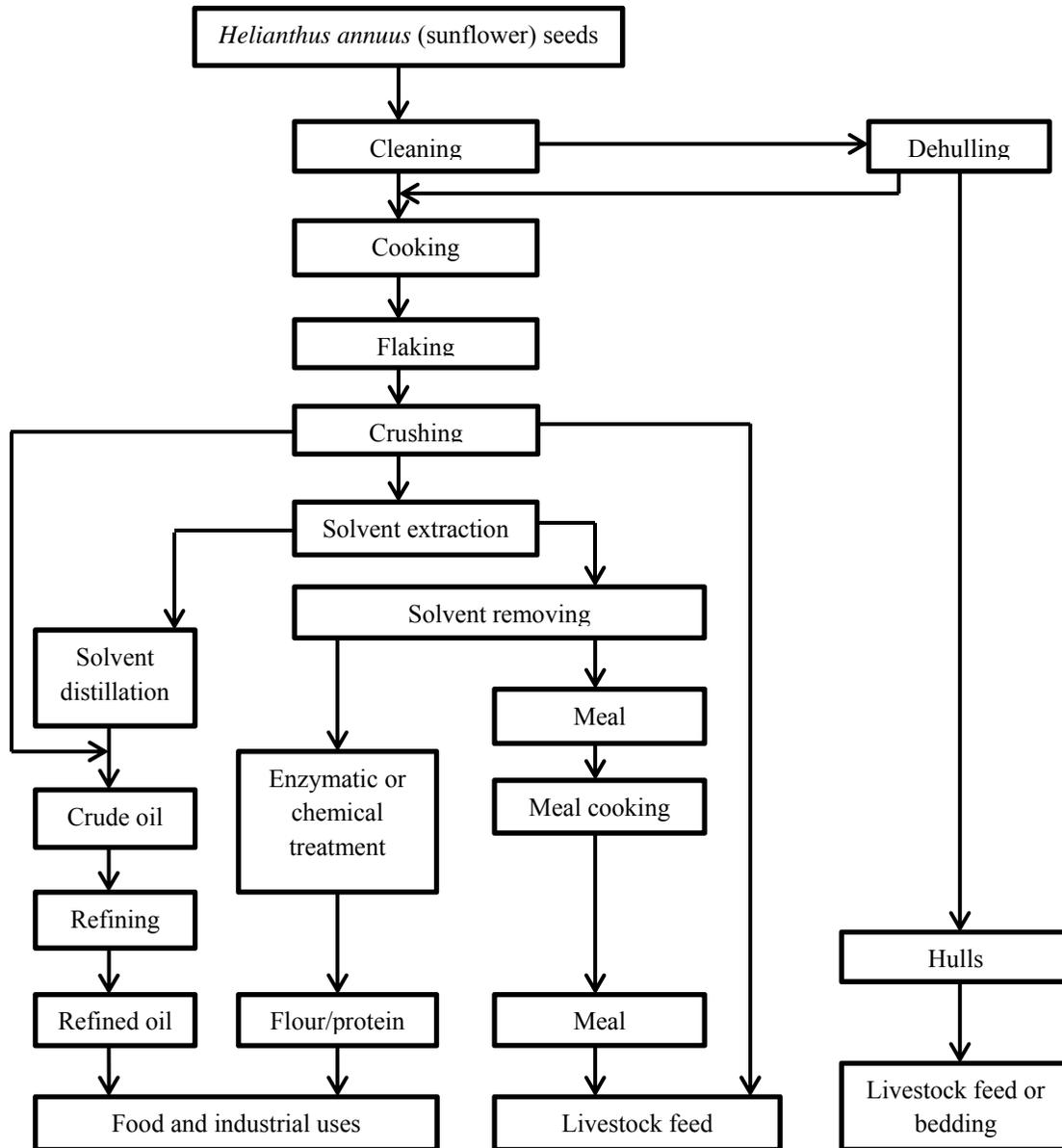


Figure 1. Method of manufacture of some *Helianthus annuus* (sunflower) seed-derived products.³¹

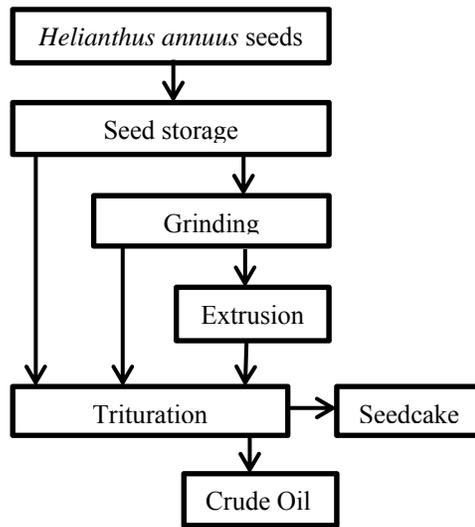


Figure 2. Method of manufacture for *Helianthus Annuus* (Sunflower) Seedcake.³⁰

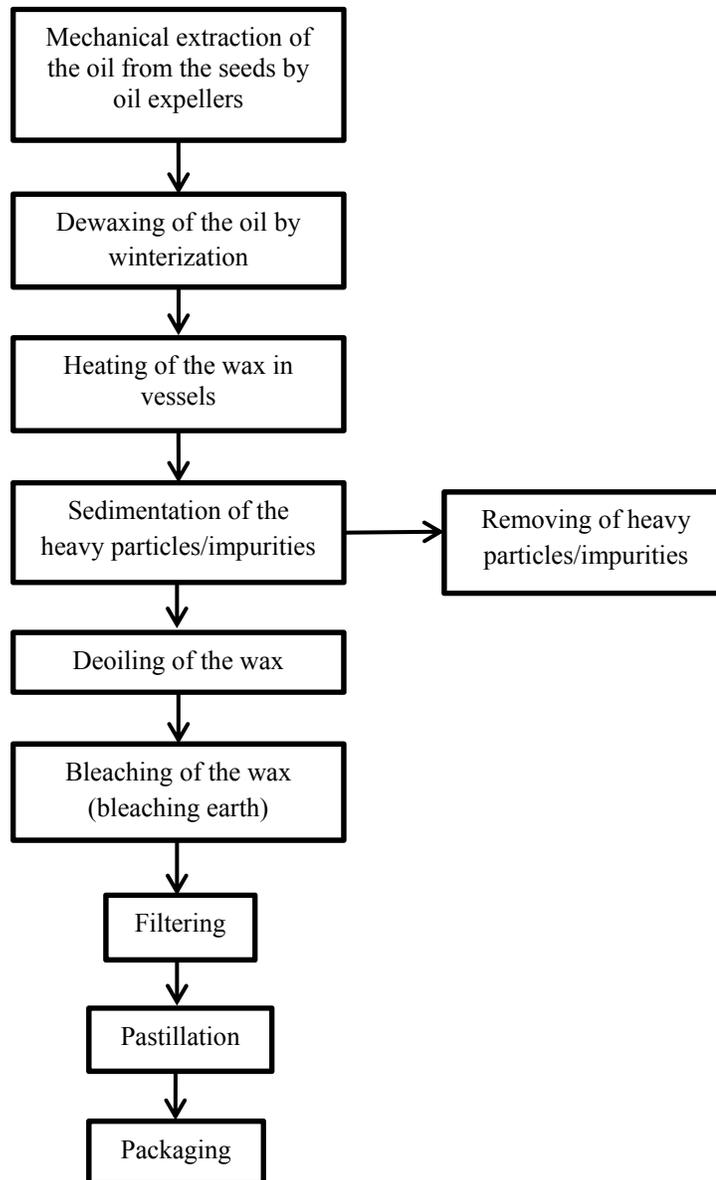


Figure 3. Method of manufacture of some *Helianthus Annuus* (Sunflower) Seed Wax.¹⁰⁰

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2016 VCRP Data – *Helianthus annuus* (Sunflower)-Derived Ingredients

02D - Other Bath Preparations	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
03D - Eye Lotion	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
03E - Eye Makeup Remover	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
03G - Other Eye Makeup Preparations	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	2
04A - Cologne and Toilet waters	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	3
04C - Powders (dusting and talcum, excluding aftershave talc)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
04E - Other Fragrance Preparation	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	2
05A - Hair Conditioner	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	13
05B - Hair Spray (aerosol fixatives)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	2
05C - Hair Straighteners	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	3
05F - Shampoos (non-coloring)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	15
05G - Tonics, Dressings, and Other Hair Grooming Aids	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	15
05I - Other Hair Preparations	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	5
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
06D - Hair Shampoos (coloring)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
10B - Deodorants (underarm)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
10E - Other Personal Cleanliness Products	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	4
11B - Beard Softeners	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	2
12A - Cleansing	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	2
12C - Face and Neck (exc shave)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	6
12D - Body and Hand (exc shave)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	3
12F - Moisturizing	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	7
12G - Night	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	3
12H - Paste Masks (mud packs)	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
12J - Other Skin Care Preps	HELIANTHUS ANNUUS (SUNFLOWER) EXTRACT	1
		96

05F - Shampoos (non-coloring)	HELIANTHUS ANNUUS (SUNFLOWER) FLOWER EXTRACT	1
10A - Bath Soaps and Detergents	HELIANTHUS ANNUUS (SUNFLOWER) FLOWER EXTRACT	1
10B - Deodorants (underarm)	HELIANTHUS ANNUUS (SUNFLOWER) FLOWER EXTRACT	1
10E - Other Personal Cleanliness Products	HELIANTHUS ANNUUS (SUNFLOWER) FLOWER EXTRACT	1
12F - Moisturizing	HELIANTHUS ANNUUS (SUNFLOWER) FLOWER EXTRACT	1
		5

02B - Bubble Baths	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
02D - Other Bath Preparations	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
03C - Eye Shadow	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	2
03D - Eye Lotion	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	3
03F - Mascara	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
03G - Other Eye Makeup Preparations	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	5
04A - Cologne and Toilet waters	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	9
05A - Hair Conditioner	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	61
05B - Hair Spray (aerosol fixatives)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	16
05F - Shampoos (non-coloring)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	55
05G - Tonics, Dressings, and Other Hair Grooming Aids	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	29
05H - Wave Sets	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	2
05I - Other Hair Preparations	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	46
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	21
06C - Hair Rinses (coloring)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
06D - Hair Shampoos (coloring)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	3
06G - Hair Bleaches	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
06H - Other Hair Coloring Preparation	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	3
07A - Blushers (all types)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
07C - Foundations	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
07E - Lipstick	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	7
07F - Makeup Bases	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	2
07I - Other Makeup Preparations	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1

	EXTRACT	
10A - Bath Soaps and Detergents	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	14
10B - Deodorants (underarm)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	2
10E - Other Personal Cleanliness Products	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	3
11E - Shaving Cream	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
11G - Other Shaving Preparation Products	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
12A - Cleansing	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	8
12C - Face and Neck (exc shave)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	30
12D - Body and Hand (exc shave)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	26
12F - Moisturizing	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	16
12G - Night	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	6
12H - Paste Masks (mud packs)	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	3
12J - Other Skin Care Preps	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	4
13A - Suntan Gels, Creams, and Liquids	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	2
13B - Indoor Tanning Preparations	HELIANTHUS ANNUUS (SUNFLOWER) SEED EXTRACT	1
		389

03D - Eye Lotion	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	1
03F - Mascara	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	1
07A - Blushers (all types)	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	1
07C - Foundations	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	1
07E - Lipstick	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	16
07I - Other Makeup Preparations	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	2
12C - Face and Neck (exc shave)	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	1
12D - Body and Hand (exc shave)	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	1
12F - Moisturizing	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	3
12G - Night	HELIANTHUS ANNUUS (SUNFLOWER) SEED WAX	1
		28

03D - Eye Lotion	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	5
03G - Other Eye Makeup Preparations	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	5
05G - Tonics, Dressings, and Other Hair Grooming Aids	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	1
07C - Foundations	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	1
12A - Cleansing	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	9
12C - Face and Neck (exc shave)	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	9
12D - Body and Hand (exc shave)	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	3
12F - Moisturizing	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	26
12G - Night	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	5
12H - Paste Masks (mud packs)	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	2
12J - Other Skin Care Preps	HELIANTHUS ANNUUS (SUNFLOWER) SEEDCAKE	10
		76

There were no reported uses in the 2016 VCRP for:

Helianthus Annuus (Sunflower) Seed
Helianthus Annuus (Sunflower) Seed Butter
Helianthus Annuus (Sunflower) Seed Flour
Helianthus Annuus (Sunflower) Sprout Extract
Hydrogenated Sunflower Seed Extract
Hydrolyzed Sunflower Seed Wax
Helianthus Annuus (Sunflower) leaf/stem extract
Ozonized Sunflower Seed Oil

Copy of Email Correspondence with Dr. Stefano Luccioli and Dr. Ivan Boyer
RE: Allergenicity of 2S Protein Fractions of Seeds and Nuts

From: Luccioli, Stefano [<mailto:Stefano.Luccioli@fda.hhs.gov>]
Sent: Friday, May 20, 2016 5:20 PM
To: Ivan Boyer
Subject: RE: Allergenicity of 2S Protein Fractions of Seeds and Nuts

Ivan, thanks for your reminder email. I have reviewed the two papers.

In the Axelsson paper, although a history of allergic sensitization from airborne/environmental exposure to sunflower seeds seems feasible (in at least 3 of 4 patients), there is lack of any objective markers to demonstrate how sensitization occurred or whether it occurred to specific proteins (i.e., 2S). Moreover, this reported type of exposure may not necessarily mimic airborne exposure to the cosmetic product.

In the Crespo et al, they recruited 65 patients with fruit or seed allergies and found 2 (3%) with sunflower seed allergy. This rate is much lower than that of other common allergens. Also, since this was already an atopic population to begin with, sensitization/reactivity to sunflower seed is not unexpected. This information does not predict a true prevalence of sunflower seed allergy in the US population, which I would expect to be rather low (and lower than most allergens of public health significance).

Although these two studies raise concerns that sunflower seeds are likely allergenic in some people and may be cross-reactive with other foods, there is no evidence that the frequency of sunflower seed allergies reach a level of public health importance. It is difficult to predict whether use of this cosmetic product may cause new sensitization to sunflower seed. However, since the product is not likely to be ingested, I would not be able to justify a reaction risk to individuals with seed or tree nut allergies. As long as the cosmetic products are labeled as containing sunflower seed derived ingredients, this would likely satisfy a condition of safety for these ingredients. My clinical opinion is that there is no need for a warning label for seed or tree nut allergic individuals.

Hope this helps.
Best,
Stefano

From: Ivan Boyer [<mailto:boyeri@cir-safety.org>]
Sent: Tuesday, April 19, 2016 1:41 PM
To: Luccioli, Stefano
Subject: Allergenicity of 2S Protein Fractions of Seeds and Nuts

Dear Dr. Luccioli,

Dr. Linda Katz suggested that we contact you for your opinion about the potential allergenicity of proteins of the 2S fractions of seeds and nuts and other foodstuff that are used to produce cosmetic ingredients.

By way of introduction, I am the Senior Toxicologist on the staff of the Cosmetic Ingredient Review (CIR), which runs an Expert Panel of which Dr. Katz is a liaison member. For more detailed information about the CIR, please see our website: <http://www.cir-safety.org/>.

The concern about the 2S protein fraction was raised during the Panel's discussion of the safety of sunflower seeds, as used in cosmetics. I have attached the latest version of the safety assessment report for ingredients derived from sunflower plants (Helian032016Tent-fina.docx; see especially the sections titled Constituents of Concern, Discussion, and Conclusion), which has not yet been finalized, and a copy of the memo to the Panel, which includes a brief summary of the pertinent literature.

The Panel was concerned about the ubiquitous nature of 2S proteins from seeds and nuts and the potential for inhalation exposures to ingredients from these sources in cosmetic products that may be inhaled. The Panel is considering including, in the Conclusion, the following warning to address these concerns:

“Persons with known allergies to nut or seed proteins should avoid using personal care products that contain these ingredients.”

Your expert insights and recommendations on this subject will be greatly appreciated. I can best be reached by cell phone (703-728-1100) if you would prefer to call to discuss or to set up a time to discuss.

Best Regards.

Ivan.

Ivan J. Boyer, Ph.D., D.A.B.T.

Senior Toxicologist

Cosmetic Ingredient Review

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2S albumin in *Helianthus annuus* (sunflower)

Constituents of Concern

At the December 2015 meeting, the Panel was concerned about case reports of allergic reactions to oral, dermal, or inhalation exposure to sunflower seeds. In particular, the Panel was concerned that potentially allergenic 2S albumins present in sunflower seed cake and flour in cosmetic products (including products that may be inhaled incidentally) could induce or elicit type 1 hypersensitivity reactions in users of such products. The Panel noted that proteins of the 2S fraction of many different seeds and nuts have been reported to be allergenic in susceptible individuals, and they requested more information on this topic. Following is a brief summary of the relevant literature. The purpose of the summary is to help inform the Panel's safety assessment of (1) sunflower-derived ingredients, and (2) other seeds and nuts used as cosmetic ingredients.

Seed Storage Proteins

Storage proteins are major components of seeds.¹ These proteins are synthesized in the developing embryos of plants, deposited in protein bodies of seeds during seed maturation, and used as a source of nutrients during germination and seedling growth.^{2,4} The seeds of most dicotyledonous plants contain two major storage protein classes, 2S albumins and 12S globulins, which are distinguished based on their solubility characteristics and their sedimentation coefficients (S = Svedberg units), as determined by sucrose density ultracentrifugation.¹⁻⁴

2S Albumin Storage Proteins

The 2S albumin fractions of seeds are polymorphic mixtures of structurally-related proteins encoded by small gene families.⁵ The characteristics of 2S albumins include low molecular weight, high solubility in water, and high nitrogen and cysteine contents.¹⁻⁴

The 2S albumin family of seed storage proteins is widely distributed in monocotyledonous and dicotyledonous plants, including numerous species of nuts and oilseeds (e.g., sunflower, cucumber, mustard, radish, rape, cottonseed, linseed, rapeseed, almond, Brazil nut, hazelnut, peanut, walnut, peas, lupin and castor bean).^{1,3,4,6} The 2S albumins comprise from 20% (in peanut) to 60% (in oilseed rape and sunflower seeds) of the total proteins in seeds.³⁻⁶

The three-dimensional structures of 2S albumins are similar to those of other small sulfur-rich proteins of the prolamin superfamily, which includes non-specific lipid transfer proteins (ns LTPs), α -amylase/trypsin inhibitors, and soybean hydrophobic protein.^{1,3,5,7} The ns LTPs, α -amylase/trypsin inhibitors, and soybean hydrophobic protein are involved, respectively, in fruit allergies, bakers' asthma disease, and rhinitis and asthma from exposures to soybean dusts or flour.^{2,5,7}

All of the proteins of the prolamin superfamily have similar structures, comprising five α -helices arranged in a right-handed superhelix.^{3,5} In addition, they share a conserved pattern of eight cysteine residues, which form very similar patterns of inter-chain and intra-chain disulfide bonds. The pattern of eight cysteines in specific order appears to support a structural scaffold of conserved helical regions, which stabilizes the tertiary structure of these proteins.

Accordingly, all 2S albumins have a common, compact three-dimensional structural scaffold that comprises a bundle of five α -helices and a C-terminal loop folded in a right-handed superhelix, and is stabilized by the four conserved disulfide bonds.³ There is an exposed and relatively short segment known as “hypervariable region” connecting two of the α -helices. The hypervariable region has been described as the most important antigenic region of the 2S albumins.³ However, the variability in the length and amino acid composition of this region in 2S albumins across plant species suggests that it does not influence the folded structure of these molecules.

Although the skeleton of cysteine residues is conserved in 2S seed albumins, there is generally a low amino acid sequence homology (14% to 40%) within and among plant species, except for members of the Brassicaceae family (e.g., mustards and rapeseed).³

2S Albumin Allergens

Some members of the 2S albumin family have been reported to be major allergens based on their ability to bind IgE from the sera of allergic patients. These include 2S proteins from tree nuts, grains, legumes, spices, oil seeds and cereals.^{1,3} For example, a 2S albumin from castor beans was shown to be a major aeroallergen sensitizer around castor-oil mills.⁸ Cottonseed 2S albumin was allergenic in some individuals exposed by ingestion or inhalation. 2S albumins of mustard seeds were found to be major allergens. 2S albumin from Brazil nuts appeared to be the predominant protein binding to IgE from 9 patients with Brazil nut allergy.^{8,9} The peanut allergen, Ara h 2, was reported to have homology (30%) to 2S albumins.⁸ A report of occupational asthma caused by sesame seed exposure revealed the allergen to be a 2S albumin.

Seed storage proteins are emerging as the main allergens edible seeds and have been associated with cases of angioedema and anaphylaxis. 2S albumins are major allergens in sunflower, sesame, and mustard seeds.¹⁰ Other seeds and nuts contain related allergens, including peas, soy beans, castor beans, rapeseeds, cotton seeds, Brazil nuts, walnuts and peanuts.^{5,10,11} Thus, the 2S albumin storage proteins have been described as “universal allergens” and “inherently allergenic” or “intrinsically allergenic” proteins in seeds in which they occur.^{5,7,8,10} However, not all the 2S albumins should be considered major allergens,³ and those that are allergenic are not necessarily cross reactive.^{3,5,8}

Although the skeleton of cysteine residues is conserved in 2S albumins, the degree of amino acid sequence homology generally does not reflect the phylogenetic relationships among the plants.³ High amino acid sequence polymorphism has been noted even in allergenic 2S albumins belonging to the same species (e.g., in the 2S albumins from sesame seeds or the 2S albumins from castor beans).³ Thus, aligning the amino acid sequences of these proteins is not possible unless knowledge of their spatial organization is used to force the matching of the cysteines that form the conserved disulfide bonds.^{3,5,7}

Aligning the sequences of allergenic 2S albumins from a wide range of species (sunflower, brassicas, castor bean, Brazil nut, peanut, walnut and cottonseed) in this way indicated that the sequence of the hypervariable region forms a flexible, unstructured loop that is an important antigenic region.^{5,8} In addition, epitope mapping studies of 2S allergens from peanuts, Brazil nuts and cashews revealed that regions other than the hypervariable region can also bind strongly IgE in the sera of allergic patients, and

these regions are distributed throughout the molecules.³ Largely unexplored are the likely conformational epitopes comprised of amino acids distant in the primary structures of these allergens but adjacent once the protein folds.³

A case of cross-reactivity between rapeseed and mustard 2S albumins was reported, based on a study using a serum sample from a patient allergic to mustard.^{2,3,7} This finding may not be surprising because rapeseed and mustard 2S albumins have the highest sequence homology of all of the 2S albumins that have been characterized. Nonetheless, cross-reactivity seems to be uncommon in this protein family.⁷ For example, the cross-reactivity of a polyclonal antisera against 2S albumins from Brazil nuts was found to be negligible using extracts of other nuts (almond, hazelnut, pecan, cashew, walnut and peanut) or legumes (pea and chickpea).³ Further, none of the sera from 23 patients allergic to soybean was found to have IgE specific against soybean 2S albumins, indicating that these proteins are not major allergens in the patient population studied.³

Thus, 2-S allergens with a similar fold are not necessarily cross-reactive. Lack of cross-reactivity of the allergens in this protein class has been attributed to the regions of sequential variability located mainly in the hypervariable loops that are often the sites of IgE-binding.^{3,7} This view is consistent with observations that, in general, proteins with a similar fold are not necessarily cross-reactive.^{5,12}

On the other hand, the compactness and rigidity of 2S albumins, resulting from their disulfide bond arrangement and electrostatic interactions, confers high stability against thermal or surfactant-induced denaturation and digestion by proteolytic enzymes.^{3,5,7} Resistance to denaturation and digestion is a key factor for the allergenicity of food components. This property would allow 2S albumins to reach the gastrointestinal tract almost intact.⁵ The resistance of allergenic 2S proteins to food processing, cooking, and proteolytic attack may help explain their potential to cause severe food allergies.^{2,3,5}

2S Allergens of Sunflower Seeds

Clinical reports indicated that exposure to sunflower seeds can cause allergic reactions in sunflower seed-sensitized individuals.¹³ Sunflower seeds have been reported to cause anaphylactic reactions after ingestion and rhinitis and asthmatic reactions after occupational exposure to sunflower seed dust in susceptible people.^{11,14}

As noted above, sunflower seeds contain 2S albumins that in other seeds and nuts have been shown to be allergenic.¹¹ Some of the 2S albumins from sunflower seeds were first suspected to be allergens based on their high degree of homology (34%) with the allergenic mature 2S albumin of Brazil nuts.

Sunflower albumins are basic proteins with molecular masses in the 10-18 kDa range.^{4,13} In contrast to 2S albumins from other species, which consist of two chains linked by disulfide bonds, sunflower albumins consist of single polypeptide chains.^{1,3,5,13} The 2S albumin fraction of sunflower seeds contains at least 8 (most probably 11 to 13) distinct albumins, two of which are rich in methionine (16%) and cysteine (8%), like the 2S albumins from Brazil nuts.^{5,11,13} These two proteins are designated SFA-7/sunflower seed albumin (SFA-7/SSA) and SFA-8/SSA.^{11,15} The 16 kDa immature SFA-8/SSA is cleaved during seed development to form the 12 kDa mature protein.^{1,11}

Studies have demonstrated that immature and mature methionine-rich 2S albumins in sunflower seeds bind to IgE from patients allergic to sunflower seeds, and are likely to be responsible for anaphylactic reactions in some sunflower seed-sensitive subjects.¹⁴

2S Albumins and Genetic Engineering

Legume seeds in the diet are relatively deficient in sulfur-containing amino acids. In 1996, soybeans and several other legumes were experimentally enhanced by transfection and transgenic expression of a Brazil nut 2S albumin, with the goal of improving the nutritional quality of the seeds used for animal feeds and human foods.^{1,11} Like SSAs (SFA-7 and SFA-8), the 2S albumin fraction of Brazil nuts is exceptionally rich in methionine residues, as well as cysteine.^{3-5,7,8}

However, the recombinant 2S protein retained its intrinsic allergenicity.^{8,9} People who reacted to Brazil nut extracts on standard skin-prick tests had similar reactions in response to extracts of transgenic soybeans that contained the recombinant 2S Brazil nut albumins.³

These findings demonstrated the transfer of a major allergen from the 2S albumin fraction of Brazil nuts in an attempt to improve soybean varieties through genetic engineering.⁹ Similarly, the allergenic 2S albumin SFA-8/SSA from sunflower seeds would be expected to result in severe allergic reactions in some sunflower seed-allergic individuals.^{8,9,14} The results of these studies indicate that, generally, 2S proteins should be assessed carefully for allergenic potential before transferring their genes into food plants.³

Accordingly, the Food and Drug Administration (FDA) has directed developers of new plant varieties to consider the allergenic potential of donor organisms when assessing the safety of foods derived from genetically engineered plants.⁹ The food would require a label to alert consumers if there is insufficient information to demonstrate that the introduced protein cannot cause allergic reactions in a susceptible population. Based on FDA's policy, food derived from new plant varieties that are likely to contain an allergenic 2S albumin should be labeled to alert consumers.⁹

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 4, 2016

SUBJECT: Sunflower Botanical Extract

The attached statement was received from New Directions Aromatics concerning their Sunflower Botanical Extract

(<https://www.newdirectionsaromatics.com/products/botanical-extracts/sunflower-botanical-extract.html> - SDS at https://www.newdirectionsaromatics.com/msds/MSDS_SunflowerBotanicalExtract.pdf).

New Directions Aromatics. 2016. Statement Product Name: Sunflower Botanical Extract.

3/30/2016



NEW DIRECTIONS
A R O M A T I C S

STATEMENT

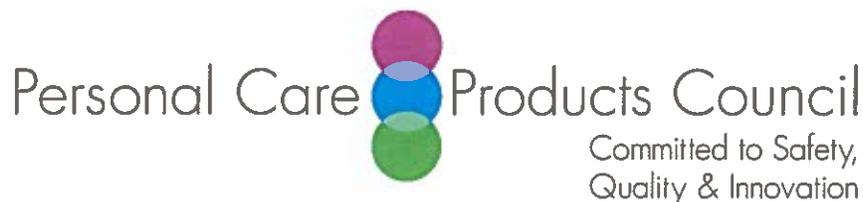
PRODUCT NAME: SUNFLOWER BOTANICAL EXTRACT

We hereby certify that, to the best of our knowledge, this product was manufactured from the seeds of the sunflower plant.

Disclaimer & Caution

Please refer to the Material Safety Data Sheet (MSDS) and all other relevant technical information specific to the product, prior to use. The user of this product is solely responsible for determining the suitability of the product for their particular use and to be in compliance with all laws and regulations applying to the use of this product. New Directions Aromatics Inc. shall not be held responsible for any damages or for any adverse physical effects (including injury or bodily harm) caused by insufficient knowledge, wrongful application or the improper handling or use of this product. As the ordinary or otherwise use(s) of this product is outside the control of New Directions Aromatics Inc., no representation or warranty, expressed or implied is made as to the effect(s) of such use(s) (including damage or injury), or the results obtained. The information on the New Directions Aromatics Inc. website is obtained from current and reliable sources but makes no representation as to its comprehensiveness or accuracy. The liability of New Directions Aromatics Inc. is limited to the value of the goods and does not include any consequential loss. New Directions Aromatics Inc. shall not be liable for any errors or delays in the content, or for any actions taken in reliance thereon.





Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel 

DATE: March 23, 2016

SUBJECT: Comments on the Draft Tentative Report: Safety Assessment of *Helianthus annuus* (Sunflower)-Derived Ingredients as Used in Cosmetics (prepared for the March 31-April 1, 2016 CIR Expert Panel meeting)

Key Issue

It is not clear why there was a request for HRIPT data on Hydrogenated Sunflower Seed Extract at 1% as there are no uses or use concentrations reported for this ingredient.

Additional Considerations

Definition - It is not clear why information on composition/constituents must be “provided”. As it is very helpful to know the potential of what might be found in a specific plant, both published and unpublished information, as well as ingredient and plant composition are helpful. Please use the word “identified” rather than “provided”.

Physical and Chemical Properties, Table 3 - Table 3 includes information on several ingredients. The way Table 3 is mentioned in the text suggests it only includes information on *Helianthus Annuus* (Sunflower) Extract.

Method of Manufacture - As reference 50 and reference 28 are from the same company, it is not appropriate to state: “Another supplier reports...” As reference 50 and 28 are no longer available on the internet, will these references be available from CIR upon request? There is a 2016 version of the MSDS on the New Directions Aromatics, Inc. website that does not state the plant part.

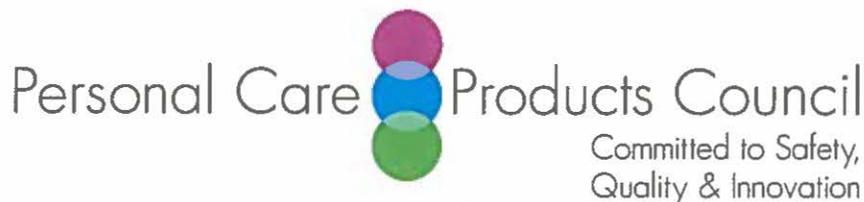
Impurities, Summary - The 0.52% protein concentration was for the material before dilution. Because the *Helianthus Annuus* (Sunflower) Seed Extract is sold as a 10% dilution, a protein level of 0.05% should be reported. Reference 51 (Institut’dExpertise Clinique, 1997) is not the correct reference for the protein concentration. In the same submission, there is a summary of information on the ingredient from Sederma. That summary is the correct reference for the protein concentration.

Cosmetic Use - At what concentration was Helianthus Annuus (Sunflower) Seed reported to be used in hair products and a suntan product?

Sensitization, Human, Summary - Please reorganize the human section and the Summary so that information on sensitization potential about one ingredient is presented together.

Table 2 - Please indicate for which ingredient the maximum use concentration was reported. It would be better to indicate the maximum use concentrations for the ingredients of interest. Sunflower seed oil was reported to be used up to 96% and there were no uses of Phytosteryl Sunflowerseedate reported.

Table 3 - If reference 50 is left in the report, it should be indicated that the first extract was reported to be an extract of "bark".



Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 19, 2016

SUBJECT: Comments on the Tentative Report: Safety Assessment of *Helianthus annuus* (Sunflower)-Derived Ingredients as Used in Cosmetics (posted April 12, 2016)

Definition - It is not correct to state that composition information can “only” be from industry. Published plant and ingredient composition information, such as references 28 and 33 cited in this report, are also helpful.

Physical and Chemical Properties - This section needs to be revised as there is no information on *Helianthus Annuus* (Sunflower) Flower Extract in Table 3.

Impurities - At the April meeting, the CIR Expert Panel indicated that reference to an “endogenous synthesis” of benzo[a]pyrene should be deleted.

Sensitization, Dermal - Animal - Please revise the following sentence: “There were no signs of a reaction under macroscopic reaction during the challenge phase of the experiment.”

Clinical Use - This section heading does not make sense as none of the exposures were from “clinical use” - it should be “Clinical Studies”.

Summary - Protein concentrations of two other seed extracts were also reported and should be mentioned in the Summary.

It appears that the same guinea pig sensitization study of a seed extract at a final concentration of 1.2% is mentioned twice in the Summary.

Discussion - It is not clear why the EU status of sunflowers in the diet rather than the status in the United States (or both) is mentioned in the Discussion.