Safety Assessment of Humulus Lupulus (Hops)-Extract and Oil as Used in Cosmetics

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The 2017 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 Interim Director is Bart Heldreth, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer and Ivan J. Boyer, Senior Toxicologist.

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MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: August 18, 2017

Subject: *Humulus lupulus* (Hops) Extract and Oil as Used in Cosmetics

Attached is the Draft Final Report on *Humulus lupulus* (Hops) Extract and Oil as used in cosmetics. [*HumLup092017Rep*] These ingredients are derived from a part of the *Humulus lupulus* (hops) plant.

In April 2017, the Panel issued a tentative report with the conclusion that *Humulus lupulus* (Hops) Extract and Oil are safe as used when formulated to be non-sensitizing. The Panel changed the name of the report to reflect the revision of the names of the ingredients being reviewed. Specifically, five INCI ingredient names were consolidated under the name Humulus Lupulus (Hops) Extract, and Humulus Lupulus (Hops) Cone Oil is now named Humulus Lupulus (Hops) Oil.

Due to the name changes of the ingredients in this report, the format of the Use table (Table 12) is different from the usual format. The Panel should examine the table and ensure it satisfies the Panel's needs.

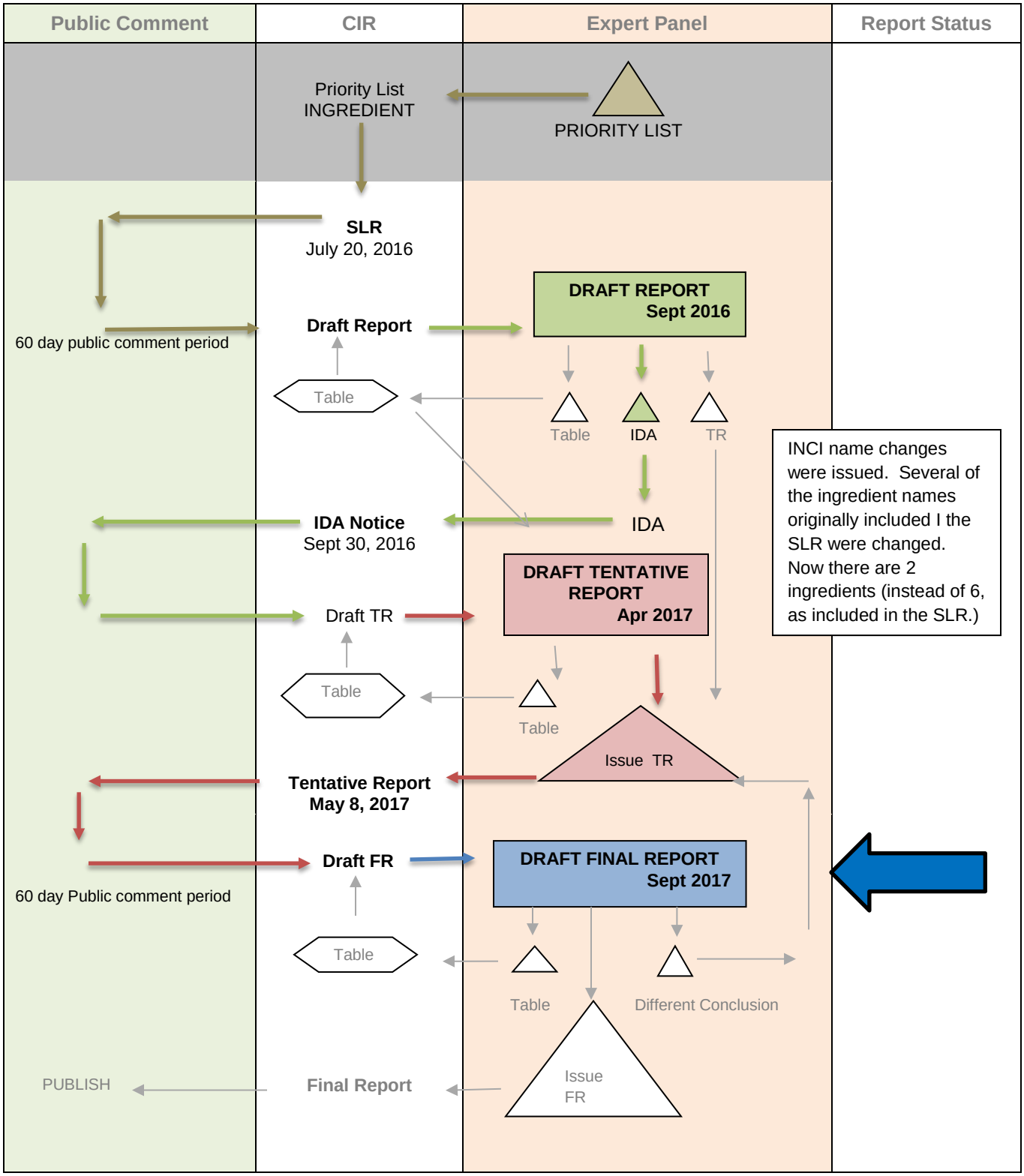
No new data have been submitted. Council comments have been addressed. [*HumLup092017PCPC_1,2*]

Please review the Discussion to ensure that it captures the rationale for the report conclusion. Please review the Abstract and Conclusion to ensure that they capture the Panel's thinking. The Panel should be prepared to issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Humulus lupulus* (hops)-derived ingredients

MEETING April 2017



History – *Humulus lupulus* (Hops)-Derived Ingredients

2015 – The ingredient group was added to the Priority List.

July, 2016 – Scientific Literature Review posted with a request for additional information.

September, 2016 – The Panel issued an Insufficient Data Announcement for the following 6 *Humulus lupulus* (hops)-derived ingredients:

Humulus Lupulus (Hops) Extract
Humulus Lupulus (Hops) Cone Extract
Humulus Lupulus (Hops) Cone Oil
Humulus Lupulus (Hops) Flower Extract
Humulus Lupulus (Hops) Stem Extract*
Humulus Lupulus (Hops) Strobile

The data needs are:

- Composition and sensitization for Humulus Lupulus (Hops) Extract at maximum concentration of use (0.6%)
- Composition for Humulus Lupulus (Hops) Stem Extract.

The Panel noted the presence of β-myrcene at 25.4% in Humulus Lupulus (Hops) Cone Oil. This constituent is a potential irritant, and there is an NTP study showing increased incidences of kidney tumors in male rats and liver tumors in male mice after oral administration of 1.0 g/kg/day β-myrcene for 2 years. The Panel noted that the increased incidence of kidney tumors in this study is likely attributable to a mechanism that is not relevant to humans, and the increased incidence of liver tumors is attributable to the high background incidence and susceptibility to the development of liver tumors that is characteristic of the mouse strain used in the study, and is also not predictive of carcinogenicity in humans. Further, the dosage rates of β-myrcene administered orally to the rats and mice in the study were much greater than any reasonable worst-case exposure to β-myrcene that could occur from hops-derived ingredients in cosmetics. However, concerns about β-myrcene, and possibly other constituents, cannot be addressed fully by the Panel, because the available information is not sufficient to characterize adequately the compositions of hops-derived cosmetic ingredients. The Panel emphasized the importance, generally, of adequately characterizing the compositions of cosmetic ingredients derived from plants, as manufactured and supplied to formulators of cosmetic products.

April, 2017 – The Panel examined the Draft Tentative Report and issued a tentative report with the conclusion of safe as used when formulated to be non-sensitizing.

INCI Name Changes The INCI committee created new monographs that combined all of the non-oil ingredients into Humulus Lupulus (Hops) Extract. The other names are now technical names for this ingredient. Humulus Lupulus (Hops) Cone Oil has been changed to Humulus Lupulus (Hops) Oil. Unpublished data have been submitted under the old Humulus Lupulus (Hops) INCI names. In the current version of the report, the old names are still used in the presentation of the use data.

New Data Concentration of use data have been updated. The highest concentration of use for Humulus Lupulus (Hops) Extract has dropped to 0.2% and the highest concentration of use with dermal contact is now 0.13%.

Data were submitted on ocular irritation, mutagenicity, and an HRIPT at 0.5% on an extract of *Humulus lupulus* (hops) “cones”.

The Panel considered the data and the names, and considered if the presentation should be adjusted further to reflect the new naming convention and that the explanation in the Introduction and

Discussion are sufficient. The Panel also considered how the name changes influence the Insufficient Data Announcement and how the new data address the data needs.

In light of the reduction in the number of ingredients in this report to two, the Panel changed the name of the report to "Safety Assessment of Humulus lupulus (Hops) Extract and Oil as Used in Cosmetics."

The Panel further developed the Abstract and Discussion, and issued a Tentative Report with the conclusion that these ingredients are safe as used when formulated to be non-sensitizing.

September, 2017 – The Panel examines the Draft Final Report. The Panel should examine the new version of the USE table to ensure that it meets the Panel's needs.

***Humulus lupulus* (Hops)-Derived Ingredients** Data Profile for ***September*, 2017**. Writer – Lillian Becker																						
	ADME			Acute toxicity			Repeated dose toxicity			Irritation						Sensitization						
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Animal	Human Ocular	Ocular In Vitro	Dermal Animal	Dermal Human	Dermal In Vitro	Animal	Human	In Vitro	Repro/Devel	Genotoxicity	Carcinogenicity	Phototoxicity
New INCI Names																						
Humulus Lupulus (Hops) Extract			X				X				X	X		X			X			X		
Humulus Lupulus (Hops) Oil																						
Historic INCI Names																						
Humulus Lupulus (Hops) Extract			X				X				X			X			X					
Humulus Lupulus (Hops) Cone Extract			X				X					X		X			X			X		
Humulus Lupulus (Hops) Cone Oil																						
Humulus Lupulus (Hops) Flower Extract			X														X					
Humulus Lupulus (Hops) Stem Extract																						
Humulus Lupulus (Hops) Strobile			X									X		X			X					

Search Strategy – Humulus lupus (Hops)

SCIFINDER

"toxicity of Humulus Lupulus" – "toxicity" and "Humulus Lupulus" closely associated – 22; in same report – 155. 147 combined hits. English – 83. Remove patents – 60. 2 possibly useful.

CAS Nos. – 0 hits

"hops" – 323 hits for tissue non-specific alkaline phospatase.

PUBMED
"Humulus Lupulus" – 374 hits. ~25 possibly useful.

ECHA
"Humulus Lupulus" – 13 hits, 12 of mixtures containing hops. 1 useful (CPL info card).

Online Edition: "Combined Compendium of Food Additive Specifications"
"Humulus" "Lupulus" "Hops" – no hits

Journal of the Institute of Brewing – "essential oil", toxicity, lots of hits, ~15 potentially useful.

Internet
"Humulus lupulus" or "hops" in general and with "FDA", "NICNAS", "EU", "IFRA", and "toxicity"

Transcripts – *Humulus* lupulus (Hops)-Derived Ingredients
September, 2016

Dr. Marks' Team

DR. MARKS: Okay. Next ingredient is hops.
DR. SLAGA: I'll drink to that.
DR. MARKS: Humulus lupulus.
MS. BECKER: As far as I know, this is correct.
DR. MARKS: This is a first review of these ingredients, and Tom, Ron, Ron, do you like the ingredients? All these should be included? This is of course, a botanical, and they are various plant parts here, I wanted to clarify, Lillian as the strobuli which was the last ingredient on this list, when I looked that up it said cone, and then we have several ingredients, which are not using that same name, but called cone extract, cone oil. Is that all the same cone?
MS. BECKER: As far as I can discern in the literature, cone and strobile or strobuli, I don't, I'm not sure which, are the same part of the flower, or the same part of the plant, excuse me.
DR. MARKS: Okay.
MS. BECKER: That develops after the flower has done its thing.
DR. BERGFELD: That's the sexual piece.
MS. BECKER: Yes.
DR. BERGFELD: It's on the female only.
MS. BECKER: Yeah, or not. It still develops even if there is no, correct, I mean even if there is no pollination.
DR. BERGFELD: Essentially (inaudible).
DR. MARKS: So, Tom, Ron, Ron, ingredients okay? It's hard to--
DR. SLAGA: Yes.
DR. MARKS: I can't imagine we eliminate any of these. So what needs--
DR. SLAGA: I have a question, does the extract from the whole plant, I mean that's the way it comes across for me.
DR. HELDRETH: That's the way it's defined.
DR. SLAGA: Huh?
DR. HELDRETH: That's the way, that's the way an (inaudible) defined it, it says whole plant.
DR. EISENMANN: That's the way it's defined, but again I have my doubts that any of these whole plant (inaudible).
DR. HELDRETH: Right.
DR. EISENMANN: That's it's all this problem with changing names, because the original name was hops extract, once hops, I still, I keep pushing the INCI committee to try to work on these whole plant extracts. We'll see what happens, but I suspect that hops, and the whole plant, cone extract and strobile are probably the same thing.
DR. SLAGA: Yeah.
DR. EISENMANN: That somebody submitted it at different time periods under different criteria when they were naming things differently, and then that those three are probably the same.
DR. HILL: So does that suggest we need more about method of manufacture, or are we just not going to get it because nobody's labeling it that way anymore? What would you think?
DR. EISENMANN: You know, I have asked and I got one company for the strobile that says that it's an ex-, that they describe they're making an extract. I've asked other company that sensitization data on the finished project [product?] and what, what's their material made of and they've said we'll, we're not sure, it's hops. Probably because they're used at such low concentrations--
DR. HILL: Yes.
DR. EISENMANN: That that's going to be the issue there. And part of this, you probably are aware of. I was driving this in China, if you are using the new name, you can't use it in China, so they want to use a name that exists already. So that's one hesitancy about changing names also.
MS. BECKER: And there's also the issue in the literature that a lot of it is based on beer making and not cosmetics and hops in general refers to the plant as well as the, what they're using to make the beer with and they don't always differentiate.
DR. SLAGA: I thought this was very interesting that this must be the first example of the antimicrobial

that was added to a food or a drink, in this case and then they started adding a little bit more because it had, it made it a little better taste.

DR. MARKS: Yeah, good. So, Tom, Ron, Ron, any needs? There are a lot of blanks in here. Is there any needs -- for me, I wanted to see sensitization data of the whole plant extracted at .06 percent. That's the highest leave one [on?] concentration, as a lot of uses of all these, it's the most, 362. We have a human maximization sensitization test that's okay at .125 percent. But we don't have anything at 0.6 percent. So I'd like to see it at a higher concentration, the safety. I'm not sure five times as much in concentration, that we could use that. And let me see. The rest of them, the concentration of the hops, like the cone extract and the flower extract, very low concentrations, .0005, you wonder why it's in there as an antimicrobial at that level, or does it make the cosmetic taste better, Tom, and then with the flower extract, that's at .001 I have, no, we don't know the number of uses. So that was the need I had from my perspective. From yours, Ron, do you need any tox data? Or are you happy with the safety with beer drinkers?

DR. SLAGA: Yes.

DR. SHANK: I'm, you want either the sensitization for--

DR. MARKS: Yeah, the whole at .06 percent because it was five times what we had in the report. We have a human max that it's okay at point .125 percent. Now I guess if Don said tomorrow, you know, that's close enough and we don't need any more sensitization data. But that was the one, one thing I was a bit concerned from a safety point of view. Probably not vaguely concerned.

DR. SLAGA: No, I agree. I mean it's a concentration difference, so.

DR. MARKS: Yeah, five times difference.

DR. SLAGA: Yeah.

DR. MARKS: And we're using this, much, much higher concentration than the other ingredients we have a concentration for, so I, I would suggest moving tomorrow insufficient data notice sensitization of the whole plant extract at 0.6 percent. And that would be the only data need we'd visit. So Ron Hill?

DR. HILL: Yeah, I think you know, I'm prefacing what I'm about to say with the acknowledgement that the concentrations are very low, which is really important in this case.

DR. MARKS: Other than the whole extract.

DR. HILL: Other than the whole extract, but even there we're at .6.

DR. MARKS: Yeah.

DR. HILL: So that's pretty low even if that's real, it's pretty low. I'm not talking about -- the reason I bring this up, I'm getting a ring from the microphone, but anyway, there's a genotox study in there that's completely sketch, but that's not a technical term, but it's sketch. There's, we don't have any standardization that provides anything useful about the "concentration" of the extract. We don't know the details of the solvent used to make the extraction and we have a range of concentrations, 10 to 400 milligram per microliter. I don't think that's even physically possible. So something is off.

DR. MARKS: So you would clarify the method of manufacture?

DR. HILL: No, this is a genotox study.

DR. MARKS: Okay.

DR. HILL: Because we, we don't have any published carcinogenicity seeking studies, at least none that were dredged up.

DR. SLAGA: But there's been this genotox?

DR. HILL: I'm saying the genotox data is probably bogus or at least very sketchy. And I'm not sure we can have any comfort from that. Maybe again, because the concentrations are so low. If we knew that it was hops, strobile and I like beer.

DR. SLAGA: I have no problem with the genotoxies.

DR. HILL: How can you have a concentration of 100 milligram per micro liter? That didn't, I don't think that's physically possible, so something is off with that study. Maybe it's just the data reporting. But that's what it says. And I'm not sure the 10 milligram per micro liter is even reasonable, so something is amiss. And it's, isn't that a direct report from some industry source without any paper that we can go out and get the original data?

MS. BECKER: (inaudible) to get published. I'll see if I can get it.

DR. MARKS: While you're looking up that, I'll just make one more comment, why I want the sensitization data on the whole planet, 0.6 percent, what alerts to me was the clinical data that their farmers I

believe it was a Polish publication, farmers have, although they didn't call it allergic contact dermatitis, it clearly was. It was on exposed skin, and there was quite an outbreak. And so, therefore, hops does contain allergens that cause allergic contact dermatitis, so I would just like to be safe at the .06 percent. They did skin prick testing in that study, but that really doesn't relate to allergic contact dermatitis.

DR. SLAGA: (inaudible) results are on report about the estrogenic effect among people that harvest, they have an altered menstrual cycle or something like that.

DR. MARKS: I didn't catch that.

DR. SLAGA: I, we, we, can deal with it. It's the estrogenic effect is so weak or so little that I think we can deal with that in a discussion.

DR. HILL: Right, I agree.

DR. MARKS: So that would we, we should put that in here. What page was that, Tom? Estrogenic effect.

DR. SHANK: Page 13.

DR. MARKS: Weak and in discussion and handled. Did you hear that, Lillian?

MS. BECKER: It could bear repeating, thank you.

DR. MARKS: Pardon?

MS. BECKER: It would be nice if you repeated it, thank you.

DR. MARKS: So the point that Tom made and Ron Shank was seconding is there was at page 13, discussion on the estrogenic effect of hops.

DR. SLAGA: Of a specific ingredient.

DR. MARKS: Yeah, was weak and we can handle that. We shouldn't ignore it, just handle it in the discussion. That that would not be a reason to declare it unsafe or insufficient.

MS. BECKER: I agree. It's something that should be discussed.

DR. MARKS: Any other comments?

DR. BERGFELD: Yes. I think you should bring the (inaudible) studies in about pulmonary disease, hyposensitivity, just as a mention when you're mentioning the farmers.

SPEAKER: And no, I don't think, you could forward me that paper (inaudible) find initially how that maps to this without spending some time.

[DR. HILL and MS. BECKER conferring off the record in a loud whisper.]

DR. MARKS: Yeah, I, I had difficulty dealing with that because it started out, you know, describing allergic contact dermatitis and then they did prick testing. So, yeah, I think that certainly can be--

DR. BERGFELD: But they had elevated IGEs in one study.

DR. MARKS: Carol?

DR. EISENMANN: I have a comment. Is essential oil, which is not used, just to make sure you understand it, contains about 25 percent beta myrcene, and you know there's a positive NCC [NTP?] (bio asset) in beta myrcene so I think that's something you're going to have to discuss. It's, it's, has positive for male rat kidney tumors, which might be (alpha 2u1) related but, but not proven, and positive for male mouse liver tumors. And there's some question that the material that was tested was not very pure. So there's some issues with the study, but I think you need, because it's an (anti p bioassay) you should probably mention because there's 25 percent of beta myrcene in the essential oil. But it's not showing up, at least in the one company that provided me information, they looked for it in their extract and it's not showing up in the extract.

DR. SHANK: Why do you want to--

DR. EISENMANN: Because it's an essential oil and I, if you're going to say safest use for all the ingredients and not mention that it contains beta myrcene I think it is an oversight and is not helpful to the industry.

DR. HILL: I think it's also important to note that even if that particular compound isn't in there, it could be in there in some other form and you'd like some confidence that it's not. But the other thing is since these are used in such small amounts, in routes of exposure, we wouldn't expect anywhere near the levels that would reach something where we would have concern based on that end point we do, do need to capture in the discussion. Here's what we see the exposure being maximally and conservatively, and we're nowhere near.

DR. MARKS: Tom, how would you handle that? How do you want to handle that 25 percent beta myrcene in the essential oil? Now, we don't have essential oils in here. Are we going to handle it at--

DR. EISENMANN: There's one essential oil in there. It has no uses.

DR. HILL: Yeah.
DR. MARKS: Oh, yeah, the cone oil you're talking about.
DR. EISENMANN: Correct. Right, right. That's where, that's what contains approximately 24 percent.
DR. BERGFELD: Does it make a difference that it states its volatile? It's under the cone oil listing.
DR. HELDRETH: It's kind of pointing to the fact that it's an essential oil. They're always volatile.
DR. BERGFELD: Okay. But I mean s far as hazard.
DR. MARKS: So, Tom, how would you handle in the discussion? Give Lillian some guidance in terms of the beta myrcene has induced tumors in bioassay?
DR. SLAGA: Well, it, the concentration to do that is so high versus what's in the cosmetic, you know, product that, you know, there's really no concern. And it's a male related rat thing that doesn't seem to be related to humans.
DR. SHANK: Did NTP conclude it was a carcinogen?
DR. SLAGA: Well, they have to conclude that it's a potential. But they don't get it on a basis of dose.
DR. SHANK: If you get it in only male rat kidneys--
DR. SLAGA: And no male humans--
DR. SHANK: -- and it's a highly lipid soluble compound, it's likely to be alpha 2-globulin mechanism--
DR. SLAGA: Right.
DR. SHANK: -- which is irrelevant to humans.
DR. SLAGA: Right.
DR. HILL: It would be nice to know that for sure.
DR. SHANK: And they were liver tumors in mice, probably an increase in incidents, not de novo tumors, but--
DR. EISENMANN: So, clear evidence was the NTP's conclusion for male mice and male rats.
DR. SHANK: Right.
DR. EISENMANN: And based on those two, but that's the language they use.
DR. SHANK: Right.
DR. HILL: But they don't have dose response in that, of any kind?
DR. SLAGA: No, they have the response.
DR. HILL: Okay.
DR. SLAGA: But even the low dose is way higher than you would have it in this product.
DR. HILL: So they're not coming up with some sort of (inaudible) or--
DR. SLAGA: No.
DR. HILL: Okay. That's not very helpful is it.
DR. SLAGA: Not relevant in humans, the mechanism.
DR. HILL: If we know that's the mechanism, we can strongly suspect that's the mechanism and write it that way?
DR. SLAGA: Right.
DR. HILL: Okay.
DR. MARKS: But that wouldn't answer the mouse liver tumors though.
DR. SLAGA: No, it wouldn't (inaudible) mouse liver tumors.
DR. MARKS: That the mouse liver tumors I suspect was just an increase in incidents over control.
DR. SLAGA: Yeah. Because there is a background.
DR. MARKS: Pretty weak evidence for a carcinogen.
DR. SLAGA: Yeah. Once again, you could argue the dose. The cause that increase is way below the dose, or the level that would be found in a cosmetic product.
DR. HILL: It would be nice to have some estimate based on that point six in leave on in some body area which we could use. While we are on the essential oil, I just wanted to state, or at least raise the question, this was just in the introduction, page eight, that it says, "panel also reviewed citrus peel oils, which are essential oils like cumulus, lupulus, hops cone oil". How valid is that statement? Are we saying that the essential oil from hops cones is the same as what we would expect roughly in composition from orange peel?
MS. BECKER: No, just that that's an essential oil, and we've looked at essential oils before.
DR. HILL: Yeah, but I think if you look at the distribution of essential oils, the components of composition vary wildly, depending on where that oil is coming from, so, yeah, it's an essential oil, but to say that hops is like orange, I don't think the evidence backs that up in terms of constituent composition.

MS. BECKER: Okay.
DR. MARKS: So let me summarize, unless there are more comments. Tomorrow, I'm going to move that we issue an insufficient data announcement, that we want the sensitization data of the whole plant extract to 0.6 percent. We have clinical data that farms [farmers?] develop allergic airborne contact dermatitis, and we have a human max only up to .125 percent. In the discussion, we discussed the weak estrogenic effect of hops, the pulmonary effects on farmers, and the issue of myrcene induced tumors, basically that 25 percent myrcene is in essential oil, the cone oil and much higher concentrations for induced rat and mice tumors in the NTP bioassays. Does that capture that right, Tom?
DR. SLAGA: Yes.
DR. MARKS: If I don't have it right, I'll call on you tomorrow. So, three points in the discussion, one sensitization requirement and the insufficient data sound good? Tom, Ron, Ron? Okay.
DR. HILL: I just wanted to ask you beer drinkers, is it a reasonable statement to say hops strobile is an ingredient in food most commonly in beer? I mean, don't we, for men, to make the beer, to sort of cook it up, we're not just adding the strobile in there and then eating it as is? Or is that, I don't know beer making well enough to know that answer. Anybody brew?
MS. BECKER: It's been done at my house a couple of times. It is cooked.
DR. HILL: So it's an ingredient, well, but, but I guess that we say anything that we put in the food and then cook it, we still call it an ingredient in the food. Okay. I'm all right with that.
DR. MARKS: Is Wilbur here? Michael?
MR. BEST: This raises what we were talking about earlier about how we talk about the grass [GRAS] stuff, and the method of manufacture, and I just noticed that so the FDA has them list and there's a limit on things like benzene in it. Is that something that would matter, would be okay for ingestion, but could raise problems on the skin? (inaudible) matters, no, (inaudible).
DR. MARKS: Okay.
DR. HILL: Not benzene that I know of. In fact, it's probably worse by ingestion.
MR. BEST: Really? Okay.

Dr. Belsito's Team

DR. BELSITO: …Okay. Hops, for those who like beer. Humulus lupulus.
MS. BECKER: And there is Wave 2 data for that.
DR. BELSITO: Yeah, it was very limited though; right?
MS. BECKER: Yes.
DR. BELSITO: It was flour [flower] extract. So this is another one where, you know, again, certificate of analysis. So whatever that boilerplate is that we have for botanicals not to be contaminated with other plant species or whatever we need to add.
And then under the introduction, Lillian, I just had issues with putting do not contain more than, you know, ppm 5 MOP. I mean, 5 MOP is not going to be in hops. So that needs to come out of there. And I'm not even sure how much the hops oils are similar to the citrus oils in terms of composition.
DR. LIEBLER: Yeah, I had the same comment. I'm not sure if that was a good analogy, a good comparator. I'm not sure what is a good comparator but I think that one doesn't smell right.
MS. BECKER: I wouldn't know. I have no sense of smell.
DR. LIEBLER: Although some hops impart a fruity character.
DR. BELSITO: Yeah, I mean, I would just get rid of everything. We also reviewed citrus peel oils. And I would just get rid of that whole thing.
DR. LIEBLER: I agree.
DR. SNYDER: So are we sufficient for everything except the core extract now?
DR. BELSITO: Yeah. I thought insufficient for composition and sensitization of hops extract at 0.6 percent, and I didn't know that we needed other data. Is that what you were saying, the hops extract? Or what were you --
DR. SNYDER: Well, we said we were -- before we said we needed composition for the core extract, the flour [flower] extract, the strobe aisle [strobile], and the core oil. Is it cone or core?
MS. BECKER: It's cone.
DR. SNYDER: Cone, I'm sorry.
DR. BELSITO: We found the cone and the strobile were the same; right?

MS. BECKER: Yes.
DR. SNYDER: So we got data on those. We got the flour [flower] extract, but we didn't get the cone extract. But we got cone oil.
DR. BELSITO: So we got cone oil but not extract?
DR. SNYDER: Correct. We got flower [flower] extract but not cone extract.
DR. LIEBLER: So we do have Table 7, which is constituents found in aqueous extract of 10 cultivars of humulus lupulus cone extracts analyzed by GCMS. Because I didn't have any data needs on composition.
DR. BELSITO: Yeah.
DR. LIEBLER: I thought we were okay because we've got hops cone oil as well, which isn't the same as the cone extract. We do at Table 7, which did it for me for cone extracts. And actually, we've got -- yeah, we've got -- yeah, Table 7 has two parts. I just said we needed sensitization and highest concentration of use.
DR. BELSITO: For?
DR. LIEBLER: For the hops extract.
DR. BELSITO: Yeah, that's what I have.
DR. LIEBLER: Because they have a .125 test.
DR. BELSITO: But we don't have composition for hops extract either unless you assume by having the composition of the cone and the --
DR. LIEBLER: Well, that's a good point because if it just says hops extract, it could be the whole plant.
DR. BELSITO: Right. So I had insufficient for composition and sensitization of the hops extract at 0.6 percent. I thought everything else was sufficient, particularly because all the others are used at 0.001 percent and the hops extract is at 0.6 percent.
And then I had a question. Under toxicokinetic studies on page 12, you say that the data on the hops-derived ingredients would not be practical because some ingredients are complex mixtures. And you go on to say exposure to components of these ingredients, cosmetics are suspected to be lower than dietary exposures when consumed as food and drink. And I said, is this true of the whole plant, stem, and flower? Because the consumption of hops, I mean, I don't know. Do we consume hops other than beer? And beer is made from whatever. It's not made from the whole plant, right?
DR. LIEBLER: No, it's made from the cone.
DR. BELSITO: Right.
DR. LIEBLER: Essentially, yeah. Other than the flowers.
DR. BELSITO: It's not made from the stem or the - - it's made from the flower?
DR. LIEBLER: Right.
DR. BELSITO: So the cone and the flower?
DR. LIEBLER: Yeah, the cone is what happens when the flowers kind of dry out and kind of form that, like a used up -- yeah.
MS. BECKER: Whether or not they've been fertilized.
DR. BELSITO: So it's not true for the whole plant?
MS. BECKER: In the introduction --
DR. LIEBLER: She has it as edible.
MS. BECKER: -- (inaudible) and most of the other parts of this plant are edible – chutes [shoots], leaves, flowers, seed, rhizomes, and essential oils.
DR. BELSITO: Are edible?
MS. BECKER: Are edible.
DR. BELSITO: It doesn't mean you can eat it and survive though; right?
MS. BECKER: Apparently, the chutes [shoots] --
DR. BELSITO: I mean, everything is edible. Nickels are edible.
MS. BECKER: Some people eat the chutes [shoots] like asparagus.
DR. BELSITO: Do we have grass [GRAS] studies? Hops chutes [shoots]?
DR. LIEBLER: Hops chutes [shoots].
MR. ANSELL: So they say grass [GRAS] is essential oils, (inaudible) natural extractives, including distillates.
DR. BELSITO: Okay. So I guess natural extractives would mean from the whole plant since it doesn't say -- doesn't limit it?

Jay, is that how you're taking that?
MR. ANSELL: Well, I mean, this is the first review so we can certainly ask those questions, but yeah, the extract within the Table 1 is defined as the whole plant.
DR. BELSITO: Okay.
MR. ANSELL: And then they draw it down in specificity to the cone, the flower, the stem, and the strobile, which is, I think, the flower as well; right?
MS. BECKER: Yes.
MR. ANSELL: That's the extract of one of the other ones.
DR. BELSITO: I didn't have an issue for the safety assessment. I just, you know, was wondering if that's a true statement.
DR. LIEBLER: So I think the ambiguity is in the noncosmetic use and the implication that the essential oils, oleoresins and natural extractives refers to the whole plant or the flower or strobile cone stuff. And if that can be clarified, that would bring the whole plant in for us.
MS. BECKER: It's as clear as I can get in the literature, unless somebody's got something I can't find. Unfortunately, most of the information is toward beer-making, not towards cosmetics or even (inaudible). So everything -- it'll make a comment about how it's edible and then just go talk about how se [we?] use it in beer.
DR. LIEBLER: Well, and for that matter that would only deal with the systemic toxicology issue for us as opposed to the composition. So we have to decide if we're satisfied with the composition, because what we do have is Table 6. And Table 6 is composition of polyphenols and their concentrations in hops. It doesn't say hops extract. It just say hops. And so these include many of the things that we would be potentially concerned about, and so this table is the reason I didn't list that as a composition need. I mean, it's, you know, it's the flavonoids, the tannins, and the phenolic acids.
DR. BELSITO: Quercetin.
DR. LIEBLER: Yeah. Given that, and given the descriptions of the, you know, consumption of these, I didn't have a problem. I didn't flag that as a data need for method of manufacture, composition, and impurities for the hops.
MS. BECKER: When you're saying hops, are you saying the plant or are you saying --
DR. LIEBLER: I'm saying hops not defined any further. That's why I only said hops. Or hops extract in this case, which is the ingredient.
DR. SNYDER: Safe as used except for everything except for the hops extra [extract].
DR. BELSITO: Yeah. So I just want to go back to Table 1. I don't understand. It says hops strobile, and then it has no reported functions?
MS. BECKER: Correct.
DR. BELSITO: How does that -- how can it be in a cosmetic dictionary without a function?
MR. ANSELL: Because the cone and strobile are synonymous. I think that's the confusion we've been having.
DR. BELSITO: But we don't even have cone listed there.
MS. BECKER: We have cone extract.
DR. BELSITO: We have cone extract.
MR. ANSELL: Cone oil is the same as strobile oil.
DR. BELSITO: We have the cone and the strobile are the same.
MR. ANSELL: Right. And the cosmetic product is the whole plant.
DR. BELSITO: There's no cone listed there. And then the strobile has no reported function. I just don't understand how, you know --
DR. LIEBLER: It seems like an omission.
DR. BELSITO: Is this real?
MR. ANSELL: Yeah.
DR. BELSITO: You can have a product listed in the INCI dictionary and then it goes reported function and cosmetics none. (Inaudible) I mean, that is like the worst thing I've ever seen.
MR. ANSELL: You're right, it's a good question but it's not the worst thing we've ever seen.
DR. BELSITO: Well, it's getting there. Okay. So just make sure that there's nothing there. Then, under the cone oil, the only function is as a fragrance ingredient? If it's strictly a fragrance should we be reviewing it?
MS. BECKER: We have been reviewing them if they have not been done by --

DR. BELSITO: Has not been checked. That's my question.
MS. GILL: If it isn't on the RFM [RIFM] list. And I believe Bart checked. And you can double check. Yes.
DR. BELSITO: Okay.
SPEAKER: Is that true?
MS. GILL: And we're working on that clarification because it doesn't make sense to say it's RFMs [RIFMs] if it's a fragrance but we're reviewing it. So we're working on that language.
MR. ANSELL: Okay. Because I don't think we have reviewed anything which is not a mixed use product, whether RFM [RIFM] has gotten through it as a fragrance use or not.
MS. GILL: We have.
MR. ANSELL: It had no other application?
MS. GILL: The dictionary stated it was a fragrance.
DR. BELSITO: We'll just confirm that. And then we don't have composition on the hops and we don't have composition on the stem extract.
DR. SNYDER: Sounds like we have two insufficient.
DR. LIEBLER: Yep.
DR. BELSITO: And then we also are insufficient for the hops extract, the concentration of use which was (inaudible).
DR. LIEBLER: Sensitization.
DR. BELSITO: For sensitization.
DR. LIEBLER: Yeah, I think we're okay. I don't think we're insufficient for hops extract because we've got Table 6 for composition.
DR. BELSITO: Okay. Go back to Table 6.
MS. BECKER: Hops extract or cone extract?
DR. LIEBLER: Table 6 is hops. It didn't say extract; it just said hops, Table 6.
DR. BELSITO: Okay. So you're okay with composition? So does that cover stem as well?
DR. LIEBLER: Well, we could use that to cover stem because hops is -- hops extract is the whole plant. Stem --
DR. BELSITO: But this is just the composition of polyphenols. It's not the total composition.
DR. LIEBLER: It's polyphenols, phenolic acids, and the tannins.
DR. BELSITO: Right. But then at least 93 percent of this is not telling us what it is.
DR. SNYDER: Insufficient. Okay. Do you want to go with insufficient and see if we can scare up some more?
DR. BELSITO: So insufficient for composition for the whole hops and the stem, and also for sensitization of the hops at 0.6 percent.
DR. LIEBLER: Right. If we can come up with that complements what we have in Table 6, I think we can get there.
MS. LORETZ: The introduction has a sentence about the presence of beta myrcene in the context of irritation and sensitization.
DR. BELSITO: Right.
MS. LORETZ: But I don't believe there's a mention of the NTP. There's bioassays -- chronic bioassays for rats and mice which are considered positive by NTP.
DR. BELSITO: For?
MS. LORETZ: For -- they're positive in mouse liver and --
DR. BELSITO: For myrcene?
MS. LORETZ: For beta myrcene, right.
DR. BELSITO: They're specifically talking about it?
MS. LORETZ: Yeah. So this probably should be addressed.
DR. BELSITO: And then you have laminin and linalool in the cone oil, so again, you need to point out about the IFFR [IFRA] standards for hydroperoxide there. And IFFR [IFRA] also has a standard for geraniol. I don't believe there are standards for citronal, farnesol, or citronal, but we should check those. I know there are no standards in terms of beta myrcene. If we've done that. I don't remember. I mean, the pinings don't have standards, but again, the standards were set only -- I'm trying to think when. They were used by concentrations. They were used by concentrations above where there were issues; right?
MR. ANSELL: For which material?

DR. BELSITO: For IFFR standards. Are they set for any cosmetologic endpoint? I think they're set only when the 97.5 or now the 95 percent cumulative (inaudible) is potentially exceeded; right? That's what we've been doing; right?
But anyway, several of these cone oils have IFFR [IFRA] limits. We should point that out.
DR. LIEBLER: Okay.
DR. SNYDER: So hops cone oil, Table 9, has 29 -- 25.4 percent beta myrcene.
DR. BELSITO: But then what's the use concentration? It's like 0.00 something; right?
MS. BECKER: Which table are you on?
DR. SNYDER: Table 9. Cone oil. What's the highest cone oil use?
DR. LIEBLER: There's none. It's only cone extract.
DR. SNYDER: So we can't say that's safe as used if we don't have concentration (inaudible).
DR. LIEBLER: Are there any uses of the cone oil? Because it's not listed in these tables.
MS. BECKER: That would be why.
DR. LIEBLER: So there's cone extract in these tables, and it's .00055.
DR. BELSITO: So are we going insufficient with a concentration of use of the cone oil?
DR. LIEBLER: So cone oil has no concentration -- no reported uses.
DR. BELSITO: Paul is concerned about the level of beta myrcene, which there's NTB studies.
DR. LIEBLER: I mean, we don't have that data to know what levels they're talking about.
DR. BELSITO: Right.
DR. LIEBLER: And cone oil is extracted from the strobile, so it could be a strobile extract.
DR. SNYDER: Did you pull the NTP report.
MS. LORETZ: Pull it from?
DR. SNYDER: NTB [NTP] results, what levels it was (inaudible)?
MS. LORETZ: Oh, gosh, tested levels? No, I mean, it's non-genotoxic. I don't think it would be a problem. It was just I need to point it out and go there because NTB [NTP] considered it to be positive.
DR. BELSITO: Yeah, but then we need to discuss that.
MS. LORETZ: Right.
DR. BELSITO: Given the level of beta myrcene.
MS. LORETZ: Right, right, exactly.
DR. SNYDER: We're not talking about, you know, 0.1 percent or 0.25 percent. We don't know the use.
DR. BELSITO: So insufficient for composition of hops extract and stem extract and sensitization of hops extract at 0.6 percent. We also want the NTB [NTP] study on beta myrcene pulled into this and we were assuming that it's going to be not genotoxic and that it will be some ridiculously high level but we won't reach in a cosmetic product, but we don't know that yet, so we need the NTB [NTP] data from the myrcene study.
Obviously, we need to update the Wave 2 data, particularly on flower extract. We're deleting that reference to the citrus peel oils. Then I had at page 9 of the PDF, the third paragraph about humulus hops is a climbing perennial vine. It grows in a helix. Do we need anything in that paragraph? Lateral arms develop at the nodes, producing flowers. I mean, it was like, give me a break. I just thought we could just delete that whole -- I mean, it's like --
MS. BECKER: The main thing I thought was important (inaudible) on both sides of agenda because the people who pick it who develop a sensitization to it, it's not because of abraded skin. And also, I thought that might be something you want to address.
DR. LIEBLER: I think we could do that with the appropriate reference. So in the - well, we haven't written the discussion yet.
DR. BELSITO: No. We don't have developmental or repro tox. Is anyone concerned about that? And we don't have in vivo genotox, and we have two in vitro studies, one saying it was weakly mutagenic and the other not mutagenic. We don't have a tiebreaker. Do we use that? It's page 13 of the PDF, the bottom, in vitro genotox and the top of page -- or 14 says we don't have in vivo. And we have no carcinogenicity studies.
Drinking too much beer from Canada can give you a cardiomyopathy presumably because of the cobalt levels, but not because of the hops is my understanding.
DR. KLAASSEN: (Inaudible) that whole quote, but it's hard to - people have difficult repeating that.

DR. LIEBLER: Lillian, you might want to look in the first of the two listed genotox studies. It says increased (inaudible) of two to four times the controls to TA98 and TA100 with and without metabolic activation. Is that normalized or is that corrected for the toxicity?
MS. BECKER: I don't know. No further details were provided.
DR. KLAASSEN: Because two to four times the controls may not be statistically significant in that assay. And so if it's not statistically significant, and not enough details are provided to evaluate it, it's probably incorrect to say it's weakly mutagenic. It may simply be not a significant result, but we need to know from the publication what the story is.
MS. BECKER: That's the same one that Dr. Hill is looking at. I sent him a copy of the papers.
DR. BELSITO: When we have two of our fine people (inaudible) same thing, it's always good.
DR. LIEBLER: So we just need to know what the context is. I can respond to Ron's comment in the morning.
DR. BELSITO: Okay.
DR. LIEBLER: I mean, Rob had the same issue. That may not be a true positive result.
DR. BELSITO: Okay. So you'll get that to both Dan and Ron.
DR. LIEBLER: Send it to me. Thanks.
MS. BECKER: Make sure I get your email address, please.
DR. LIEBLER: Yeah.
DR. BELSITO: On page 13 of the PDF under possible estrogenic effects, second paragraph, you say more recently PN. What is 8 PN?
DR. LIEBLER: It's defined.
DR. BELSITO: Is it?
DR. LIEBLER: Yeah, it was defined.
DR. KLAASSEN: It's an estrogenic compound.
DR. BELSITO: Where was it defined in this report though? I couldn't find it.
DR. KLAASSEN: It is --
MS. BECKER: Go back to the original. Aprenyl narnogenic [prenylnaringenin]
DR. KLAASSEN: What page though?
MS. BECKER: And that's on page nine. The last sentence above physical and chemical properties.
DR. KLAASSEN: Aprenyl --
DR. BELSITO: Okay. So we don't need that. We've got that definition.
DR. LIEBLER: Lillian, what's your email.
MS. BECKER: beckerl@cir (inaudible).org.
DR. LIEBLER: Okay.
DR. BELSITO: Okay. Now, we also don't have photo on this. Do we need it?
DR. LIEBLER: We need to know special need for it and beyond what we would do for any other botanical.
DR. BELSITO: Well, based upon the compositions we have there's - do we need (inaudible) data?
DR. LIEBLER: Paul?
DR. SNYDER: Sorry?
DR. LIEBLER: Do we need -
DR. BELSITO: (Inaudible) data, type one hypersensitivity? There's the occupational exposures in farmers with a positive skin prick test.
DR. SNYDER: Is that in clinical?
DR. BELSITO: It's under clinical studies. Yeah. And then inhalation. Washington State workers' compensation claims, respiratory disease. Incidents of total respiratory disease among workers with comparator rates in field vegetable crop workers. Sixty-one percent of the cases were work-related asthma. So for that kind of airway response, I don't think our particle size cuts it.
DR. SNYDER: Well, but it was also said it was complicated because it was - they said it was (inaudible) smoking and dust exposure may have been responsible for development of respiratory impairment, so.
DR. BELSITO: I'm just - yeah, I didn't think so but I was just pointing that out that it's there.
DR. SNYDER: I read it.
DR. BELSITO: Is it something we would do in the discussion? Do we ignore it? I mean, what do we do with that data? You know, because obviously this immediate sensitivity with a hydrolyzed wheat

protein has become an issue in cosmetics. We have some data suggesting there's IGE and hypersensitivity in some of these workers. What do we do with that data?
DR. SNYDER: And it's in the respiratory what levels?
DR. BELSITO: I don't know that it says the level. It just says Washington State workers' compensation.
DR. SNYDER: No, no, but I mean as far as the concentration of use data, inhalation product. Incidental inhalation, 0.00055.
DR. BELSITO: So you want to cover it by TTC?
DR. SNYDER: Yeah. I think that's --
DR. BELSITO: But if we don't have a dose response how can we do a TTC?
MS. BECKER: (Inaudible) 0.0002 for the hops extract.
DR. LIEBLER: So we don't really know how much exposure they're talking about in these workers.
DR. BELSITO: Right.
DR. LIEBLER: But they are talking about dust inhalation. Hops dust inhalation. Fifty-seven cases of respiratory disease associated with hops dust inhalation were reported. I would presume this is a long-term exposure to dust from working either indoors with hops as they're being processed, although the control group was vegetable field -- field vegetable crop farmworkers.
DR. SNYDER: It also says it included barley and brewer yeast.
DR. LIEBLER: All cases were associated with harvesting, secondary hops processing, or indirect exposure. Incidence of respiratory disease in the hops workers was 15 cases per 10,000, which was 30 times greater than the incidence for field vegetable crop workers.
DR. SNYDER: Well, I mean, it goes to what we previously said. Smoke was reported to be the major factor and was examined and was listed as a high prevalence of chronic respiratory symptoms.
DR. LIEBLER: That looks like it was another study.
DR. SNYDER: Yeah.
DR. LIEBLER: And that's one where they couldn't disentangle hops dust exposure and smoking.
DR. SNYDER: Yeah. But the other one they didn't measure smoking, so.
DR. LIEBLER: The first one was just hops dust exposure, but without knowing exactly how much hops material they were exposed to, it's hard to say. My hunch is that this is far more exposure than would be from the small amounts used in cosmetic ingredients or cosmetic products based on the use concentrations reported to us. I think we could simply handle that in the discussion.
DR. BELSITO: Dan feels that this is far below?
DR. LIEBLER: Yeah. This is working directly with the hops, handling hops, in a work environment with plenty of hops dust.
DR. BELSITO: Okay. So we're keeping these studies and we're going to --
DR. SNYDER: Just put them in the current context in the discussion.
DR. BELSITO: Right. We're going to put in discussion that the levels of exposures in cosmetics. Overexposure from cosmetics.
DR. SNYDER: Inhalation from cosmetic use.
DR. BELSITO: Levels of exposure from incidental inhalation.
DR. SNYDER: For cosmetic use. It would be far below.
DR. BELSITO: It would be far below.
DR. SNYDER: The levels associated with. Handling of hops or working around hops dust.
DR. LIEBLER: Occupational exposures.
DR. BELSITO: So discussion of occupational -- levels of exposure from incidental inhalation from cosmetic use would be far below occupational levels associated with - -
DR. LIEBLER: Handling of hops and working around hops.
DR. BELSITO: Would be far below levels associated with occupational handling of hops?
DR. LIEBLER: Yeah, occupational handling and processing of hops, which is what I would suspect hops workers do.
DR. BELSITO: You said processing of hops, not hops dust?
DR. LIEBLER: Right. Okay, so we handled the type one respiratory issues in the discussion.
MS. LORETZ: Go back to beta myrcene for a second. I do have (inaudible).
DR. SNYDER: Yeah, I was busy reading the report - -
MS. LORETZ: Yeah, they're very high, 0.25, 0.5, and 1 gram per kilogram, so.

DR. SNYDER: And there's actually -- we need to pull some of the information in from -- there are two (inaudible) that beta myrcene protects against known genotox substances. So we can craft some language to talk about that. That won't be an issue.
DR. BELSITO: All right.
MS. BECKER: These are from the --
DR. SNYDER: Yeah, I'll send you this. I'll send you that one report.
MS. BECKER: Okay, thank you.
DR. SNYDER: So it was liver tumors in mice and kidney tumors in rats which are not very predictive, so it's a moot point.
DR. BELSITO: Okay, so (inaudible) discussion, lack of UV data, expert opinion that they won't absorb. Is that correct, Dan?
DR. LIEBLER: Yes. Well, no. I mean --
DR. BELSITO: We don't have a UV spectrum.
DR. LIEBLER: Right. Well, UV spectrum on a mixture like that is meaningless. I mean --
DR. BELSITO: Okay.
DR. LIEBLER: Of course, any botanical mixture will absorb UV light because it's got compounds with chromophores in it. So you know, if we're going to ask for phototox on this, we need to ask for phototox on all botanicals. So we don't always do that. We do that on ingredients where we know there's a constituent of concern associated with it, like citrus fuel oils.
DR. BELSITO: Right.
DR. LIEBLER: But I don't know that there's a reason to ask for that. We do have pretty extensive lists of the ingredients. Is anything in there associated as phototox? Then, no, I don't think we need it.
DR. BELSITO: Okay, because none of the constituents are photo absorbers?
DR. LIEBLER: Right. Yeah.
DR. SNYDER: We do have phytoestrogens in there though.
DR. LIEBLER: Are they phototox associated? Phytoestrogens. Paul?
DR. SNYDER: No.
DR. LIEBLER: Okay.
DR. BELSITO: So then I think I had a comment on the repro. Endocrine disruption is a huge issue. And Dan's going to clarify the in vitro genotox.
DR. LIEBLER: I'm looking at the paper right now.
DR. BELSITO: Wow.
DR. LIEBLER: Goggleman Shumer paper. It looks pretty lane [lame?]. It really looks pretty lame.
DR. BELSITO: And in one lame study on in vitro genotoxicity.
DR. LIEBLER: It says humulus lupulus and it's just shown with a plus. One symbol means an increase in the (inaudible) two to four times relative to the control value, which is what you quoted. But it doesn't indicate whether it -- how many times the assay was done. I mean, this isn't even in a peer review journal; it's in book chapter.
DR. SNYDER: Is that in a book by Liebler?
DR. LIEBLER: Liebler and Schneider actually. It's that one we did over two bottles of scotch. Okay. Are we finished with hops?
DR. BELSITO: No, I mean --
DR. KLAASSEN: We're waiting for the hops.
DR. LIEBLER: So I'm going to argue, I'll look at this a little bit more thoroughly, but I'm going to argue in the morning that this is probably not a positive -- this can't be reviewed as a positive result in the way that we normally expect these data to be presented to us.
MS. BECKER: Okay.
DR. BELSITO: Okey-doke. So a lot of work on the body of the paper but in the end, insufficient for the composition of hops extract and stone extract and sensitization of the hops extract at 0.6 percent. And then just a whole bunch of other stuff that needs to be brought into the report, like the NTB [NTP], beta myrcene, therefore limits on some of the sensitizers present, et cetera. Getting rid of the citrus oil and algae, adding the new boilerplate for botanicals about noncontamination with other plants during harvest. And that's it. Good, okay.
DR. LIEBLER: So now that we're finished with hops, this brought to mind a joke. So since I think we're dragging a little bit we need a joke. So it's a short joke.
DR. BELSITO: We only have one.

DR. LIEBLER: Guy works in a brewery. He falls in a vat of beer and drowns, and his workmates go to tell his widow the bad news and she says, "Oh, my gosh, that's terrible. Did he have a chance?" And they said, "Well, he got out three times to go to the bathroom."
DR. SNYDER: Lame.
DR. LIEBLER: It is lame but it's --
DR. SNYDER: Very lame.
DR. BELSITO: And you got that from the minutes?
DR. SNYDER: It's in there.
DR. BELSITO: Okay.
DR. SNYDER: Ivan, I hope you're proud.
DR. BELSITO: He's just shaking his head, Dan. Okay. So --

DAY TWO

DR. BERGFELD: … The next to the last ingredient is hops. Dr. Marks, a very interesting review.
DR. MARKS: Absolutely, for those beer lovers in our audience. There are six Humulus lupulus or hops-derived ingredients in this draft report, so this is the first time we've reviewed these ingredients. Our team felt we should move forward with an insufficient data announcement, so that's a motion.
We wanted sensitization data of the whole plant extract is 0.6 percent, which is the use concentration. And it's a much higher concentration than the other five ingredients. And I was concerned because of the report of a case series of airborne allergic contact dermatitis to hops in farmers.
And so that was the only data need that our team felt we needed. And then I'll talk about the discussion a little bit later unless you want me to now.
DR. BERGFELD: Just a minute. Dr. Belsito?
DR. BELSITO: Yes, we felt insufficient for sensitization on a hops extract on hops extract, again, at 0.6 percent absorption, photoabsorption. And I'm trying to look, I just put some for composition. Dan, can you help me out which ones we wanted composition on?
DR. SNYDER: Stem extract for composition. Hops extract for sensitization at concentration use .6 percent.
DR. BELSITO: Yes, so stem composition and sensitization for the hops extract.
DR. MARKS: Fine.
DR. BERGFELD: Good. Anything else?
DR. MARKS: Just in the discussion, our team wanted to emphasize several points. One, that these are phytoestrogens, so they would have weak estrogenic effect in the estrogenic endocrine dysfunction or disruptors are becoming a hot topic. Again, the pulmonary effects that were seen in farmers should be in the discussion.
And the 25 percent beta-myrcene in essential oil, that's the cone oil. There's a much higher concentration and that's induced rat and mice tumors in the NPT [NTP] bioassay. Do you want to comment about that, Tom, at all? That was just a discussion issue since there was a paper.
DR. SLAGA: The cancer is not particularly relevant in humans. It's only related to a rodent model.
DR. BERGFELD: Is that the rat or the mice or both?
DR. SLAGA: Well, no, the kidney (inaudible).
DR. SNYDER: I reviewed those today. So it's the rat was only in male rats and it was non-genotoxic, secondary to chronic progressing necropathy, which is a rat- specific phenomenon not relative to humans.
DR. SLAGA: Right.
DR. SNYDER: And then in the mice it was liver tumors and they used a strain of mice that have exceptionally high incidents of background liver tumors, which was even higher in this study, and so there's nothing there. Plus the levels are very high. The lowest dose tested was 250 milligrams per kilogram, so I think it's okay. I think we needed to address it in the discussion.
I think the point to be made from that is that that actually came out from getting composition data, that (inaudible) was in the composition data. Otherwise, we wouldn't have been alerted to that, I don't believe.
DR. SLAGA: Right.

DR. SNYDER: And so I think it's, again, why we needed to have some of this extra data to know what we're hearing is safe because that wasn't a primary constituent. It was an impurity in the ingredients listed in the table used up to 24.5 percent. I mean, as a constituent, 24.5 percent is an end period.
DR. BERGFELD: Thank you. Ron Hill?
DR. HILL: Yes, I just raised an issue about the Aimes [Ames] test study yesterday, and got a copy of the original paper and looked at it early this morning. And the units are not correctly reported in this document because there was a bit of lack of clarity in how the experiment was done, but I'm now clear on that and I'll share it with the writers. So it's doesn't change the conclusion in any way, it's just a have issues that once I saw the original paper were resolved.
DR. LIEBLER: So, Ron, this is the term -- the description of the cone extract as being weakly mutagenic. And I looked at the paper, too, and I felt that it was a very arbitrary and not satisfactorily quantitative description of the data. In fact, the data were not presented in any quantitative form. There was no real data presented.
DR. HILL: What I could at least garner from the paper is, if you read it, is that there was extract. And what they did was they took 100 milligrams of the material and extracted it into ethanol, and so there's microliters of the ethanol extract. And then tincture, you have 20 milligrams and that's in an ethanol suspension. But it was just the units didn't even look physically possible with the way they were reported in this document and so looking into that.
And then beyond that, I mean, the way they did the testing, it's just that there's -- it's a pretty limited set of data. I don't question the validity of the study, but it's one sampling of that one hops preparation.
I'm not using that to call into the question the conclusion at all. It's just that I made a comment about it yesterday and I felt the need to follow up with it today.
DR. LIEBLER: So I call into question their conclusion that it was weakly mutagenic --
DR. HILL: It may not be.
DR. LIEBLER: -- and that's an exaggeration.
DR. HILL: Yes, it may not be.
DR. BERGFELD: Well, we have a motion. If you'll repeat it, Dr. Marks, because it's been added to by Dr. Belsito. So what do we have in this motion now?
DR. MARKS: Insufficient data announcement, the sensitization data for the whole plant extract is 0.6 percent, and then composition data on --
DR. BELSITO: The stem.
DR. MARKS: -- the stem.
DR. BELSITO: And just we need clarification on the hops cone oil, that it's listed simply as a fragrance ingredient, whether RIFM is reviewing that or we should review it.
And then just a comment that I raised yesterday. How can you have a cosmetic ingredient that has no reported function? So hops strobile for function, it says none reported.
DR. BERGFELD: Beth? Carol?
DR. JONAS: I have no idea.
DR. HELDRETH: I can comment.
DR. BERGFELD: Okay, Bart can --
DR. EISENMANN: They just have -- I mean, some (inaudible) when suppliers provide the information, they don't provide a function and the committee doesn't see fit to put a function in.
DR. HELDRETH: Right. Up until a few years ago, they allowed that kind of submission. Now they have to list a function, but they're given an out and can list something called skin conditioning miscellaneous, which really doesn't mean anything. So when you see that, that also means nothing, just like not reported.
DR. BELSITO: Okay.
DR. HELDRETH: But the thing with the functions is none of these are vetted anyway. These are just what was reported, so these ingredients may function in other ways or not the ways that are listed. It's just a suggestion.
DR. BELSITO: Okay.
DR. BERGFELD: I'm a little bit unclear exactly where we stand with the needs again.
DR. BELSITO: So sensitization at point 6 --
DR. BERGFELD: Six.
DR. BELSITO: -- and composition of the stem.

DR. BERGFELD: And composition. But you did mention absorption and phototox data. You don't conclude that now. I wrote that down when you were speaking. No?
DR. BELSITO: No.
DR. BERGFELD: Okay.
DR. SHANK: Do you need composition for a GRAS ingredient?
DR. BELSITO: We also wanted composition -- I don't know why my PDF is acting so crazy. So now it says, "Insufficient for composition of hops extract and stem extract," so both --
DR. SNYDER: And sensitization.
DR. BELSITO: -- and sensitization at .6.
DR. SNYDER: Correct.
DR. BELSITO: And then we wanted the NTP from beta-myrcene study --
DR. SNYDER: That's been added.
DR. BELSITO: -- added.
DR. SNYDER: We just wanted a discussion.
DR. BELSITO: Okay.
DR. MARKS: Composition of stem and what was --
DR. BELSITO: Hops extract, the whole hops.
DR. SNYDER: That's in deference to your saying the whole plan [plant].
DR. SHANK: And then to Ron Shank's point for GRAS?
DR. LIEBLER: But the whole plan [plant] is GRAS. So I think GRAS addresses the question of potential systemic toxicity, but it doesn't address the question of what it is, you know, what its composition is. So I don't see the GRAS as solving a problem in that respect.
MS. BECKER: And just to clarify, Humulus lupulus hops extract, by definition, is the extract of the whole plant. I keep seeing that.
DR. BERGFELD: So we have a motion of insufficient with two data needs, and it's been proposed by Dr. Marks and I assume now because of the discussion seconded by Dr. Belsito. Correct?
DR. BELSITO: Mm-hmm.
DR. BERGFELD: And it will go out as an insufficient data announcement.
DR. MARKS: Correct.
DR. BERGFELD: Correct, okay. Any other comments?
DR. BELSITO: Again, the slight change to our botanical boilerplate for this ingredient.
DR. BERGFELD: That's accepted. I'll call the question then. All those in favor of moving forward as an insufficient data announcement? Thank you. Unanimous.

April, 2017

Dr. Marks' Team

DR. MARKS: Okay. Let's move on to hops, *Humulus lupulus* derived ingredients used in cosmetics. We had a March 17th memo from Lillian Becker which starts out with -- after the first paragraph. There's been a significant development since -- so, do you want to -- I could summarize it. But, Lillian, do you want to summarize the change in the (inaudible)? It's gotten simpler.

MS. BECKER: Yes. All of the plant-derived non-oil ingredients are now the same ingredient. The old names are now the technical names for this ingredient. And, so the Humulus lupulus, hops, extract [Humulus Lupulus (Hops) Extract] is the lone INCI name. So, all of the information under all those other names apply to this ingredient. And, then we just had a name change from the cone oil to oil. So, the information request for constituents of one of these ingredients is now covered by the other information submitted.

DR. MARKS: So, I think, with that in mind, -- and I'll get to a couple of the tables, because we still have some of the old names in there, which I know, like, in the use concentration table, do we condense that to just two ingredients nor not. We'll get into that. I think it makes a little bit, perhaps, more complex for the reader of this report, to say there are only two and then we go into the use concentration and there are four. But, we'll deal with that in a minute.

At the September meeting, we issued an insufficient data announcement and a composition and sensitization hops extract, the maximum concentration of use at 0.6 percent. We actually now have an HRIPT with the extract at 10 percent, which was okay. So, I think that eliminates that need. And, we wanted the comp (inaudible) [composition?] for the hops stem extract. Well, that's now been deleted, yes.

So, I'll be moving for our team tomorrow, and I thought we could move forward with a tentative report with the conclusion of safe, like obviously my team members. Did you find any needs now? We have two ingredients, the extract and the oil.

DR. SHANK: The extract is safe.

DR. MARKS: Yes.

DR. SHANK: But, the oil, we don't have sensitization data for the oil.

DR. MARKS: Exactly.

DR. SHANK: So, that's insufficient.

DR. MARKS: Okay. I was concerned about that, but I didn't know whether or not we should put that -- okay. Safe for --

DR. HILL: I concur, by the way.

DR. MARKS: Safe for the extract, insufficient for the oil. Needs --

DR. HILL: I have a couple more comments about the --

DR. MARKS: -- sensitization data. Okay. And, that would still, at this point, go out as a tentative report.

DR. BERGFELD: Tentative final?

DR. SHANK: Yes.

DR. MARKS: Pardon?

DR. BERGFELD: Tentative final.

DR. MARKS: Yes. Anything else? You were going to say something, Ron.

DR. HILL: Yes, it actually relates to exactly what he said. So, (inaudible) page -- somewhere around page 31, and then you see a little more clarity at the top of page 32. When we have information that says 10 percent, for example, and that's what we're looking at there. Ten percent of the extract doesn't really tell us much about the specifics of the concentrations of the hops-derived ingredients.

So, you can see there's more clarity provided at the top of page 32. I can get there and find that

language in a second, because I can't look at both things at once on this device that traces to the lost laptop. But, anyway, somewhere down the line when you're looking for -- this is going to be complicated for a long while. So, there are people at my institution working on trying to get at the immunostimulatory versus toxicology data for echinacea, because there's some question mark about efficacious or not and so forth.

And, they're really looking at pattern recognition and constituents than are thought to have effects, but then what you find out is it's a combination of things that are causing -- in that case we're talking about pharmaceutical efficacy in principle. So, that's a totally different beast. But, toxicology endpoints are still biology.

So, if we tried to standardize for read-across, you wouldn't, right now, even know what to standardize on it except when we have something specific like linalool or beta- mercine [myrcene] in this particular case. But, the point is, at least when you say 10 percent but it's really mostly butylene glycol, for example, then how much is actually hop-derived ingredients.

And, that relates to what Dr. Shank brought up, because in the discussion right now as it's drafted, it says because there was sufficient profile data on the constituents of the hops oil, the panel was not concerned about the safety data -- let's see -- on the extract.

The thing that bothered me about that was the way that you'd get the oil, because we have the method of manufacture, and it's steam distillation, so you're getting volatile oils versus when you have an extract made with methylene chloride or hexane, for example, you're not just getting those oils, you're getting triglycerides, basically anything greasy. And, so those concentrations are less, and so then when you do a sensitization study the question is how much are you actually getting on the skin.

So, we do have good tables in here that give a sense of this versus that. But, it's what he said. We haven't quite captured at a level where we could be more assured about the safety of that, because of the way -- what we do and do not know about the way extracts that were tested were prepared.

So, I mean, because, as Dr. Bergfeld mentioned, we're going to see a lot more of these botanicals, and because we still have question marks about how to proceed, but it's the same sort of thing since we've gotten into these that I've mentioned. Did you do super-critical fluid extraction? Is there a steam distillation? Is it hexane, methylene? You get different things and different amounts, and then how much do you concentrate at the end.

And, the language always needs to be clear if something's being sold as 50 percent butylene glycol, 48 percent water, and 2 percent of stuff that's taken out of the plant. How does that relate to what we have data for when the testing is done, to evaluate toxicological endpoints?

I only say this because I'm being asked to assess the validity of read-across, and if I don't have good information about what was actually tested, then that makes it really hard to do, and I have to build in mental margins of safety.

DR. MARKS: Let me bring up this -- that you were talking about composition. Let's go to page 40. I know what my reasoning why I did include the oil for sensitization, and this may not be -- how do I say -- the best reasoning. But, when I went in the composition and I looked at the aqueous extracts, I looked at the concentration of the sensitizers, like geraniol and linalool, they gave you a percentage composition range. And, that's in Tables --

DR. HILL: Nine?

DR. MARKS: Seven. And, then when I looked at the composition in the oil in Table -- yes, Table 9, -- Ron Hill, you're right -- it seemed to me that both geraniol and linalool were similar in terms of percentage of composition. So, to me, that was reassuring that even though I didn't have either a guinea pig max or a HRIPT, that since we have percent concentration for the extract, which is safe with HRIPT, that I thought it could move over and use that as an inference for the oil.

Now, we have zero uses, so I don't think we're going to get any data for the oil. So, I don't know. Ron, Ron, and Tom, do you find that reassuring that the level of the sensitizers are similar. They aren't orders of magnitude difference, that you could infer that the oil should be okay from a sensitization point of view. Because, we aren't going to get the sensitization data, I would think, since there's zero uses.

DR. HILL: You know, what I found strange about that particular table is, they're -- in an aqueous extract reporting 52 percent of mercine [myrcene]. And, I had difficulty believing that that could be. How would you get 50 percent of such a lipophilic compound into an aqueous extract. I mean, I've got to go back and look at Reference 45 and see what they really did and how, because I realize that's what they reported, but it looks a little bit squirrelly, and everything else is much less than that, if that is, in fact, the case. And, I agree with what Dr. Marks just said.

DR. MARKS: Ron Shank, I had not clarified before my reasoning of why I didn't include the oil as insufficient. What's your sense with that reasoning? We could put that in the discussion. I mean, obviously it isn't as good as an HRIPT or a guinea pig max, but it's (inaudible) --

DR. SHANK: That's right.

DR. MARKS: But, like we do a lot of things, we --

DR. SHANK: Comparing the composition of these extracts and oils in Tables 7 and 9 did not substitute well for me --

DR. MARKS: Okay.

DR. SHANK: -- in the absence of actual sensitization data.

DR. HILL: I'm sorry. I don't have a copy of this Journal of Distilling and Brewing here, but maybe we can get hold of it. I'm wondering if that's really a steam distillation and they're looking at the oil, because based on the composition ranges and constituent groups they're reporting, I don't know how you could get that result in something that is mostly water. So, maybe we're looking at a steam-distilled oil fraction and that's what they really mean by aqueous extract, and if that's the case, we need to probably clarify that table with a footnote or something.

DR. MARKS: What I'll do tomorrow is I'll still move a tentative conclusion, or a tentative report with a conclusion safe for the extract, insufficient for the oil, that we need sensitization data, even though Table 7 and 9 have similar concentration to sensitizer. And, we'll see how the Belsito team reacts to it. If they feel strongly that they're reassured with that, particularly Don Belsito, then that's fine with me, obviously since that's the angle I was coming at. But, I'm going to go with the team. The team wants to see a GPM or an HRIPT. Yes.

DR. SHANK: I do.

DR. MARKS: Well, I assume Tom does and Ron Hill does. Ron, I can't imagine you wouldn't want more data.

DR. HILL: I think, you know, it's just because that constituent listing, looking at it, it just about got to be volatile oil obtained by steam distillation, which is going to be something very different than an aqueous extract described other places in here, which is we soaked this stuff in warm water for a while and then captured what was there. And, that would be a very different thing than what you got, if you distill off the essential oils.

I think all of us did a limonene distillation in organic labs somewhere along the line and remember how this goes.

DR. MARKS: I'll throw in here also a local lymph node assay. How's that?

DR. SHANK: Okay.

DR. MARKS: (Inaudible) modeling, molecular modeling also. (chuckles) Okay. That would be very difficult with all the constituents.

DR. BERGFELD: I'm having trouble with the re-declaration [re-definition?] of what this actually is. You know, we have leaves and stems and strobilus and cones, and now we're down just to two.

DR. MARKS: Well, the way I interpret it, (inaudible) cone --

DR. BERGFELD: They're not using the rest of the plant?
DR. MARKS: Yes, that's what Lillian --
DR. BERGFELD: I think somewhere you've got to explicitly say that.
DR. MARKS: Oh, yes, that's in the memo, --
DR. BERGFELD: Yes.
DR. MARKS: -- and that will go in the discussion.
DR. BERGFELD: Yes.
DR. SHANK: Should we change the title?
DR. MARKS: Yes. I had Humulus lupulus (hops), extract and oil. Does that sound good to you guys?
DR. SHANK: Yes.
DR. SLAGA: Let's make sure that all the tables are stated (inaudible).
DR. MARKS: Yes. So, page 35 is the discussion, and then we'll go to 43. So, 35, and, Lillian, I'll -- you know, where do I have highlighted? Oh. Deleted it was noted. HRIP okay, page -- oh. Just what I had in the discussion didn't do with the known (inaudible). So, if we go to 35, the sentence, the last sentence in the paragraph, which begins with -- There were instances of sensitization of persons who worked with hops in the field. Then, it says the HRIP at 0.18 percent assured the panel. It was noted the HRIPT at 10 percent.
DR. BERGFELD: Ten?
DR. MARKS: Ten percent I have now. Was that waived, too? I don't know.
MS. BECKER: Yes.
DR. MARKS: Yes. So, 10 percent instead of 0.18. And, then, -- what did I say -- the table at 45 -- how are we going to handle -- where's the use one? If we go to page 43, just as you said, Wilma, I think it's going to be confusing to the reader if they look at Table 12 and they see we're told there's one ingredient but now we have four. And, --
DR. GILL: We did go back and forth on whether or not to --
DR. MARKS: I figured you did.
DR. GILL: -- provide you -- that is the breakout so that you could see what concentrations were there versus to merge the data. But, we thought once the names were all the same we would just merge the information, --
DR. MARKS: Okay.
DR. GILL: -- if we could.
DR. MARKS: I think we should merge --
DR. GILL: Monice is telling me we have trouble doing that.
MS. FIUME: There's been confusion in the past when there's more than one name in the VCRP for the same ingredient. We found out that they may be sometimes submitted in both places, so instead of just doing an addition, if there was a main heading or something in the use section that informs the reader that it may -- these are all the same thing, but it may have been done under one or more names. Therefore, the name that it was submitted under is reflected in the table, but they're all the same ingredient. Would that be an acceptable way to go for that?
DR. BERGFELD: Yes and no. I think you have to have it at the top of the -- or asterisk at the Table 12, too. You've got to re-explain that table there.
DR. MARKS: See, to me, I would like one ingredient, the one that has the most uses, that name, the extract, combine the other -- what is that -- 20, 32 uses under the extract, get rid of cone extract, flour [flower] extract, and strobila, and then just have an asterisk there -- this includes the previous names. But, that's the way I would go. Because, how many of us immediately would read a Table 12, look at the asterisk, and go to the bottom? I don't know.
DR. SHANK: I would.
DR. MARKS: You would, yes. Ron, you, too. (chuckles) I have a tendency to look at the table first, then look at the bottom. So, which would you prefer, Ron? Do you prefer the way Monice said, put all

four at the top and then an asterisk that these all four are the same?

DR. EISENMANN: You could put it at the top.

DR. MARKS: Yes, I could put it at the top, but you still have an asterisk, then you've got to go to the bottom of the table to look. And, you have a lot of things at the bottom now, NR, A, B, C, D, E.

DR. SHANK: It's explained in the introduction.

DR. MARKS: True.

DR. SHANK: The situation. And, if you put an asterisk or any kind of notation in the title –

(Break in audio from 17:55:12 to ??)

DR. MARKS: What was happening. But, somebody who maybe didn't read it as carefully might look at that and say, well, there are four different ingredients in use, particularly when you have a flower extract as one of the ingredients. But, Ron Hill, Tom, what do you think the better way? And, I would ask Beth and -- I'm sorry --

DR. SADRIEH: Nakissa Sadrieh.

DR. MARKS: Nikki.

DR. SADRIEH: Nakissa.

DR. MARKS: Nakissa.

DR. SADRIEH: Yes.

DR. MARKS: What do you feel, from a formulator's point of view? They're going to be the most likely ones to read this. You would like to keep it the way it is with an asterisk. Ron Shank.

DR. SHANK: I don't feel strongly about it.

DR. MARKS: Ron Hill?

DR. HILL: I simply don't feel strongly. I just want to make sure when the reader reads this table that they do notice. Either change the title so that it's prominent in the title, and then maybe still asterisk --

DR. SLAGA: It doesn't matter which way it's -- as long as any place it's not stated, like, I mean, if it's stated the stem -- it has to have something in that table or whatever to emphasize that it's the same.

DR. MARKS: So, unless there's strong feelings here, --

DR. JONAS: I think it was how Monice proposed it, to clarify that all the same ingredients, although submitted under different names, but keep the table as is, because that's how it's reported in the VCRP. And, I'd prefer to keep the integrity of the data as reported.

DR. MARKS: Yes.

DR. GILL: I would suggest putting that at the top of the table as well, because --

DR. SLAGA: Yes. Not at the bottom.

MS. BECKER: Would it make people happy to have a separate table with it all combined with the explanation as well?

DR. MARKS: No. I think we've agreed now. There's not strong feelings, but there's a recommendation that it be put at the top. The table will remain the same, and the proviso will be at the top of the table, so the reader won't miss the nuance that these are actually all the same ingredient, they'd just been reported by different names. Okay.

DR. HILL: It actually bothered me more in the report in places where it wasn't explicitly pointed out as you were going down. And, I think I dropped comments everywhere but the summary. I tend to skip over summaries when I'm looking at the reports, so. But, there were places where it didn't seem like it jumped out at me as we were going through.

DR. MARKS: Okay.

DR. HILL: Yes, we were talking about these. I do have one more general issue before you move off of this ingredient.

DR. MARKS: Go ahead. You have the --

DR. HILL: There are a couple of places where you're talking about hair conditioners, and then you move to the next and say, but on the other hand in things that come in contact with the skin there are leave-on hair conditioners, and even though a good bit of it -- I mean, it's unreasonable to think that somebody uses a leave-on hair conditioner and it doesn't come in contact with the skin.

And, you know, I think about -- partly because of where I live -- people with very tightly-braided hair and then they have a hair net on while they're working and they're sweating. This stuff, if it's leave-on, does, in fact, contact the skin and not just skin but scalp and possibly warm, sweaty scalp.

So, I think, just look at those places where it's written. And, unless we know for sure it's only rinse-off conditioners, still it'll contact the scalp while it's being applied, at least -- I haven't used conditioner in years, because it just makes my hair (inaudible) and limp, but.

MS. FIUME: Carol?

DR. EISENMANN: Yes.

MS. FIUME: When we get concentration of use information from you, is there ever a clarification for the conditioner, whether it's a leave-on versus a rinse-off?

DR. EISENMANN: If somebody tells me it's a leave- on, I might put it in a different category other than conditioners, but I don't know. I mean, it's not a question I specifically ask.

DR. HILL: And, it was just the writing in this report that bothered me. Whenever I hear hair conditioner I think -- at least some of those are leave-on -- a significant fraction of them are leave-on, so to suggest that it doesn't contact the scalp at any point when it's a hair condition, -- I mean, because even if it's rinse-off it still contacts the scalp, which is skin. At least my scalp is skin.

MS. BECKER: Yes, been the way we operate with hair products is that they're not dermal products. I have the same --

DR. HILL: It was the writing, the wording. And, there's just two spots, and I think I flagged them, --

MS. BECKER: Okay.

DR. HILL: -- so at least maybe we could look at that and decide if there's a better way to say it so it's not quite so blatantly -- this can't be true.

MS. BECKER: Do you want to say anything in the conclusion about nonsensitizing -- formulated to be nonsensitizing? That's a general thing we do with botanicals.

DR. MARKS: Well, it's interesting with all botanicals, but we have a 10 percent level that's nonsensitizing. To me, that's a cop-out. I think in this case when we're dealing with one botanicals -- well, two botanicals, really, the extract and the oil, and we said explicitly the extract -- the maximum concentration is 10 percent, and the oil, at least today, it's insufficient. If we put nonsensitizing in, then we could delete the insufficient.

I hadn't thought about that, Ron Shank, but, I like it the way it is now. I find, as I've commented before, we could put nonirritating and nonsensitizing in every ingredient and then there wouldn't be any reason to look at the data.

DR. BERGFELD: But, we have a load of clinical data here, though.

DR. MARKS: Yes.

DR. BERGFELD: Case reports of sensitization, inhalation, and --

DR. MARKS: Oh, I agree, Wilma, but we have a load of data (inaudible) Quaternium-15 that are sensitizers, and methylchloroisothiazolinone, even though I reclused (sic) myself from that -- or methylisothiazolinone. And, there is a safe level. We don't put in there don't formulate to be nonsensitizing. We put a limit.

DR. GILL: But, I think part of the boilerplate language if set up to address the multiple botanicals that could be in product. So, when it's formulated to be nonsensitizing, sort of it's getting at the panel's concern that more than this ingredient -- botanicals other than this ingredient may be in formulation.

DR. MARKS: Yes. My interpretation -- maybe I'm wrong, correct -- of the botanical boilerplate is that it's for all toxic endpoints. So, in some cases the various botanical ingredients may add up to have,

say, a carcinogenic effect. They may add up to have some other toxic effect. Sensitization is just one of them.

So, to me, for the botanical, boilerplate would cover the sensitization along with others. But, again, I'll ask for Tom, Ron, and Ron's input on that. To me, I think the conclusion is okay and we don't need to put nonsensitizing in it.

DR. SHANK: I agree.

DR. SLAGA: I agree.

DR. HILL: Yes, part of it --

DR. MARKS: We'll see what the Belsito team says tomorrow, how strongly they feel.

DR. HILL: Part of this is these are used at very low levels. At least the state of use as captured in here, the percentages are very low. So, I think is what we said is we're insufficient on the oil, but the insufficiency really relates to the sensitization, right, so.

DR. MARKS: Yes. Well, we don't know (inaudible) --

DR. HILL: Safe as used.

DR. MARKS: -- because there's no use.

DR. HILL: Right. So, you'd say safe as used, safe for the oil you formulated to be nonsensitizing. (Laughs)

DR. MARKS: Well, that's what we talked about (inaudible).

DR. SHANK: But, we don't have toxicology.

DR. HILL: No, we don't. I agree.

DR. SHANK: There are other issues.

DR. MARKS: There are others besides the sensitization with the oil?

DR. SHANK: Yes.

DR. MARKS: Yes. Okay. That's important. So, we normally say what else we need in the oil, so what else would you need for the oil as insufficient? Because, the last time we didn't even say the oil in the insufficient data announcement.

MS. BECKER: No, you didn't mention it at all.

DR. MARKS: No, I know. That's why I'm asking Ron Shank what else.

DR. GILL: It's in the transcript, the discussion (inaudible).

DR. EISENMANN: We don't have any concentrations of use. So, you could ask for concentrations of use if you wanted.

DR. SHANK: That's one of them, method of manufacture, --

Well, I think by definition you have the method of manufacture. It's a distillation. That's the material on (inaudible).

SPEAKER: Basically, (Inaudible).

DR. MARKS: (Inaudible) need concentration of use, yes. And, with no uses we aren't going to get that. Although, your point is well taken, Ron Hill, is that there's always an asterisk at the bottom of our conclusion -- if used, it would be in similar products at a similar concentration, and the concentration and the use of the extract is quite low. What is it? Something like .00, is it?

DR. HILL: I can find the table, but they're quite low.

DR. MARKS: The flower extract was .001. The cone extract -- this, of course, was the previous – was .005. But, the extract alone was .6, so it's not that low.

DR. HILL: But, the problem is with that, I think that's the one where I concluded -- isn't most of that solvent? Let me just --

DR. EISENMANN: I can tell you when I ask they're supposed to tell me the ingredient without the solvent. That's what they're supposed to tell me.

DR. HILL: But, the problem is --

DR. EISENMANN: Are they telling me that? I don't know for sure. But, the .6, it's possible that that's the hops extract of the hops material.

DR. HILL: Because, I'm looking at the Table 12. Is there other information besides Table 12? Frequency of use.
DR. MARKS: Forty-three.
DR. HILL: And, the highest number I see in here is.13.
MS. BECKER: Right. Dr. Marks' concentration was before the last two updates.
DR. HILL: Yes, they've reduced.
DR. MARKS: Okay. That's the original one.
MS. BECKER: Right.
DR. MARKS: Okay. So, now the highest --
MS. BECKER: .2.
DR. HILL: .2 in the --
DR. MARKS: .2.
MS. BECKER: In a rinse-off.
DR. HILL: In a rinse-off.
DR. MARKS: How about leave-on? What's the highest?
MS. BECKER: .13.
DR. MARKS: .13. So, yes, a small amount. And, for instance, the constituents are similar concentrations, you wouldn't think it would be a sensitizer. But, we'll see how that works tomorrow. Anything else other than concentration and use, Ron Shank, from a toxicology point of view, insufficient data?
DR. SLAGA: How about genotox, 28-day dermal?
DR. MARKS: Okay. Now, we're getting more meat to this.
MS. BECKER: You mentioned the guinea pig maximization test and/or HRIPT and LLNA as well earlier.
DR. MARKS: Yes. That would be the typical sensitization data I want to see, particularly the guinea pig max and the HRIPT. The local lymph node assay just tells me is it a sensitizer or not. If it was a nonsensitizer --
DR. BERGFELD: You take the animal and/or the human?
DR. MARKS: Yes. Mm-hmm. And, if the guinea pig max was okay, --
DR. BERGFELD: (Inaudible)
DR. MARKS: I'd feel fine. Okay. So, again, I'll move that a tentative report be issued tomorrow with a conclusion safe for the extract, insufficient for the oil. We need sensitization data. We also need the concentration of use in genotoxic. We'll see where that runs.
DR. SLAGA: Can you add irritation and sensitization in genotox?
DR. MARKS: We don't have any data on irritation.
MS. BECKER: No, we do not.
DR. MARKS: Presumably, if we got the sensitization data, that would include irritation, obviously, in doing that. But I'll put that -- let me put irritation and sensitization. Okay. And, then Tom, I'll ask you to justify the genotox. What were you pointing out?
MS. BECKER: Just that you could see it from the table, from the profile right there. There is nothing in the oil.
DR. MARKS: Yes. Nothing in the oil. I know.
MS. BECKER: Including use.
DR. MARKS: Yes. Okay. Any other comments?
SPEAKER: I was trying to figure out (inaudible).
DR. MARKS: Well, that was robust.
SPEAKER: Yes, because (Inaudible).
DR. MARKS: I hope nobody drinks beer tonight. (chuckles)
DR. HILL: If you think anything in this is going to prevent that, think again. (Laughter)
SPEAKER: As long as you don't put it on (inaudible).

Dr. Belsito's Team

DR. BELSITO: So, hops. At the September meeting we issued an insufficient announcement for all six of these ingredients and we requested data on composition of the hops stem extract and the sensitization potential of the hops extract at .6. And then since then we found that the cosmetic ingredient dictionary has been totally changed, and all of these different things are just actually extracts of the cone. So I think we probably had all the data we need, and we're just asking for redundant data under --

SPEAKER: Right.

DR. BELSITO: -- different names. But --

DR. LIEBLER: Yeah, I felt the same way. I think our data needs are now met and I was wondering how we -- do we reconfigure the use tables? Because when it gets --

DR. BELSITO: Yeah, that was my --

DR. LIEBLER: -- (inaudible) --

DR. BELSITO: -- big question.

DR. LIEBLER: The information was requested, according to the uses, but the uses --

DR. SNYDER: No longer are valid.

DR. LIEBLER: -- or the ingredients, I'm sorry --

DR. SNYDER: No longer valid.

DR. LIEBLER: -- the uses -- the ingredients blend together now into two categories, and can't we just combine those and then add up the uses and have a simpler use table?

DR. SNYDER: I think that would certainly work well for the maximum concentrations of use because we know, we understand that source and how that survey works. I always use caution adding numbers from the VCRP together because it's a little bit of a black box. We don't know if the supplier went in and marked three different names for one formulation, just making sure that they got the right thing marked in there. And so adding the numbers together might give you an inflated value that is even further from the truth, even though this is an estimation. And we've seen this happen before with the citrus ingredients where they gave it the name citrus aurantium dulcis and citrus this and citrus this and --

SPEAKER: Uh-huh.

DR. SNYDER: -- and the same supplier reported one formulation, you know, in four different places.

DR. LIEBLER: So I was merely asking, you know, whether we could do it to simplify and if you feel that it would obscure information that needed to be kept separate, then I'm fine with that. I think the main point for us is that our data needs are now met because --

DR. BELSITO: Right.

DR. LIEBLER: -- we don't really have these distinct ingredients. So, you know, I don't really care if the use table's got four columns or two columns.

DR. HELDRETH: I mean, we could certainly restructure it so that we know. We put three of these all under one category and then --

DR. LIEBLER: Put some kind of unique --

DR. HELDRETH: -- maybe put the ECRP [VCRP] name next to each --

DR. LIEBLER: Yeah.

DR. HELDRETH: -- number so that we know what it --

DR. LIEBLER: Right.

DR. HELDRETH: -- came from.

DR. LIEBLER: I mean, that would be fine, sort of a customized use table --

DR. HELDRETH: Sure.

DR. LIEBLER: -- in this one instance.

DR. HELDRETH: Right
DR. LIEBLER: We already have a company language in the report to explain what was going on. So yeah, my question --
DR. BELSITO: So --
DR. LIEBLER: -- for you was going to be, do we run into a problem by blending all the uses together? You've just explained that we potentially do. So we don't need to ask for that.
DR. SNYDER: So there's three of the columns are extracts and one is the (inaudible). Which one of those captures oil use?
MS. BECKER: None of them.
SPEAKER: None of them.
DR. SNYDER: So we have no oil use.
MS. BECKER: We have no oil --
DR. SNYDER: Right.
MS. BECKER: -- use.
DR. SNYDER: Okay, thank you.
DR. BELSITO: So I'm just putting for table 12, we're going to customize the uses and the table (inaudible) will determine how to do this. Is that fair?
DR. HELDRETH: Yes.
DR. BELSITO: Okay. Does that take care of hops?
DR. LIEBLER: I think so.
DR. BELSITO: All right.
MS. DEWA: The --
DR. BELSITO: Yes, (inaudible)?
MS. DEWA: The question is, in some of their functions it's also mentioned that it's used as an antimicrobial. Is that a cosmetic function?
DR. BELSITO: You know, I mean, I -- it's not up to us to determine whether that's an appropriate function.
MS. DEWA: Yes.
DR. BELSITO: It's up to us to determine whether if it was used for that at a level that is reported as being used in this whether it would be safe, not whether it would be functional. So I don't think we can comment on that.
JAY ANSELL: Well, only to the extent that it's included as a cosmetic use as opposed to other use.
MS. DEWA: Yes.
DR. BELSITO: I see.
MS. DEWA: It wasn't ODC otherwise. From FDA point, if you're antimicrobial --
DR. BELSITO: Oh, I see.
MS. DEWA: -- antibacterial that goes into the (inaudible). But it has other function. So if it's --
DR. BELSITO: Okay.
MS. DEWA: -- also used as function as antimicrobial (inaudible) then we are moving --
DR. BELSITO: Yeah, I guess I wasn't think antimicrobial in terms of OTC drug. I was thinking of it in terms of a preservative.
MS. DEWA: Oh.
DR. BELSITO: Which are also antimicrobial.
MS. DEWA: Yeah.
SPEAKER: Like the name.
DR. HELDRETH: Yeah, we get all of these functions directly from the INCI dictionary, so it's whatever they have listed there under cosmetic functions. We don't --
SPEAKER: (Inaudible.)
DR. HELDRETH: -- you know, try to pick and choose which ones are regulated --

SPEAKER: (Inaudible.)
DR. HELDRETH: -- (inaudible) bodies.
SPEAKER: Okay.
SPEAKER: It's just where you report --
SPEAKER: (Inaudible.)
DR. BELSITO: Okay.
SPEAKER: A separate conversation is going to get everything (inaudible).

Day Two

DR. BERGFELD: Okay. All right. Then we'll move on, because we've agreed to what our needs are for that ingredient. Moving onto hops, since you've both been on that one (Laugher). Jim Marks.
DR. MARKS: Yeah, we couldn't wait to hop on this ingredient. Group of ingredients. Yeah, that's a bad joke, isn't it?
DR. SNYDER: Jim, that's my department. (Laughter)
DR. MARKS: So, in September 2016, the panel issued an insufficient data announcement for these ingredients. Which, interestingly, there's been a significant development in the nomenclature for these ingredients. Which is outlined by Lillian. So, five previous ingredients have now been consolidated to the hops extract. Or both the hops extract and the oil, come from the cone or the strobile. So, this report focuses on those two ingredients. And our team felt that we could move on with a tentative report, with a conclusion safe for the extract. Insufficient for the oil. And we wanted to see irritation and sensitization data for the oil. And also, concentration and use in genotox data.
DR. BERGFELD: Belsito team comment. Or --.
DR. BELSITO: Well, we thought they were all safe as used.
DR. SHANK: The oil as well?
DR. BELSITO: Mm-hmm.
DR. BERGFELD: And the reasoning. Could you give your reasoning for that?
DR. BELSITO: I didn't see any issues with sensitization. I'll have to back and look. We had hops extract.
DR. SNYDER: We received immunogencity data. And then we also got extract.
DR. MARKS: Yeah. The extract. But we felt the oil potentially could be different enough. It's interesting. When I reviewed, what was reassuring from an irritation sensitization, particularly sensitization, was that when you look at Table 7 and 9, they have similar concentration of sensitizer's in the extract and the oil. Specifically generiol [geraniol] and linilol [linalool]. So, I actually felt we could move on with -- that the sensitization wasn't an issue. But my team wasn't totally reassured by that reasoning. So, I would be interested Don, in --.
DR. BELSITO: So in looking at it, I mean, basically we're dealing with an oil that has multiple turpenes [terpenes].
DR. MARKS: Yeah.
DR. BELSITO: So we're automatically going to put in, when formulated to be non-sensitizing, so since so many other botanicals could contain turpenes [terpenes]. So I wasn't -- that's why I wasn't concerned.
DR. MARKS: Okay. I think when you put in -- we didn't have one formulated to be non-sensitizing. That certainly addresses that issue.
DR. BERGFELD: So you would restate your conclusion?
DR. MARKS: Yes. I'll retract the present motion. And change that to a tentative report, with a conclusion safe for the oil. And for the extract as long as formulated to be non-sensitizing.
DR. BERGFELD: Is there a second?
DR. BELSITO: Second.

DR. BERGFELD: Any --?
DR. MARKS: Is that okay with you Tom? Because you brought up the genotox.
DR. SLAGA: Yeah.
DR. MARKS: Yeah. Okay.
DR. BERGFELD: Okay. Any other questions or comments?
DR. BELSITO: Well, just the constituents concern. There's linalool, which, it has to limit, an IFRA limit for the hydro peroxides. There's geraniol. So --
DR. BERGFELD: You'd like --.
DR. BELSITO: -- just to point out some of the sensitizer's of concern in the hops oil.
DR. BERGFELD: And you're going to put that in your discussion.
DR. BELSITO: In the discussion.
DR. BERGFELD: Yes. Ron Hill.
DR. HILL: I think some of the discussion centered around my belief that Table 7, although it says aqueous extract, that that might be the steamed distillate, because if that's an extract obtained by simply soaking in hot water, or even boiling water for a particular period of time, there's no way that that "aqueous extract" could have what appears to be percent or more of hydrocarbons in it. So I think that's actually referring to the steamed distillate, rather than aqueous extract. And we need to clarify with Reference 45 to see what the story is there. Because that was important to the read-across.
DR. BERGFELD: Well, that would be considered editorial. So, we could move on.
DR. HILL: Right.
DR. BERGFELD: Okay.
DR. BELSITO: So, the constituents of concern in the oil, the strobile oil that we have, that I would point out, would be limonene and linalool for the hydro peroxides. And then, geraniol, citroneliol, farniciol and citriol for other known allergens that are required to be labelled as the 26th in the EU.
DR. MARKS: Linalool? Did you mention that?
DR. BELSITO: Hydro peroxides of linalool.
DR. MARKS: Yeah.
DR. BELSITO: And Limonene.
DR. MARKS: Yeah.
DR. BELSITO: Yes.
DR. BERGFELD: Okay. That would appear in the discussion.
DR. BELSITO: Yes.
DR. BERGFELD: Any other points of interest?
DR. BELSITO: Don, did you want to include in the discussion, my comments about, it's also reassuring, even though we're going to have a conclusion formulate that made non-sensitizing. It appears the levels of these sensitizer's are similar between the extract in the oil. And we have sensitization data for the oil.
DR. BELSITO: I'm fine with that --
DR. MARKS: Yeah.
DR. BELSITO: -- in the discussion.
DR. MARKS: To me that's reassuring also.
DR. BELSITO: Right.
DR. MARKS: I didn't get a sense these were irritating. So we don't need to put -- we normally with the botanicals, put formulate to be non-irritating and non- sensitizing. Do we want to purposely leave out non-irritating?
DR. BELSITO: I didn't see any really --
DR. MARKS: Yeah.

DR. BELSITO: -- significant issues with irritation.
DR. MARKS: Okay. I agree. I just wanted to confirm that.
DR. BELSITO: Then the only other point that we had, was to ask Bart to sort of somehow come up with a nice customization of the use table to indicate that the Strobile and all these other things, are actually no longer that ingredient. But how do that, we'll leave to him.
DR. MARKS: And then the other thing that came up with our team was changing actually the title of the report. And we recommend that a title be changed to Humulus Lupulus, in parentheses (Hops Extract and Oil) [(Hops) Extract and Oil ?]. So we're very specific in the title, what part of hops we're dealing with.
DR. BERGFELD: That's it. I gather there's agreement to that.
DR. BELSITO: Mm-hmm.
DR. BERGFELD: Okay. Then I'll call the question. If there are no more comments, all those in favor or approval of this ingredient with those -- that discussion. Thank you. Unanimous.
MS. BECKER: Dr. Belsito.
DR. BERGFELD: Yeah.
MS. BECKER: Dr. Belsito, did you mark all of those that you have a concern with in your notes?
DR. BELSITO: No. I just mentioned them. They should be picked up in the --
MS. BECKER: Yeah. I couldn't write that fast. So.
DR. BELSITO: -- the transcript. Okay. So, let me go back and --.
DR. BERGFELD: You could just say which ones weren't. I mean, that was a long list.
DR. BELSITO: No. No. No. (Laughter) Ones that weren't --.
DR. BERGFELD: In the table. Which ones aren't on?
DR. BELSITO: Okay. Well, I'm doing the next one Lillian. Before I leave, I'll go to Table 9 and whatever table it is, and I will highlight in yellow the ones that are a concern. And put the comment, that these are a concern. And that the concerns for limonene and linalool are hydro peroxides. Not the linalool and limonene.
MS. BECKER: Okay. Thank you very much.
DR. BELSITO: So let me keep that open. Okay.
DR. BERGFELD: Okay.
DR. BELSITO: So, polyurethanes.
DR. BERGFELD: Yes. Don, you're up for those. All right.
DR. MARKS: So that, just to be clear, I don't -- they're fragrance ingredients.
DR. BELSITO: Yes.
DR. MARKS: And that's the concern is sensitization. And they're the ones, as you mentioned on there -- on the label, required to be labeled.
DR. BELSITO: They're required to be labeled. And some of them have IFRA standards that can't be exceeded --
DR. MARKS: Yeah.
DR. BELSITO: -- by the hydro peroxides.
DR. BERGFELD: That probably should be put into the discussion as well.
DR. BELSITO: It typically has been.
DR. BERGFELD: Yeah.
DR. MARKS: Yeah.
DR. BERGFELD: Yeah. Can we move on then?
DR. BELSITO: Yeah.
DR. BERGFELD: All right.
DR. MARKS: Don's already there.
DR. BERGFELD: Well, yes and no he's there. Are you there now Don?
DR. BELSITO: No. I'll go back and do that for Lillian. I've kept that report open. So we should move on.

Safety Assessment of Humulus Lupulus (Hops)-Extract and Oil as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of Humulus Lupulus (Hops) Extract (reported functions include antimicrobial agent and hair conditioning agent) and Humulus Lupulus (Hops) Oil (reported function is fragrance). The Panel reviewed the relevant data related to these ingredients. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For these ingredients, the Panel was concerned about the presence of 8-prenylnaringenin, β-myrcene, and quercetin in cosmetics, which could result in estrogenic effects, dermal irritation, and genotoxicity, respectively. Industry should use current good manufacturing practices to limit impurities and constituents of concern. The Panel concluded that Humulus Lupulus (Hops) Extract and Humulus Lupulus (Hops) Oil are safe in cosmetics in the present practices of use and concentration when formulated to be non-sensitizing.

INTRODUCTION

This is a safety assessment of Humulus Lupulus (Hops) Extract and Humulus Lupulus (Hops) Oil as used in cosmetics. According to the *Web-Based Ingredient Dictionary* (wINCI), the functions of Humulus Lupulus (Hops) Extract in cosmetics include antimicrobial agent, hair conditioning agent, and skin-conditioning agent – miscellaneous; Humulus Lupulus (Hops) Oil is reported to function as a fragrance ingredient (Table 1).[1] Antiperspirant agent is also listed as a function of Humulus Lupulus (Hops) Extract; however, antiperspirant agent is not a cosmetic function and is not evaluated in this safety assessment. Both of these ingredients are derived from the strobile of the *Humulus lupulus* (commonly called hops) plant. The strobiles of this plant are generally known as an ingredient in the brewing of beer.[2,3]

Previously, the wINCI listed four other *Humulus lupulus* (hops)-derived ingredients: Humulus Lupulus (Hops) Cone Extract, Humulus Lupulus (Hops) Flower Extract, Humulus Lupulus (Hops) Stem Extract, and Humulus Lupulus (Hops) Strobile (Table 1).[4] It was determined by the International Nomenclature Committee (INC) that these ingredients were all extracts of the inflorescence (hops cone) of the *Humulus lupulus* (hops) plant. It was also determined that the previous definition of Humulus Lupulus (Hops) Extract, i.e., the extract of the whole plant, was erroneous and that this ingredient is also the extract of the inflorescence (hops cone). To correct these errors, these five ingredients were deemed synonymous and the single name Humulus Lupulus (Hops) Extract is now the official INCI name. Additionally, Humulus Lupulus (Hops) Cone Oil (the volatile oil obtained from the cones of *Humulus lupulus*), has been changed to Humulus Lupulus (Hops) Oil and the definition is now "the volatile oil obtained from the inflorescence (hops cone) of *Humulus lupulus*". Data have been submitted under the revised names; with the exception of the cosmetic use data, these data are presented under the corrected names, Humulus Lupulus (Hops) Extract and Humulus Lupulus (Hops) Oil.

The terms "inflorescence", "cone," and "strobile" refer, synonymously, to the structures formed by the female *Humulus lupulus* (hops) plant after the flowers have bloomed, whether or not they have been fertilized. Thus, for example, "cone oil" is the same as "strobile oil. Both "cone" and "strobile" are used in the literature. Also, "hops" is used commonly for the plant name as well as for the harvested strobiles; in the literature, it is not always clear if authors are referring to the whole plant or just the strobiles. In this report, it is assumed that the authors are referring solely to the strobiles, unless otherwise indicated.

Most of the parts of *Humulus lupulus* (hops) (i.e., shoots, leaves, flowers, seeds, rhizomes, and essential oils) are edible; the strobile is the most commonly consumed in food (mostly in beer).[5,6] The U.S. Food and Drug Administration (FDA) has determined that essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Humulus lupulus* (hops) are generally recognized as safe (GRAS) for human consumption. [21CFR182.20] Consumption of these *Humulus lupulus* (hops)-derived foods would result in much larger systemic exposures than what is expected from use of ingredients in cosmetic products, even if there was 100% dermal absorption. Thus, the systemic toxicity potential of *Humulus lupulus* (hops)-derived ingredients is not the focus of this safety assessment (although such information may be included). The primary focus of this safety assessment is the review of safety based on local effects (e.g., topical exposures).

Botanical cosmetic ingredients, such as *Humulus lupulus* (hops)-derived ingredients, may contain hundreds of constituents, some of which have the potential to cause toxic effects. For example, sesquiterpene lactones, which are present in the *Humulus lupulus* (hops) plant, may cause Type IV allergic reactions (cell-mediated, delayed-type hypersensitivity) and other toxicity when present in sufficient amounts. Another example, β-myrcene, is reported to be a dermal irritant and a possible carcinogen.[7-11] In this safety assessment, CIR is reviewing information available to evaluate the potential toxicity of each of the *Humulus lupulus* (hops)-derived ingredients as whole, complex ingredients. 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 the *Humulus lupulus* (hops) plant.

The Panel has reported on related ingredients that can be used to support the safety of the *Humulus lupulus* (hops)-derived ingredients. The information on these related ingredients may be relevant for this safety assessment. The Panel reviewed the safety of phytosterols, which are plant-derived sterols that are likely constituents of most of the *Humulus lupulus* (hops)-derived ingredients,[12] in 2013 and concluded that the phytosterols are safe as used.[13]

The names of the ingredients in this report are written in accordance with wINCI, as shown above, capitalized without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the standard taxonomic practice of using *italics* will be followed (e.g., *Humulus lupulus*).

Often in the published literature, the information provided is not sufficient to determine how well the tested substance represents the cosmetic ingredient; the taxonomic name is used, unless it is clear that the test substance is similar to

the cosmetic ingredient. If it is similar to the cosmetic ingredients, then the INCI name is used.

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

CHEMISTRY

Definition

The definitions of these *Humulus lupulus* (hops)-derived ingredients (with technical names, included for cross reference) are provided in Table 1.

The terms "cone" and "strobile" are synonymous and refer to the structures formed by the female *Humulus lupulus* (hops) plant after the flowers have bloomed, whether or not they have been fertilized.

Plant Identification

The genus *Humulus* consists of dioecious, perennial, climbing vines and bines (i.e., a twining plant stem or flexible shoot).[14] This genus belongs to the Cannabaceae family of the Urticales order which, in 2003, was incorporated into the natural order of Rosales.[15] The plant, which is native to Europe and western Asia, is now cultivated in North and South America, Africa, Asia and Australia and is invasive in many areas.[3] Cultivation is predominately in the northwestern United States and Germany.[2] Within *Humulus lupulus*, there are five taxonomic subspecies based on morphological properties and geographical location: *Humulus lupulus* var. lupulus, *Humulus lupulus* var. cordifolius, *Humulus lupulus* var. neomexicanus, *Humulus lupulus* var. pubescens, and *Humulus lupulus* var. lupuloides.[16] Over 100 cultivars have been named.[17] It is not known whether a single or multiple varieties are used in cosmetics.

While the *Humulus lupulus* (hops) plant is typically dioecious (i.e., the male and female flowers usually develop on separate plants), occasional fertile monoecious individual plants have been reported.[18] When grown for beer, viable seeds are undesirable; therefore, only female plants are grown in hops fields to prevent pollination. Female plants are propagated vegetatively, and male plants are culled if plants are grown from seeds. Under natural conditions, the flowers are wind pollinated and the female inflorescence develops to form a strobile (or cone). Only the strobiles of the female plants are able to develop the lupulin glands that secrete a fine yellow resinous powder.[2] These glands secrete predominantly bitter acids and hop oil, the constituents of which include phytoestrogens such as 8-prenylnaringenin (8-PN) and other prenylflavonoids.[19,20]

Humulus lupulus (hops) is a climbing perennial bine, which means that it grows in a helix around a support and uses downward-facing bristles/hooked hairs for grip instead of tendrils or suckers as would a vine.[3,6,21] Generally, the bines are trained to 25 ft (7.6 m) or higher on a trellis. Lateral arms develop at the nodes, producing flowers at their terminal buds. The green to yellowish-brown leaves have three or five lobes, depending on the variety, and are hairy on both sides; the margins of the cordate (heart-shaped) leaves are serrated and the petioles are slightly fleshy with stout hooked hairs. *Humulus lupulus* (hops) is a perennial plant that regrows each spring from the rhizomes of an underground rootstock in commercial hops production.

Physical and Chemical Properties

The chemical and physical properties for Humulus Lupulus (Hops) Extract are presented in Table 2.

Once harvested, *Humulus lupulus* (hops) strobiles deteriorate upon aging and exposure to atmosphere.[3] The stability of stored strobiles and ethanol extracts, as measured by humulones, lupulones, and xanthohumol content, is optimal in 70% ethanol.[22]

Green *Humulus lupulus* (hops) strobiles have a variety of odors including: citrus, tropical fruit, stone fruit, pine, cedar, floral, spicy, herbal, earthy, tobacco, onion/garlic and grassy.[23]

Preparation/Extraction

Humulus lupulus (hops)

In general, when the strobiles are harvested from *Humulus lupulus* (hops) bines for beer production, the strobiles are immediately dried by forced hot air, and are often pressed into dense cylindrical pellets, 5 to 8 mm in diameter and up to 25 mm long.[17] The pelletization reduces the overall surface area and therefore reduces the rate of chemical oxidation/ degradation, and provides a more compact product for shipping. Not all suppliers dry the strobiles; the strobiles may be harvested fresh as whole, wet cones at the farm, and shipped for immediate use within 36 h of harvest.[23]

Sometimes, hops are treated with sulfur dioxide to improve the color and prevent change of active constituents.[3]

Methylene chloride is the most common solvent used for the extraction of *Humulus lupulus* (hops) for beer brewing; hexane and methanol are also employed.[24] Typically, at least 95% of the available α-acids (source of the bitter flavorings) can be extracted from fresh *Humulus lupulus* (hops) strobiles. Methanol is the most efficient solvent for the extraction of α-acids (approximately 25%), followed by methylene chloride (approximately 20%) and hexane (approximately 18%).

Supercritical fluid extraction (SFE) with carbon dioxide is also used to collect the extract for beer brewing.[25-28] Another modern method is pressurized fluid extraction (PFE), which is employed for extracting different polyphenols.[29-33] PFE has been developed to extract bitter acids.

FDA regulations on the method of manufacture of "modified hop extract," as a food additive intended for use as a flavoring agent in the brewing of beer, are provided in Table 3. Six of the eight listed methods follow extraction with isomerization of the extracted substance. The allowed solvents include benzene, light petroleum spirits, methyl alcohol, *n*-butyl alcohol, and ethyl acetate. [21CFR172.560]

In general, oils are extracted from *Humulus lupulus* (hops) by steam distillation at 100˚C.[34]

Humulus Lupulus (Hops) Extract

One manufacturer reported that the method of manufacture of Humulus Lupulus (Hops) Extract for use in cosmetics begins with extraction with water and propylene glycol.[35] The extract solution is then pressed, clarified, and decontaminated. Further details were not provided.

Another manufacturer reports that Humulus Lupulus (Hops) Extract may be extracted with either a 50% volume ethanol solution or a 50% volume butylene glycol solution.[36] After the dried raw material (the flower head) is extracted with the solution, the extract is filtered and concentrated. After sedimentation, the filtrate is "adjusted" and packaged.

To manufacture a product mixture containing Humulus Lupulus (Hops) Extract, dried whole strobiles of *Humulus lupulus* (hops) are dispersed and solubilized with stirring in caprylic/capric triglyceride.[37] The solution is then filtered to obtain the desired mixture.

Composition

Humulus lupulus (hops)

The components of fresh and dried *Humulus lupulus* (hops) strobiles/cones are listed in Table 4 and Table 5, respectivly.[2,38] Analysis of dried food grade *Humulus lupulus* (hops) strobiles grown for beer production showed α-acids at 3.0% to 15.5% (w/w) and β-acids at 3.0% to 5.5% (w/w).[23] *Humulus lupulus* (hops) bitter acids are classified as either "α-acids" or "β-acids" that are, respectively, di- or tri-prenylated phloroglucinol derivatives. In addition, they each contain a 3-, 4-, 5-, or 6-carbon oxo-alkyl side chain.[6,39] Historically, the α-acids were distinguished because they precipitated from a crude extract of hops with the addition of lead acetate. The β-acids, by definition, would remain in solution. The α-acids, particularly humulone (35% to 70% of total α-acids), cohumulone (20% to 65%), and adhumulone (10% to 15%) are regarded as the most important constituents determining the quality of hops.[6,39]

In an analysis of *Humulus lupulus* (hops) samples by high-performance liquid chromatography (HPLC)-diode array detection, over 100 compounds were in the polyphenol fraction of *Humulus lupulus* (hops).[40] The composition of the polyphenols in *Humulus lupulus* (hops) is provided in Table 6.

Flavonoids are composed of different chemical classes such as flavones, isoflavones, flavonols, flavanols, flavanones, and chalcones. These compounds differ in the level of oxidation of the flavane nucleus and in the number and position of hydroxyl, methyl, and methoxyl substituents.[41] Flavonoids, which make up 0.5% to 1.5% of the dried strobile, include quercetin and kaempferol glycosides.[42,43] Thirty prenylated, geranylated, oxidized and/or cyclized chalcones have been isolated from the secretions of the lupulin glands.[17] The prenylated, geranylated flavonoids constitute up to 1% of the dried strobile and 80% to 90% of total flavonoids.[19,20,44-46] The chalcone xanthohumol is the most abundant prenylated flavonoid in fresh and properly preserved strobiles (approximately 0.01% to 0.5%); desmethylxanthohumol, dehydrocycloxanthohumol, and the flavanones isoxanthohumol, 8-PN (25 to 60 mg/kg) and 6-prenylnaringenin are also found in the strobiles.[19,20,44-47] A majority of the known flavonoids from *Humulus lupulus* (hops) strobiles can be considered to be derivatives of the compound 2',4,4',6'-tetrahydroxy-3'-prenylchalcone (chalcone numbering), commonly known as desmethylxanthohumol.

The constituents and their ranges of concentration of aqueous (hydrodistilled) *Humulus Lupulus* (hops) extracts from 10 different cultivars are provided in Table 7.[48]

Humulus lupulus (hops) oil

The cone oil of *Humulus lupulus* (hops) contains secondary metabolites of the plant, which are secreted in the lupulin glands (located on the female flower cones/strobiles).[2] The strobile oil makes up 0.5% to 1.5% of the dried inflorescence of *Humulus lupulus* (hops) strobile.[49] The strobile oil contains many volatile constituents, including simple oxidized alkanes, monoterpenes, and sesquiterpenes.[17,50-52] It is possible that the strobile oil contains over 1000 compounds. The primary volatile constituents are the monoterpene β-myrcene, and the sesquiterpenes β-caryophyllene and humulene, which together were shown to comprise between 57% and 82% of the volatile oil, depending on the cultivar and the method of detection. There are only traces of 2-methyl-3-buten-2-ol found in freshly harvested strobile; after drying and storing, the amount is higher, increasing to a maximum of approximately 0.15% of the dry weight (up to 20% of the volatile constituents) after 2 years due to degradation of humulones and lupulones.[49] The constituents in *Humulus lupulus* (hops) oil are not consistent across years or cultivars and not all of the constituents are detectable in every essential oil sample; β-myrcene, linalool, α-humulene, β-caryophyllene, undecanone-2, geranyl acetate, humulene epoxide-2, and α-selinene are always present.[53] Lists of some of the compounds in strobile oil are provided in Table 8 and Table 9.

Humulus Lupulus (Hops) Extract

The ethanol extract of Humulus Lupulus (Hops) Extract is reported to contain flavonoid and tannin.[36] The butylene glycol extract of Humulus Lupulus (Hops) Extract is reported to contain tannin and amino acid.

Constituents of Concern

Humulus lupulus (hops)

Humulus lupulus (hops) plants are reported to contain linalool, quercetin, β-myrcene, 8-PN (or hopein), and other prenylated flavonoids (Figure 1).[42,43,52,54-56] *Humulus lupulus* (hops) oil is reported to contain sesquiterpene lactones.[17,50-52] The potential adverse effects of exposures to these constituents are summarized in Table 10.

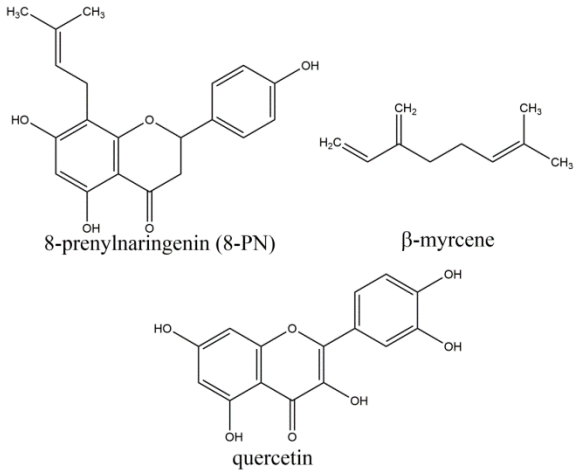

Figure 1. Constituents of concern of *Humulus lupulus* (hops) plants

The International Fragrance Association (IFRA) publishes restrictions for fragrance ingredients. Constituents of *Humulus lupulus* (hops) that have restrictions established by IFRA are listed in Table 11.

Humulus Lupulus (Hops) Extract

According to one supplier, the butylene glycol extract of Humulus Lupulus (Hops) Extract does not contain β-myrcene (detection limit 0.01 mg/100 g).[36]

A product mixture that contains approximately 0.18% Humulus Lupulus (Hops) Extract (extracted with caprylic/capric triglyceride) reports a theoretical content of β-myrcene of 22 ppm based on the content of the starting materials.[37] However, it is noted that the method of manufacture does not favor β-myrcene retention. The HPLC profile of this mixture shows a peak at xanthohumol and no other prenylflavonoides.

Humulus Lupulus (Hops) Oil

Humulus Lupulus (Hops) Oil is reported to contain geraniol (0.2%), limonene (1%), and linalool (0.6%).[57]

Impurities

Humulus lupulus (hops)

Multiple fungi and bacteria may be found on *Humulus lupulus* (hops) plants.[3] Analysis of the dust in air samples collected during harvest showed that total concentrations of microorganisms ranged between 2.08 to 129.58 × 10^3 cfu/m^3; the concentrations of endotoxin ranged between 26 to 6250 ng/m^3.[58] In samples of the settled dust after harvest, the concentrations of total microorganisms ranged from 0.25 × 10^6 to 2.87 × 10^8 cfu/g; the concentrations of endotoxin ranged between 312.5 to 6250 µg/g (median 6250 µg/g).

FDA regulations restrict the amounts of residuals from solvents in the manufacture of "modified hop extract" as a food additive (Table 3). [21CFR172.560] These restrictions include: boron, 310 ppm; benzene, 1.0 ppm; light petroleum spirits, 1.0 ppm; methyl alcohol, 250 ppm; hexane, 125 ppm; ethylene dichloride, 150 ppm; methylene chloride, 250 ppm; trichloroethylene, 250 ppm; and isopropyl alcohol, 250 ppm.

Analysis of dried food grade *Humulus lupulus* (hops) strobiles (possible source material for Humulus Lupulus (Hops) Extract) produced for beer production had the following results: lead < 1.0 ppm, arsenic < 0.5 ppm, cadmium < 0.03 ppm, and total heavy metals < 10 ppm.[23] Heavy metals, pesticides, herbicides, fungicides, nitrates, and radioactivity are reported to be below tolerance levels. Another analyses of leaves and strobiles of *Humulus lupulus* (hops) plants had the

following results: copper, 102.3 and 81.1 ppm; vanadium, 0.07 and 0.05 ppm; molybdenum, 0.07 and 0.12 ppm; iron, 49.3 and 54.2 ppm; tin, 1.4 and 1.2 ppm; lead, 3.1 and 2.3 ppm, and nickel, 7.9 and 5.5 ppm, respectively.[59]

The levels of residual solvent present in commercial hop extracts used for brewing beer are reported to be < 100 ppm.[60]

Humulus Lupulus (Hops) Extract

Authors of an analysis of a product mixture that contained Humulus Lupulus (Hops) Extract (0.6% to 1.2%) reported that heavy metals were certified to be present at ≤ 5 ppm, microbes at < 100 cfu/mL, yeasts and molds at < 100 cfu/mL, and enterobacteria absent.[61]

USE

Cosmetic

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

The *Humulus lupulus* (hops)-derived ingredients were reported to the 2017 VCRP and surveyed by the Council in 2015 and 2016 under the former INCI names, and that is how they are reported here.[62,63]

According to VCRP data received in 2017, Humulus Lupulus (Hops) Extract was reported to be used in 375 formulations, including 317 leave-on formulations and 54 rinse-off formulations (Table 12).[62]

The results of the concentration of use survey conducted by the Council in 2015 (and updated in 2016) indicate that Humulus Lupulus (Hops) Extract is used at up to 0.2% in hair conditioners.[63,64] The highest reported maximum concentration of use with dermal contact was reported to be 0.13% in eye lotion and in the category of other skin care preparations.

Humulus Lupulus (Hops) Cone Oil is not in use according to the VCRP and the industry survey results.

Humulus Lupulus (Hops) Extract is reported to be used in formulations that are used around the eyes at up to 0.13% and in formulations that come in contact with mucus membranes at up to 0.084% (e.g., bath soaps and detergents, bubble baths).

Humulus Lupulus (Hops) Extract is used in cosmetic sprays and could possibly be inhaled; for example, this ingredient is reported to be used at up to 0.0002% in hair sprays. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[65,66] 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.[67,68] There is a reported use in face powders at up to 0.00055%. Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[69-71]

Neither of the *Humulus lupulus* (hops)-derived ingredients named in the report (under the new or revised names) are restricted from use in any way under the rules governing cosmetic products in the European Union.[72]

Non-Cosmetic

Humulus lupulus (hops) strobiles are predominantly used to make beer.[2,3] They were originally added to beer for their antimicrobial properties. Brewers then began using strobiles (and their extracts) to add bitterness, flavor, and aroma.[24]

FDA determined that essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Humulus lupulus* L. (hops) are GRAS for human consumption. [21CFR182.20] Modified *Humulus lupulus* (hops) extract may be safely used in beer in accordance with the following prescribed conditions: (a) the food additive is used or intended for use as a flavoring agent in the brewing of beer, and (b) the food additive is manufactured by one of the prescribed processes (Table 3). [21CFR172.560]

Most parts of the *Humulus lupulus* (hops) plant (shoots, leaves, flowers, seeds, rhizomes, and essential oils) are edible.[5,6] The shoots are consumed as a delicacy and resemble asparagus.

In Europe, *Humulus lupulus* (hops) is administered as an herbal supplement in the form of powders, liquid extracts (ethanol extract drug ratio/dry extract ratio [DER] 1:1; sweet wine extract DER 1:10), tinctures (ethanol extract DER 1:5), and dry extracts (50% methanol extract DER 4 to 5:1) of the inflorescence of the plant.[49,73] It is also administered as a tea. *Humulus lupulus* (hops) strobiles are used in European, Indian-Ayurvedic, and Native American traditional medicines for the relief of insomnia, excitability, and specifically for restlessness associated with nervous tension, headache and/or indigestion.

It has been shown that *Humulus lupulus* (hops) byproducts, after harvesting of the strobiles, can be used to absorb lead from contaminated waters.[74]

TOXICOKINETIC STUDIES

Obtaining data on the toxicokinetics of *Humulus lupulus* (hops)-derived ingredients would not be practical because these ingredients are complex mixtures. Exposure to the components of these ingredients in cosmetics is expected to be lower than that from dietary exposure because these ingredients are incorporated into cosmetic products only at very low concentrations.

TOXICOLOGICAL STUDIES

Acute Toxicological Studies

Acute toxicity data on *Humulus lupulus* (hops)-derived ingredients were not found in the published literature and no unpublished data were submitted.

Short-Term Toxicity Studies

Oral

Wistar rats (n=7/group) were fed a low-fat diet, a high-fat diet, or high-fat diet supplemented with 1% xanthohumol-rich *Humulus lupulus* (hops) extract for 41 days.[75] There were no mortalities or other adverse effects observed in any of these groups. The addition of the extract reduced the effects of the high-fat diet on weight gain from days 21 to 41 of the study. The weights of livers of rats fed the supplemented high-fat diets were similar to the controls, as were the plasma glucose levels, at the end of the test period.

Subchronic Toxicity Studies

Oral

In a study on the effects of *Humulus lupulus* (hops) extract on high-fat diets, male C57BL/6J mice (n = 10/group) were fed a normal diet, a high-fat diet, or a high-fat diet supplemented with 2% or 5% of various *Humulus lupulus* (hops) extracts for 20 weeks.[76] The high-fat diet was supplemented with one of the following: aqueous *Humulus lupulus* (hops) extract, ethyl acetate-soluble fraction of the aqueous *Humulus lupulus* (hops) extract, ethyl acetate-insoluble fraction of the aqueous *Humulus lupulus* (hops) extract, methanol-soluble fraction of the ethyl acetate-insoluble fraction of the aqueous *Humulus lupulus* (hops) extract, or methanol-insoluble fraction of the ethyl acetate-insoluble fraction of the aqueous *Humulus lupulus* (hops) extract. There were no mortalities or adverse effects reported for any group. The addition of any *Humulus lupulus* (hops) extract reduced the effects of the high-fat diet on weight gain. The weights of livers and mesenteric and epididymal adipose tissues of mice fed the supplemented high-fat diets were similar to that of the controls, as were plasma glucose levels, at the end of the test period; the extract had no additional effect on the effects of the high-fat diets.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Developmental and reproductive toxicity data on *Humulus lupulus* (hops)-derived ingredients were not found in the published literature and no unpublished data were submitted.

GENOTOXICITY STUDIES

In Vitro

Humulus Lupulus (Hops) Extract

An aqueous Humulus Lupulus (Hops) Extract (10 to 400 mg/µL in ethanol) was weakly mutagenic (a 2- to 4-fold increase in induced revertants compared with controls) in *Salmonella typhimurium* (strains TA 98 and TA100), with or without metabolic activation.[77] No further details were provided.

A Humulus Lupulus (Hops) Extract (0, 1000, 2500, 5000, 7500, and 10,000 µg/plate; extract solvent not specified; water control) was not mutagenic in *S. typhimurium* (strains TA98 and TA100) or *Escherichia coli* (strain pKM101), with or without metabolic activation.[78] The positive and negative controls yielded the expected results.

An Ames test was performed on a product mixture containing 5% Humulus Lupulus (Hops) Extract (extracted in water/glycerin 50/50) at 10% in deionized water (effective concentration of 0.5% hops) with and without metabolic activation using *S. typhimurium* (strains TA97a, TA98, TA100, TA201, and TA1535).[79] The test substance was not mutagenic in this assay with or without metabolic activation.

CARCINOGENICITY STUDIES

Carcinogenicity data on *Humulus lupulus* (hops)-derived ingredients were not found in the published literature and no unpublished data were submitted.

OTHER RELEVANT STUDIES

Estrogenic Activity

Historically, there is circumstantial evidence of potential estrogenic activity connected to *Humulus lupulus* (hops) exposure, including menstrual disturbances reported to be common among female *Humulus lupulus* (hops) harvesters.[80,81] In an investigation of the folk legend that women who normally live “a distance” from hop gardens regularly begin to

menstruate two days after arriving to pick hops, it was reported that hops contain "the equivalent of 20 to 300 μg estradiol/g".[49] *Humulus lupulus* (hops) extracts have been reported to reduce hot flashes in menopausal women and, in Germany, hops baths containing approximately 30% *Humulus lupulus* (hops) extracts (which have been discontinued) were used to treat gynecological disorders.[49,82] However, early studies to confirm this activity experimentally were inconclusive or contradictory because of inadequate sensitivity of the methods used.[80,83]

More recently, 8-PN has been shown to be the source of the estrogenic activity of *Humulus lupulus* (hops). 8-PN mimics the action of 17β-estradiol, albeit with less (10- to 20,000-fold) potency.[84-88] It is a potent ligand for the α-estrogen receptor (ER) with an IC_{50} value in the nanomolar range; it stimulates the production of alkaline phosphatase in Ishikawa cells, and stimulates the growth of estrogen-dependent MCF7 breast cancer cells.[44,89] It was reported that 8-PN has a greater affinity for the ERα (where it is 70-fold less potent than estradiol) than for ERβ (reported to be 20,000-fold less potent than estradiol).[90]

In a screening for drugs derived from plants for estrogenic activity, an ethanolic *Humulus lupulus* (hops) extract (50%; 0.2 g/mL) exhibited binding to ERs in intact, estrogen-dependent [ER(+)], human breast cancer MCF-7 cells with a potency equivalent to 0.5 μg of estradiol per 2 g of dried *Humulus lupulus* (hops) strobile (for comparison, the potencies of 2 g of thyme or red clover were equivalent to 0.5 or 3 μg of estradiol, respectively).[91] *Humulus lupulus* (hops) extract also showed significant ability to stimulate cell proliferation in ER (+)T47D, but not in ER(-) MDA 468, breast cancer cells.[91] In contrast, in a different series of experiments, a similarly prepared *Humulus lupulus* (hops) extract at concentrations of 0.01%-1.0% v/v was found to inhibit serum-stimulated growth of ER(+)T47D breast cancer cells.[92] Ovarian cells isolated from immature female rats, which 48 h previously had been injected (primed) with pregnant mare's serum gonadotropin, were incubated with follicle-stimulating hormone to induce estradiol secretion. The addition of purified water-soluble fractions from defatted *Humulus lupulus* (hops) extract to the culture medium reduced the estrogen E_2 released from the ovarian cells with a probably related decrease in cyclic adenosine monophosphate (cAMP) release.[49]

A *Humulus lupulus* (hops) extract activated the estrogen response element (ERE) in Ishikawa cells and induced ERE-luciferase expression in MCF-7 cells. In the MCF-7 cell line, progesterone receptor (PR) mRNA was significantly upregulated by *Humulus lupulus* (hops) extract with an EC_{50} of 1.1 μg/mL.[93] *Humulus lupulus* (hops) consisted of a chloroform partition of a methanolic extract from a previously SFE-CO_2-extracted Nugget *Humulus lupulus* (hops) cultivar; the individual constituents included prenylated flavanones and isoflavonoids. The estrogenic activity proved to be considerably greater than that of established phytoestrogens such as coumestrol (present in red clover) and genistein and daidzein (present in soy).

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Human

Humulus Lupulus (Hops) Extract

In a 2-week cumulative irritation test (n = 26) of a formulation containing Humulus Lupulus (Hops) Extract (0.125%), the test formulation did not demonstrate a significant irritation potential in human subjects.[94]

A formulation containing Humulus Lupulus (Hops) Extract (0.6% to 1.2%; 20 μL) was patch tested (n = 12) at 10% (final concentration 0.06% to 0.12%) using 8-mm aluminum cups covering 50 mm^2 skin.[95,96] The patches were administered to the upper back for 24 h. Controls were water and sodium lauryl sulfate (1%). The test sites were examined 30 min to 1 h and 24 h after patch removal. One subject had a reaction at the site of the negative control and was not included in the final analysis of the results. No reactions to the test material were observed in 9 subjects; two subjects showed very slight erythema. The controls had the expected results in the rest of the subjects. The irritation index was 0.04 (out of 5) and the test article was rated a non-irritant.

A patch test (n = 12) was conducted on a product mixture that contained Humulus Lupulus (Hops) Extract (approximately 0.18% in caprylic/capric triglyceride).[37] The test substance was applied to the skin on the back under a patch for 48 h. No adverse reactions were observed. It was concluded that the test substance had good cutaneous compatibility.

Sensitization

Humulus Lupulus (Hops) Extract

In a human maximization test (n = 26) of a product containing Humulus Lupulus (Hops) Extract (0.125%), the test product did not demonstrate contact sensitization potential.[94] No further information was provided.

A human repeated insult patch test (HRIPT; n = 52) of Humulus Lupulus (Hops) Extract (10%; extracted with butylene glycol) had negative results.[36] No further information was provided.

An HRIPT (n = 102) was conducted of a product mixture that contained Humulus Lupulus (Hops) Extract (approximately 0.18% in caprylic/capric triglyceride).[37] The test substance was applied to the same site three times per week for 9 applications. The challenge was applied two weeks after the last induction application. All patches were in place for 48 h. Patch sites were examined for reactions when patches were removed and at 72 and 96 h. No reactions were observed.

An HRIPT (n = 102) was conducted of a product mixture that contained Humulus Lupulus (Hops) Extract (approximately 5% in glycerin/water).[97] The induction and challenge phases were conducted at 10% (0.5% Humulus Lupulus (Hops) Extract). Induction and challenge patches were in place for 24 h. The test sites were observed before the

application of the next patch and at 24 and 72 h after the application of the challenge patch. There were no signs of irritation or sensitization at any time during the test period; there was no indication of a potential to cause dermal irritation or contact sensitization.

OCULAR IRRITATION STUDIES

In Vitro

Products and product mixtures containing Humulus Lupulus (Hops) Extract were assayed at up to 0.5% (Table 13). Humulus Lupulus (Hops) Extract was predicted to be a slight ocular irritant in hen's egg test-chorion-allantoic membrane (HET-CAM) and cornea fibroblast (CFIO) assays and a non-irritant in an EpiOcular assay. [95,96,98] Another Humulus Lupulus (Hops) Extract was predicted to be non-irritating in an HET-CAM assay and to SIRC fibroblastic cells.[37]

Human

In a 4-week use study (n = 48) of an eye cream that contained Humulus Lupulus (Hops) Extract (0.125%), the test material did not demonstrate a potential to cause eye irritation.[94]

CLINICAL STUDIES

Occupational Exposure

Dermal

The causative agents of *Humulus lupulus* (hops) plant-induced contact skin reactions have not been established.[99,100] Both irritant and allergic effects have been described. In *Humulus lupulus* (hops) harvesters, dermatitis has been attributed to mechanical abrasion by the rough hairs on the climbing stem. It has also been suggested that lupulin, the yellow powdery secretion of the glandular hairs on the scales of the strobiles, may be responsible for the irritation.

Farmers (n = 73) who cultivated *Humulus lupulus* (hops) plants and other crops from 18 randomly selected farms filled out a questionnaire on their skin diseases and were administered skin prick tests (SPT) for allergens of *Humulus lupulus* (hops) as well as grain dust, straw dust, hay dust, storage mites, and antigens of microorganisms typical of farm environments.[101] Only the results of the *Humulus lupulus* (hops) are reported here. Fresh strobiles and leaves were cut into small pieces, and extracted with glycerol and saline at 1:2 (w/w) for 48 h at 4 °C. The extracts were centrifuged and clear supernatants were used in the testing. The subjects consisted of 42 males and 31 females, aged 16 to 84 (median 46) years, with duration of employment resulting in exposure ranging from 2 to 73 (median 31) years.

The questionnaire showed that *Humulus lupulus* (hops) was reported to cause the greatest number of skin problems; 14 farmers (19.2%) reported work-related skin symptoms, 2 (11%) of which were caused by *Humulus lupulus* (hops). There were no reported skin problems associated with working with *Humulus lupulus* (hops) by 65 subjects. The reported skin symptoms of the subjects with skin problems were mostly mild: four reported rashes on uncovered skin (the description of which was sufficient to diagnose airborne dermatitis), two subjects reported hand dermatitis, and two reported pruritus without visible skin changes. One case of airborne dermatitis to *Humulus lupulus* (hops) was severe enough to be classified as debilitating.

Positive skin reactions to four *Humulus lupulus* (hops) allergen preparations, i.e., cone extract in glycerol, cone extract in saline, leaf extract in glycerol, and leaf extract in saline, were found in one, two, three, and four of 65 subjects, respectively. In all, six subjects (8.2%) reacted to at least one extract. Among the subjects reporting skin problems related to *Humulus lupulus* (hops), SPTs gave positive results in two subjects, and the tests were negative in six subjects. The tests were also positive in four persons who did not report any *Humulus lupulus* (hops)-related skin problems. The predictive values for SPT of the extracts (skin reaction to at least one of the preparations) were: positive predictive value (PPV) = 0.33 and negative predictive value (NPV) = 0.91.[101]

Inhalation

Washington State Workers' Compensation claims filed by *Humulus lupulus* (hops) workers for respiratory disease between 1995 and 2011 were systematically identified and reviewed in a study of occupational respiratory disease in *Humulus lupulus* (hops) workers.[102] Incidences of respiratory disease in *Humulus lupulus* (hops) workers were compared with rates in field vegetable crop farm workers. A total of 57 cases of respiratory disease associated with *Humulus lupulus* (hops) dust inhalation were reported. The attending health care practitioner diagnosed 61% of these cases as having work-related asthma. Chronic obstructive pulmonary disease was diagnosed in 7% of these cases; the remaining cases were diagnosed as allergic respiratory disorders (e.g., allergic rhinitis [18%] or asthma-associated symptoms [e.g., dyspnea; 14%]). All cases were associated with *Humulus lupulus* (hops) harvesting, secondary hops processing, or indirect exposure. The incidence of respiratory disease in *Humulus lupulus* (hops) workers was 15 cases per 10,000 full-time workers, which was 30 times greater than the incidence for field vegetable crop workers. A strong temporal association between *Humulus lupulus* (hops) dust exposure and respiratory symptoms and a clear association between an increase in *Humulus lupulus* (hops) dust concentrations and the clinical onset of symptoms were apparent in 3 cases. The authors concluded that occupational exposure to *Humulus lupulus* (hops) dust is associated with respiratory disease; respiratory disease rates were higher in *Humulus lupulus* (hops) workers than in a comparison group of agricultural workers.

In a study of occupational exposure of brewery workers to organic dusts such as *Humulus lupulus* (hops), barley,

and brewery yeast, the potential to affect respiratory function and immunological status was examined.[103] Male subjects (n = 97) employed in a brewery plant had a mean age of 40 years, and the mean duration of employment was 16 years. The control group consisted of unexposed workers (n = 76). Respiratory symptoms were recorded. Lung function was measured by recording maximum expiratory flow-volume (MEFV) curves. Immunological testing was performed on all brewery workers and 37 of the control volunteers using SPTs with *Humulus lupulus* (hops), barley, and yeast antigens as well as other non-occupational allergens, and by determining total serum IgE levels. There was a higher prevalence of most of the chronic respiratory symptoms in brewery workers compared to controls. Occupational asthma was recorded in only 2 (2.1%) of the brewery workers; smoking was reported to be the major factor (that was examined in this study) responsible for the high prevalence of chronic respiratory symptoms in workers, not exposure to dust of the brewing ingredients, including *Humulus lupulus* (hops). A large number of brewery workers complained of acute symptoms that developed during the work shift. Lung function test scores were decreased compared to predicted levels. Multivariate analysis of these respiratory function parameters suggested the importance of workplace exposure in explaining lung function abnormalities. There was a greater instance of positive SPTs in brewery workers for *Humulus lupulus* (hops) than in controls (15% vs 3%). There were increased serum levels of total IgE in 34 out of 97 (45.1%) brewery workers compared to controls, 1 out of 76 (2.7%). However, workers with positive SPTs had a prevalence of chronic respiratory symptoms and lung function changes similar to those of workers with negative SPTs. The authors concluded that the data suggest that both smoking and dust exposure in the brewery industry may be responsible for the development of respiratory impairment and immunological reactions.

Case Reports

Case reports of irritation and sensitization to *Humulus lupulus* (hops) or the constituent β-myrcene while working with the plant on farms, laboratories, and in breweries are recited in Table 14.[11,54,104-106]

SUMMARY

This is a safety assessment of Humulus Lupulus (Hops) Extract and Humulus Lupulus (Hops) Oil as used in cosmetics. Both of these ingredients are derived from the strobile of the *Humulus lupulus* plant, commonly called hops. The reported functions of Humulus Lupulus (Hops) Extract in cosmetics include antimicrobial agent, hair conditioning agent, and skin-conditioning agent – miscellaneous; Humulus Lupulus (Hops) Oil is reported to function as a fragrance ingredient.

Previously, the wINCI listed four other names for Humulus Lupulus (Hops) Extract. Data submitted under those deleted names have been assigned to Humulus Lupulus (Hops) Extract and the deleted names are now technical names for Humulus Lupulus (Hops) Extract.

Humulus lupulus (hops) strobile is an ingredient in food (most commonly in beer) and most of the other parts of this plant (shoots, leaves, flowers, seeds, rhizomes, and essential oils) are edible. The FDA determined that essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Humulus lupulus* L. (hops) are GRAS for human consumption.

Humulus lupulus (hops) plants are reported to contain several constituents of concern, including 8-PN, β-myrcene, and quercetin; these constituents could result in estrogenic activity, dermal irritation, and genotoxicity, respectively, if concentrations were high enough. Geraniol, limonene, linalool, and sesquiterpene lactones are potential dermal sensitizers. Humulus Lupulus (Hops) Oil is reported to contain sesquiterpene lactones.

The butylene glycol extract of Humulus Lupulus (Hops) Extract is reported to contain no detectable β-myrcene. A product mixture that contains approximately 0.18% Humulus Lupulus (Hops) Extract is reported to have a theoretical content of β-myrcene of 0.0022% based on the content of the starting materials; it is noted that the method of manufacture does not favor β-myrcene retention.

The *Humulus lupulus* (hops)-derived ingredients were reported to the VCRP database and surveyed by the Council in 2015(and updated in 2016) under the revised INCI names, and that is how they are reported herein.

According to VCRP data received in 2017, Humulus Lupulus (Hops) Extract was reported to be used in 375 formulations, including 317 leave-on formulations and 54 rinse-off formulations. The results of the concentration of use survey conducted by the Council in 2015 (and updated in 2016) indicate that the highest reported maximum concentration of use of Humulus Lupulus (Hops) Extract is up to 0.2% in hair conditioners.

Humulus Lupulus (Hops) Oil is not in use according to the VCRP and the industry survey.

Rats fed a low-fat diet, a high-fat diet, or high-fat diet supplemented with 1% xanthohumol-rich extract of *Humulus lupulus* (hops) extracts for 41 days and male mice fed a normal diet, a high-fat diet, or high-fat diets supplemented with 2% or 5% of various *Humulus lupulus* (hops) extracts for 20 weeks had no mortalities or adverse effects reported for any group. The additions of any of the *Humulus lupulus* (hops) extracts reduced the effects of the high-fat diet on weight gain. The weights of livers and mesenteric and epididymal adipose tissues of mice fed the supplemented high-fat diets were similar to those of the controls, as were the plasma glucose levels at the end of the test period.

An aqueous Humulus Lupulus (Hops) Extract (10 to 400 mg/µL in ethanol) was weakly mutagenic (an increase in induced revertants 2 to 4 times the controls) to *S. typhimurium* with and without metabolic activation. In another assay, a Humulus Lupulus (Hops) Extract was not mutagenic to *S. typhimurium* and *E. coli* at up to 10,000 µg/plate, with or without metabolic activation. A product mixture containing 5% Humulus Lupulus (Hops) Extract at 10% (0.05% hops in deionized water) was not mutagenic to *S. typhimurium* with or without metabolic activation.

Historically, there is circumstantial evidence of potential estrogenic activity connected to *Humulus lupulus* (hops)

exposure, including menstrual disturbances reported to be common among female *Humulus lupulus* (hops) harvesters. 8-PN has been shown to be the source of the estrogenic activity of *Humulus lupulus* (hops) plants. It mimics the action of 17β-estradiol, albeit with a lesser (10- to 20,000-fold) potency.

In a 2-week cumulative irritation test of a product containing Humulus Lupulus (Hops) Extract (0.125%), the test product did not demonstrate a significant irritation potential in human skin. In a human patch test of a product containing Humulus Lupulus (Hops) Extract at 0.06% to 0.12%, the irritation index was 0.04 (out of 5) and the test article was rated a non-irritant. No adverse reactions were observed in a patch test of a product mixture that contains Humulus Lupulus (Hops) Extract (approximately 0.18%).

The causative agents of *Humulus lupulus* (hops) plant-induced contact skin reactions have not been established. In *Humulus lupulus* (hops) harvesters, dermatitis has been attributed to mechanical abrasion by the rough hairs on the climbing stem. It has also been suggested that lupulin, the yellow powdery secretion of the glandular hairs on the scales of the strobiles, may be responsible for the irritation.

In a human maximization test of a product containing Humulus Lupulus (Hops) Extract (0.125%), the test product did not demonstrate contact sensitization potential. An HRIPT of Humulus Lupulus (Hops) Extract (10%; extracted with butylene glycol) gave negative results. No reactions were observed in an HRIPT that was conducted of a product mixture that contains Humulus Lupulus (Hops) Extract (approximately 0.18%). There were no signs of irritation or sensitization in an HRIPT of a product mixture that contained Humulus Lupulus (Hops) Extract (approximately 5%).

In vitro assays showed that products and product mixtures containing Humulus Lupulus (Hops) Extract up to 0.5% were predicted to be either non-irritating or slight ocular irritants. Humulus Lupulus (Hops) Extract was predicted to be a slight ocular irritant in HET-CAM and cornea fibroblast assays and a non-irritant in an EpiOcular assay. Another Humulus Lupulus (Hops) Extract was predicted to be non-irritating in an HET-CAM assay and to SIRC fibroblastic cells.

In a 4-week use study of an eye cream that contained Humulus Lupulus (Hops) Extract (0.125%), the test material did not demonstrate potential for eliciting ophthalmic irritation.

In a survey of farmers, exposure to *Humulus lupulus* (hops) was reported to cause the greatest number of skin problems; 14 of 73 (19.2%) of the farmers reported work-related skin symptoms, 11% of which were caused by *Humulus lupulus* (hops). There were one, two, three, and four positive SPTs to the following *Humulus lupulus* (hops) allergen preparations, respectively: cone extract in glycerol, cone extract in saline, leaf extract in glycerol, and leaf extract in saline.

In a study of occupational respiratory disease in *Humulus lupulus* (hops) workers, using Workers' Compensation claims filed by *Humulus lupulus* (hops) workers for respiratory disease, the incidence rate of respiratory disease in *Humulus lupulus* (hops) workers was 15 cases per 10,000 full-time workers, which was 30 times greater than the incidence rate for field vegetable crop workers. The authors concluded that occupational exposure to *Humulus lupulus* (hops) dust is associated with respiratory disease; respiratory disease rates were higher in hop workers than in a comparison group of agricultural workers.

In a study of occupational exposure of brewery workers to organic dusts, including *Humulus lupulus* (hops), the potential to affect respiratory function and immunological status was examined. A large number of brewery workers complained of acute symptoms that developed during the work shift. Lung function tests were decreased compared to predicted levels. There was a greater instance of positive SPTs in brewery workers for *Humulus lupulus* (hops) than in controls (15% vs 3%). There were increased serum levels of total IgE in 34 of 97 (45.1%) brewery workers compared to controls, 1 of 76 (2.7%). However, workers with positive SPTs had a prevalence of chronic respiratory symptoms and lung function changes similar to those of workers with negative SPTs. The authors concluded that the data suggests that both smoking and dust exposure in the brewery industry may be responsible for the development of respiratory impairment and immunological reactions.

There were case studies of subjects becoming sensitized to *Humulus lupulus* (hops) plants or the constituent β-myrcene while working with the plant on farms, laboratories, and in breweries.

DISCUSSION

The Panel examined the oral toxicity, genotoxicity, dermal and ocular irritation, and sensitization studies of *Humulus lupulus* (hops)-derived ingredients, as well as studies on occupational exposure. Essential oils, oleoresins, and natural extracts of *Humulus lupulus* (hops) are GRAS for human consumption.

The Panel noted the presence of β-myrcene at up to 25.4% in *Humulus lupulus* (hops) oil. This constituent is a potential irritant, and there is a National Toxicology Program (NTP) study showing increased incidences of kidney tumors in male rats and liver tumors in male mice after oral administration of 1.0 g/kg/day β-myrcene for 2 years. The increased incidence of kidney tumors in this study is likely attributable to a mechanism that is not relevant to humans, and the increased incidence of liver tumors is attributable to the high background incidence and susceptibility to the development of liver tumors that is characteristic of the mouse strain used in the study, and is also not predictive of carcinogenicity in humans. Further, the dosage rates of β-myrcene administered orally to the rats and mice in the study were much greater than the highest possible exposure to β-myrcene that could occur from *Humulus lupulus* (hops)-derived ingredients in cosmetics. However, concerns about β-myrcene, and possibly other constituents, cannot be addressed fully by the Panel, because the available information is not sufficient to characterize adequately the compositions of *Humulus lupulus* (hops)-derived cosmetic ingredients. The Panel emphasized the importance, generally, of adequately characterizing the compositions of cosmetic ingredients derived from plants, as manufactured and supplied to formulators of cosmetic products.

There were possible estrogenic effects in persons who worked with *Humulus lupulus* (hops) in the field. The Panel was not concerned because studies showed that the purported estrogenic effects were weak and the degree of the exposure to the workers is far greater than any exposure that could occur from the use of cosmetics that contain these ingredients at the reported concentrations of use.

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 example, in *Humulus lupulus* (hops)-derived ingredients, the Panel's concerns included the presence of 8-PN, β-myrcene, and quercetin in cosmetics, which could result in estrogenic effects, dermal irritation, and genotoxicity, respectively, as well as other constituents of concern. The Panel noted that IFRA standards to avoid adverse effect have been published for several *Humulus lupulus* (hops) constituents; for example, limits have been set for geraniol, sesquiterpene lactones, and the oxidation products of limonene and linalool, which are potential dermal sensitizers. At the reported concentrations of use of these ingredients, the constituents that may cause these effects will be present at levels far below levels of concern, including for sensitization. However, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

There were instances of sensitization of persons who worked with *Humulus lupulus* (hops) in the field and in laboratories. The studies showed that the degree of the exposure of these persons is far greater than any exposure that could occur from the use of cosmetics that contain these ingredients at the reported concentrations of use. Additionally, the plant has hairs and bristles that could abrade the skin, thus increasing the chance of dermal penetration of constituents that could cause sensitization. Such abrasion would not occur with exposure to these cosmetic ingredients

The Panel is assured by the HRIPT of 10% Humulus Lupulus (Hops) Extract that sensitization should not be a problem under the reported conditions and concentrations of use in cosmetics because the highest reported concentration of use was 0.2% Humulus Lupulus (Hops) Extract in hair products and 0.13% in products that come in contact with the skin. Overall, sensitization and constituent profile data show that there should not be any issue with sensitization at the low concentrations of use of these ingredients. The Panel cautions that manufactures use cGMP to formulate products that are non-sensitizing.

There is a substantial data profile on the constituents of the Humulus Lupulus (Hops) Oil; many of these constituents, including potential sensitizers, are similar to those in the Humulus Lupulus (Hops) Extract. Therefore, the safety data on one ingredient informs the other. Concern, however, was expressed about alternative approaches to extraction that might not produce material with the same safety profile described in this safety assessment. There are multiple methods of extraction with multiple solvents (e.g., water/propylene glycol, water/ethanol, water/butylene glycol, and caprylic/capric triglyceride) presented for the ingredient Humulus Lupulus (Hops) Extract and steam distillation for Humulus Lupulus (Hops) Oil. The Panel's safety conclusion is applicable only for Humulus Lupulus (Hops) Extract and Humulus Lupulus (Hops) Oil that are prepared in a manner that produces a similar chemical profile as that described in this report, especially for the constituents of concern. When prepared in a manner resulting in this chemical profile, the Panel's conclusion is that these ingredients do not have significant estrogenic activity, genotoxicity, irritation, or sensitization potential. Ingredients not prepared in a manner that produces a similar chemical profile would be considered safe if a similar safety test profile was demonstrated.

The Panel expressed concern about pesticide residues, heavy metals, and substances from plants of other species (weeds) that may be present in botanical ingredients. Also, multiple fungi and bacteria have been detected co-localized with *Humulus lupulus* (hops) plants. To address these concerns, the cosmetics industry should continue to use cGMPs to limit impurities.

There were no constituents of concern associated with phototoxicity. Accordingly, there were no concerns about the lack of phototoxicity assays.

Also, the Panel noted the limited scope of the in vitro genotoxicity assay in which an aqueous Humulus Lupulus (Hops) Extract increased revertants 2-4 times that of controls. The Panel concluded that these test results were not statistically significant and that there was no significant risk of genotoxicity.

The pulmonary disease associated with working with *Humulus lupus* (hops) plants was reported to be caused by constant inhalation exposure to the plant dust over extended periods (e.g., years). This exposure is far greater than any exposure would be associated with the use of cosmetic products. In this context, the Panel discussed the issue of incidental inhalation exposure from aerosol and pump hair sprays. The limited data on occupational inhalation suggests some potential for respiratory effects at large doses over extended periods of time. Otherwise, there were no inhalation toxicity data available. These ingredients are reportedly used at concentrations up to 0.0002% in cosmetic products that may be aerosolized and up to 0.00055% in loose powder products that may become airborne. The Panel noted that 95% to 99% of droplets/particles 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 *Humulus lupulus* (hops)-derived ingredients to cause toxicity, genotoxicity, irritation, and sensitization. They noted the lack of systemic toxicity, genotoxicity, irritation, and sensitization at relevant doses by *Humulus lupulus* (Hops)-derived ingredients. 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 Humulus Lupulus (Hops) Extract and Humulus Lupulus (Hops) Oil are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing.

TABLES

Table 1. Current and revised INCI names, definitions, and functions of the *Humulus lupulus* (hops)-derived ingredients in this safety assessment.[1,4]

Ingredient	Definition	Functions
Humulus Lupulus (Hops) Extract 8016-25-9 8060-28-4	Humulus Lupulus (Hops) Extract is the extract obtained from the inflorescence (hops cone) of *Humulus lupulus.* In 2017, the definition of Humulus Lupulus (Hops) Extract was changed from "the extract of the whole plant, *Humulus lupulus.*"	Antimicrobial agent; fragrance ingredient; hair conditioning agent; skin-conditioning agent – miscellaneous; skin protectant; skin-conditioning agent – miscellaneous
Humulus Lupulus (Hops) Cone Extract (deleted monograph)	In 2017, the INCI name Humulus Lupulus (Hops) Cone Extract was revised and the name will be retained in the monograph as a technical name of Humulus Lupulus (Hops) Extract.	Antimicrobial agent; antiperspirant agent; hair conditioning agent
Humulus Lupulus (Hops) Flower Extract (deleted monograph)	In 2017, the INCI name Humulus Lupulus (Hops) Flower Extract was revised and the name will be retained in the monograph as a technical name Humulus Lupulus (Hops) Extract.	Skin-conditioning agent – miscellaneous
Humulus Lupulus (Hops) Stem Extract (deleted monograph)	In 2017, the INCI name Humulus Lupulus (Hops) Stem Extract was revised and the name will be retained in the monograph as a technical name Humulus Lupulus (Hops) Extract.	Skin protectant
Humulus Lupulus (Hops) Strobile (deleted monograph)	In 2017, the INCI name Humulus Lupulus (Hops) Strobile was revised and the name will be retained in the monograph as a technical name Humulus Lupulus (Hops) Extract.	None reported
Humulus Lupulus (Hops) Oil 8007-04-3	Humulus Lupulus (Hops) Oil is the volatile oil obtained from the inflorescence (hops cone) of *Humulus lupulus.*	Fragrance ingredient
Humulus Lupulus (Hops) Cone Oil (deleted monograph) 8007-04-3	In 2017, the INCI name Humulus Lupulus (Hops) Cone Oil was revised and the name will be retained in the monograph as a technical name Humulus Lupulus (Hops) Oil	Fragrance ingredient

Table 2. Chemical and physical properties of Humulus Lupulus (Hops) Extract.

Property	Value	Reference
Physical Form	Oil Viscous liquid[a]	57 107
Color	Greenish-yellow-reddish brown Yellow/orange to brown/green[a]	57 107
Odor	Harsh and bitter Citrus, tropical fruit, stone fruit, pine, cedar, floral, spicy, herbal, earthy, tobacco, onion/garlic and/or grassy	57 23
Density/Specific Gravity @ 20 °C	0.883 - 0.900 850 - 1100[a]	57 107
Vapor Density mmHg	> 1	57
Melting Point °C	40 - 60[a]	107
Water Solubility	Negligible Insoluble[a]	57 107

[a] A CO_2 extract of dried cones manufactured for use as a food ingredient

Table 3. FDA regulations on the method of manufacture and residual solvents in "modified hop extract", as a food additive used or intended for use as a flavoring agent in the brewing of beer. [21CFR172.560]

Method of Manufacture	Solvent/Impurities restrictions
(b)(1)The additive is manufactured from a hexane extract of hops by simultaneous isomerization and selective reduction in an alkaline aqueous medium with sodium borohydride, whereby the additive meets the following specifications: A solution of the food additive solids is made up in approximately 0.012 *n* alkaline methyl alcohol (6 mL of 1 *n* sodium hydroxide diluted to 500 mL with methyl alcohol) to show an absorbance at 253 mμ of 0.6 to 0.9/cm. (This absorbance is obtained by approximately 0.03 mg solids/mL.) The ultraviolet absorption spectrum of this solution exhibits the following characteristics: An absorption peak at 253 mμ; no absorption peak at 325 to 330 mμ; the absorbance at 268 mμ does not exceed the absorbance at 272 mμ.	The boron content of the food additive does not exceed 310 ppm (0.0310%), calculated as boron.
(b)(2) The additive is manufactured from hops by a sequence of extractions and fractionations, using benzene, light petroleum spirits, and methyl alcohol as solvents, followed by isomerization by potassium carbonate treatment. The light petroleum spirits and benzene solvents shall comply with the specifications in §172.250 except that the boiling point range for light petroleum spirits is 150°F to 300°F.	Residues of solvents in the modified hop extract shall not exceed 1.0 ppm of benzene, 1.0 ppm of light petroleum spirits, and 250 ppm of methyl alcohol.
(b)(3) The additive is manufactured from hops by a sequence of extractions and fractionations, using methylene chloride, hexane, and methyl alcohol as solvents, followed by isomerization by sodium hydroxide treatment.	Residues of the solvents in the modified hop extract shall not exceed 5 ppm of methylene chloride, 25 ppm of hexane, and 100 ppm of methyl alcohol.
(b)(4) The additive is manufactured from hops by a sequence of extractions and fractionations, using benzene, light petroleum spirits, methyl alcohol, *n*-butyl alcohol, and ethyl acetate as solvents, followed by isomerization by potassium carbonate treatment. The light petroleum spirits and benzene solvents shall comply with the specifications in §172.250 except that the boiling point range for light petroleum spirits is 150°F to 300°F.	Residues of solvents in the modified hop extract shall not exceed 1.0 ppm of benzene, 1.0 ppm of light petroleum spirits, 50 ppm of methyl alcohol, 50 ppm of *n*-butyl alcohol, and 1 ppm of ethyl acetate.
(b)(5) The additive is manufactured from hops by an initial extraction and fractionation using one or more of the following solvents: ethylene dichloride, hexane, isopropyl alcohol, methyl alcohol, methylene chloride, trichloroethylene, and water; followed by isomerization by calcium chloride or magnesium chloride treatment in ethylene dichloride, methylene chloride, or trichloroethylene and a further sequence of extractions and fractionations using one or more of the solvents set forth in this paragraph.	Residues of the solvents in the modified hop extract shall not exceed 125 ppm of hexane; 150 ppm of ethylene dichloride, methylene chloride, or trichloroethylene; or 250 ppm of isopropyl alcohol or methyl alcohol.
(b)(6) The additive is manufactured from hops by an initial extraction and fractionation using one or more of the solvents listed in paragraph (b)(5) of this section followed by: hydrogenation using palladium as a catalyst in methyl alcohol, ethyl alcohol, or isopropyl alcohol acidified with hydrochloric or sulfuric acid; oxidation with peracetic acid; isomerization by calcium chloride or magnesium chloride treatment in ethylene dichloride, methylene chloride, or trichloroethylene (alternatively, the hydrogenation and isomerization steps may be performed in reverse order); and a further sequence of extractions and fractionations using one or more of the solvents listed in paragraph (b)(5) of this section.	The additive shall meet the residue limitations as prescribed in paragraph (b)(5) of this section.
(b)(7) The additive is manufactured from hops as set forth in paragraph (b)(6) of this section followed by reduction with sodium borohydride in aqueous alkaline methyl alcohol, and a sequence of extractions and fractionations using one or more of the solvents listed in paragraph (b)(5) of this section.	The additive shall meet the residue limitations as prescribed in paragraph (b)(5) of this section, and a boron content level not in excess of 300 ppm (0.0300%), calculated as boron.
(b)(8) The additive is manufactured from hops as a nonisomerizable nonvolatile hop resin by an initial extraction and fractionation using one or more of the solvents listed in paragraph (b)(5) of this section followed by a sequence of aqueous extractions. The additive is added to the wort before or during cooking in the manufacture of beer.	Removal of nonaqueous solvents to less than 0.5%.

Table 4. Fresh *Humulus lupulus* (hops) strobile composition.[38]

Principle Components	Concentration (%w/w)
Cellulose + lignin	40.0-50.0
Protein	15.0
α-Acids	2.0-17.0
β-Acids	2.0-10.0
Water	8.0-12.0
Minerals	8.0
Polyphenols and tannins	3.0-6.0
Lipids and fatty acids	1.0-5.0
Hop oil	0.5-3.0
Monosaccharides	2.0
Pectin	2.0

Table 5. Dried *Humulus lupulus* (hops) strobile composition.[2]

Principle Components	Concentration (%)
Cellulose, etc.	43
Proteins	15
Amino acids	0.1
Moisture	10
Ash	8
Polyphenols (tannins)	4
Essential oil	0.5-3
Waxes and steroids	Trace-25
Monosaccharides	2
Pectins	2
Total resins	15-30

Table 6. Composition of polyphenols and their concentrations in *Humulus lupulus* (hops).[2]

Polyphenols and Polyphenol Groups	Concentration (%)
Phenolic carboxylic acids	
Benzoic acid derivatives	< 0.01
Cinnamic acid derivatives	0.01-0.03
Flavonoids	
8- or 6-Prenylnaringenin	< 0.01
Acylphloroglucinol derivatives (multifidols)	0.05-0.50
Catechins and epicatechins	0.03-0.30
Kaempferol	0.02-0.24
Oligomeric proanthocyanidins	0.20-0.50
Quercetin	0.05-0.23
Xanthohumol	0.20-1.70
Higher molecular substances	
Catechin tanning agents and tannins	2.00-7.00

Table 7. Constituents found in the aqueous extract[a] of 10 cultivars of "aroma"-type *Humulus lupulus* (hops) extracts analyzed by GC/MS.[48]

Constituent	Composition range (%)[b]
(2*E*)-Dodecen-1-ol	ND-0.2
(2*E*)-Hexenal	0-0.1
(2*Z*,6*E*)-Farnesol	0.2-0.9
(6*Z*)-Pentadecen-2-one	ND-2.5
(*E*)-Caryophyllene	4.1-11.3
(*E*)-Nerolidol	ND-0.3
(*E*)-β-Farnesene	ND-8.1
(*E*)-β-Ocimene	0-0.2
(*E*,*E*)-α-Farnesene	0.1-0.9
(*Z*)-Caryophyllene	ND-0.1
14-Hydroxy-(*E*)-caryophyllene	ND-0.8
1-*epi*-Cubenol	ND-0.7
1-Octen-3-ol	0-0.2
2-Decanone	0-0.5
2-Dodecanone	0-0.4
2-Methylbutanoic acid	0-0.6
2-Methylbutyl 2-methylbutyrate	0-0.3
2-Methylbutyl isovalerate	0-0.1
2-Nonanone	0-0.5
2-Pentadecanone	ND-0.8
2-Tridecanone	ND-1.6
2-Undecanone	0.1-1.6
3-Methyl-2-buten-1-ol	0-0.5
3-Methyl-2-butenal	0-0.9
3-Methyl-2-pentanone	0-1.0
4-Methyl-2-pentanone	0-3.4
4-Methyl-2-pentenolide	0.1-1.5
6,7-Epoxymyrcene	0-0.3
6-Methyl-5-hepten-2-one	0-0.4
9-Decenoic acid	0-0.5
ar-Curcumene	0.2-1.2
Cadalene	ND-0.4
Caryophylla-4(12),8(13)-dien-5-ol	ND-0.7
Caryophyllene Oxide	0.6-3.0
cis-Linalool oxide (furanoid)	0-0.2
cis-Linalool oxide (furanoid)	0-0.6
Decanoic acid	0-trace
Dendrolasin	ND-0.1
Furfural	Trace
Geranial	0-0.2

Table 7. Constituents found in the aqueous extract[a] of 10 cultivars of "aroma"-type *Humulus lupulus* (hops) extracts analyzed by GC/MS.[48]

Constituent	Composition range (%)[b]
Geraniol	0-1.1
Geranyl acetate	0-1.8
Geranyl isobutyrate	ND-2.1
Geranyl propionate	ND-1.7
Heptyl isobutanoate	0-trace
Hexanal	0-0.2
Humulene epoxide II	1.4-7.9
Isoamyl isobutyrate	0.3-1.6
Isoamyl propionate	0-0.3
Isobutyl isobutyrate	0-0.3
Isobutyl isopentanoate	0-0.8
Isovaleric acid	0-3.8
Limonene/β-Phellandrene	0-1.2
Linalool	0.2-3.2
Methyl (4*Z*)-decenoate	0.4-2.2
Methyl decanoate	0-1.0
Methyl geranate	0-0.7
Methyl heptanoate	0-1.1
Methyl nonanoate	0-0.5
Methyl nonenoate	0-0.3
Methyl octanoate	0-0.1
Myrcene	8-52.4
Neral	0-trace
Neryl acetate	0-0.1
Neryl isobutyrate	ND-trace
n-Nonanal	0-0.5
Nonanoic acid	0-0.4
Octanoic acid	0-0.1
Palmitic acid	ND-0.5
Perilla alcohol	0-0.2
Phenylacetaldehyde	0-0.1
Prenyl isobutyrate	0-trace
Tetradecane	ND-trace
trans-Cadina-1(6),4-diene	ND-0.1
trans-Cadina-1,4-diene	ND-0.1
trans-Calamenene	ND-1.2
Unidentified	0-1.5
Unidentified	0-0.7
Unidentified	0.4-9.7
Unidentified	0.1-1.8
Unidentified	0.2-3.5
α-Amorphene	ND-0.1
α-Cadinene	Trace-0.2
α-Cadinol	0.1-1.2
α-Calacorene	Trace-0.4
α-Copaene	0.3-0.9
α-Humulene	12.6-51.2
α-Humulene hydrate	0.3-2.9
α-Muurolene	0.3-0.6
α-Muurolol	ND-0.1
α-Pinene	0-0.4
α-Selinene	ND-1.8
α-Terpineol	0-0.2
α-*trans*-Bergamotene	ND-1.7
α-Ylangene	Trace-0.3
β-Copaene	0.1-0.2
β-Pinene	0.2-1.5
β-Selinene	0.2-1.2
γ-Cadinene	ND-1.5
γ-Muurolene	ND-1.7
δ-Cadinene	1.1-2.4
δ-Selinene	ND-1.2
τ-Cadinol	0.2-1.1

Table 7. Constituents found in the aqueous extract[a] of 10 cultivars of "aroma"-type *Humulus lupulus* (hops) extracts analyzed by GC/MS.[48]

Constituent	Composition range (%)[b]
Constituent Groups	
Aldehydes	ND-1.3
Aliphatic alcohols	ND-1.1
Aliphatic ketones	0.4-8.9
Carboxylic acids	ND-6.4
Carboxylic esters	1.2-9.1
Monoterpene hydrocarbons	9.4-54.5
Oxygenated monoterpenoids	0.4-3.5
Oxygenated sesquiterpenoids	3.3-18.4
Sesquiterpene hydrocarbons	0.4-3.5

[a] Hydrodistilled for 4 h with continuous extraction with dichloromethane.
[b] Percent composition determined from total ion current count without correction.
GC/MS= gas chromatography – mass spectrometry

Table 8. Compounds in *Humulus Lupulus* (hops) strobile oil.[52]

Classification	Compound
Hydrocarbon, Monoterpene	α-Pinene
	β-Pinene
	β-Myrcene
	Limonene
	ρ-Cymene
Hydrocarbon, Sesquiterpene	Caryophyllene
	E, β-Farnesene
	Humulene
Oxygenated, Ester	Methyl Heptonoate
Oxygenated, Monoterpene Alcohol	Geraniol
	Linalool
Oxygenated, Monoterpene	Citronellol
Oxygenated, Sesquiterpene Alcohol	Farnesol
Oxygenated, Other	Citral
Oxygenated, Monoterpene or Ester	Geranyl Acetate
Oxygenated, Epoxide	Humulene Epoxide 1
	Humulene Epoxide 2

Table 9. Composition and concentrations of compounds in *Humulus Lupulus* (hops) strobile oil extracted by steam distillation for constituents ≥ 1%.[108,109]

Compound	Percentage[a]
α-Caryophyllene	36.7
β-Myrcene	25.4
β-Caryophyllene	9.8
γ-Cadinene	5.5
δ-Cadinene	4.1
α-Muurolene	3.0
α-Copaene	1.5
Geraniol	1.5
Sabinene	1.4
β-Selinene	1.2
Linalool	1.1
α-Selinene	1.0
(*E*)-β-Ocimene	1.0

[a] This reference lists constituents at 1% or greater unless there is a safety concern.

Table 10. Constituents of concern found in *Humulus Lupulus* (hops).

Constituent	Concern	Reference
8-Prenylnaringenin (8-PN), 6-prenylnaringenin (6-PN), 8-geranylnaringenin (8-GN) and 6,8-diprenylnaringenin (6,8-PN)	Estrogenic activity. 8-PN is found in the strobiles of Humulus lupulus (hops) and has been proposed as a possible treatment for menopausal hot flashes. Subcutaneous administration of 8-PN to rats has estrogenic activity (as measured by the effect on uterine and vaginal weights), but is 20,000-fold less potent than estradiol. In vitro studies showed that 8-PN generally mimicked the action of 17β-estradiol with a lesser (10- to 20,000-fold) potency.	44,56,84-90,110
Geraniol	Potential dermal sensitizer	109,111-113
Limonene	Hydroperoxides are potential dermal sensitizers	109,114
Linalool	Hydroperoxides are potential dermal sensitizers. Safe at up to 4.3% (20% in a consumer fragrance)	115
β-Myrcene	Potential dermal irritant; dermatitis, conjunctivitis, somnolence, and asthma-like symptoms Oral dosing for 2 years caused kidney cancers in male rats (0.25 g/kg) and liver cancer in male mice (0.25 g/kg); may be related to the occurrence of kidney tumors in female rats and liver tumors in female rats. Associated with other lesions of the kidney in rats, the liver in mice, and the nose in male rats.	7,11,54
Quercetin	Positive genotoxic effect in an Ames assay Consistently genotoxic in in vitro tests and in some in vivo studies of i.p. exposures, but was consistently nongenotoxic in oral exposure studies	116,117
Sesquiterpene lactones	Potential dermal sensitizers	8,10

Table 11. Constituents of *Humulus lupulus* (hops) that have IFRA standards.[118]

Constituent	Standard Limits
Citral	Limited to 0.04%-5%, depending on use category* due to sensitization
Citronellol	Limited to 0.8%-21.4%, depending on use category due to sensitization
Farnesol	Limited to 0.08%-5%, depending on use category due to sensitization
Furfural	Skin contact-0.001%; non-skin contact-0.05% due to carcinogenicity
Geranial	Limited to 0.04%-5%, depending on use category due to sensitization
Geraniol	Limited to 0.03%-8.6%, depending on use category due to sensitization
(2*E*)-Hexenal	Limited to 0.01%-0.02%, depending on use category due to sensitization
Limonene	*d*-, *l*-and *dl*-Limonene and natural products containing substantial amounts of it, should only be used when the level of peroxides is kept to the lowest practical level, for instance by adding antioxidants at the time of production. Such products should have a peroxide value of less than 20 millimoles peroxides per liter due to sensitization.
Linalool	Limit peroxide level to 20 mmol/L due to sensitization. Linalool and natural products known to be rich in linalool, such as bois de rose, coriander or ho wood oil, should only be used when the level of peroxides is kept to the lowest practical level. It is recommended to add antioxidants at the time of production of the raw material. The addition of 0.1% BHT or alpha-tocopherol for example has shown great efficiency. The maximum peroxide level for products in use should be 20 mmol/L.
Neral (citral)	Limited to 0.04%-5%, depending on use category due to sensitization.
Phenylacetaldehyde	Limited to 0.02%-3%, depending on use category due to sensitization.

IFRA - International Fragrance Association
* Use categories are based on types of skin contact (e.g., skin, lips), length of contact (e.g., leave-on, rinse-off), or type of use (e.g., mouthwash)

Table 12. Frequency of use according to duration and exposure of *Humulus lupulus* (hops) Extract. Data reported under the technical names of this ingredient are also reported, but not included in the total of the named ingredient.[61,62]

Humulus Lupulus (Hops) Extract			
Use type	**VCRP Reported Name**	**Uses**	**Maximum Concentration (%)**
Total/range	**Humulus Lupulus (Hops) Extract**	**375[a]**	**0.000006-0.2[a]**
	Humulus Lupulus (Hops) Cone Extract[b]	17	0.00055
	Humulus Lupulus (Hops) Flower Extract[b]	3	0.000055-0.001
	Humulus Lupulus (Hops) Strobile[b]	12	NR
Duration of use[c]			
Leave-on	**Humulus Lupulus (Hops) Extract**	**317**	**0.00005-0.13**
	Humulus Lupulus (Hops) Cone Extract	8	0.00055
	Humulus Lupulus (Hops) Flower Extract	1	0.001
	Humulus Lupulus (Hops) Strobile	9	NR
Rinse-off	**Humulus Lupulus (Hops) Extract**	**54**	**0.000006-0.2**
	Humulus Lupulus (Hops) Cone Extract	1	NR
	Humulus Lupulus (Hops) Flower Extract	1	0.000055-0.001
	Humulus Lupulus (Hops) Strobile	3	NR
Diluted for (bath) use	**Humulus Lupulus (Hops) Extract**	4	NR
	Humulus Lupulus (Hops) Cone Extract	**8**	NR
	Humulus Lupulus (Hops) Flower Extract	1	NR
	Humulus Lupulus (Hops) Strobile	NR	NR
Exposure type			
Eye area	**Humulus Lupulus (Hops) Extract**	**9**	**0.0024-0.13**
	Humulus Lupulus (Hops) Cone Extract	1	NR
	Humulus Lupulus (Hops) Flower Extract	NR	NR
	Humulus Lupulus (Hops) Strobile	2	NR
Incidental ingestion	**Humulus Lupulus (Hops) Extract**	NR	NR
	Humulus Lupulus (Hops) Cone Extract	NR	NR
	Humulus Lupulus (Hops) Flower Extract	NR	NR
	Humulus Lupulus (Hops) Strobile	NR	NR
Incidental Inhalation-sprays	**Humulus Lupulus (Hops) Extract**	**2; 184[d]; 89[d]**	**0.00008-0.0002; 0.00005-0.1[d]**
	Humulus Lupulus (Hops) Cone Extract	3[d]; 4[e]	NR
	Humulus Lupulus (Hops) Flower Extract	1[b]	NR
	Humulus Lupulus (Hops) Strobile	2[b]	NR
Incidental inhalation-powders	**Humulus Lupulus (Hops) Extract**	**89[e]**	**0.0003-0.084[f]**
	Humulus Lupulus (Hops) Cone Extract	4[e]	0.00055
	Humulus Lupulus (Hops) Flower Extract	NR	NR
	Humulus Lupulus (Hops) Strobile	NR	NR
Dermal contact	**Humulus Lupulus (Hops) Extract**	**310**	**0.0001-0.13**
	Humulus Lupulus (Hops) Cone Extract	17	0.00055
	Humulus Lupulus (Hops) Flower Extract	3	0.000055
	Humulus Lupulus (Hops) Strobile	9	NR
Deodorant (underarm)	**Humulus Lupulus (Hops) Extract**	**8[c]**	**NR**
	Humulus Lupulus (Hops) Cone Extract	0.13[g]	NR
	Humulus Lupulus (Hops) Flower Extract	NR	NR
	Humulus Lupulus (Hops) Strobile	NR	NR
Hair-noncoloring	**Humulus Lupulus (Hops) Extract**	**65**	**0.00005-0.2**
	Humulus Lupulus (Hops) Cone Extract	NR	NR
	Humulus Lupulus (Hops) Flower Extract	NR	0.001
	Humulus Lupulus (Hops) Strobile	2	NR
Hair-coloring	**Humulus Lupulus (Hops) Extract**	NR	**0.000006-0.00001**
	Humulus Lupulus (Hops) Cone Extract	NR	NR
	Humulus Lupulus (Hops) Flower Extract	NR	NR
	Humulus Lupulus (Hops) Strobile	NR	NR
Nail	**Humulus Lupulus (Hops) Extract**	NR	NR
	Humulus Lupulus (Hops) Cone Extract	NR	NR
	Humulus Lupulus (Hops) Flower Extract	NR	NR
	Humulus Lupulus (Hops) Strobile	NR	NR

Table 12. Frequency of use according to duration and exposure of *Humulus lupulus* (hops) Extract. Data reported under the technical names of this ingredient are also reported, but not included in the total of the named ingredient.[61,62]

Humulus Lupulus (Hops) Extract			
Use type	**VCRP Reported Name**	**Uses**	**Maximum Concentration (%)**
Mucous Membrane	**Humulus Lupulus (Hops) Extract**	7	**0.0003-0.084**
	Humulus Lupulus (Hops) Cone Extract	**9**	NR
	Humulus Lupulus (Hops) Flower Extract	1	0.000055
	Humulus Lupulus (Hops) Strobile	NR	NR
Baby	**Humulus Lupulus (Hops) Extract**	NR	NR
	Humulus Lupulus (Hops) Cone Extract	NR	NR
	Humulus Lupulus (Hops) Flower Extract	NR	NR
	Humulus Lupulus (Hops) Strobile	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on Product +Diluted for (Bath) 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] Highest number of reported uses or concentration of use is in bold.

[b] Technical name for Humulus Lupulus (Hops) Extract.

[c] 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.

[d] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

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

[f] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

[g] Not a spray

Table 13. In vitro ocular assays of Humulus Lupulus (Hops) Extract.

Concentration (%)	**Assay and ingredient**	**Results**	**Reference**
(0.06-0.12)	HET-CAM. A product containing Humulus Lupulus (Hops) Extract (0.6% to 1.2%) tested at 10%.	There were no signs of potential irritation in any form of hyper-anemia, hemorrhage, or coagulation. The IP-CAM score was 0.00 and the product was rated a practically non-irritating under these conditions.	95,96
(0.06-0.12)	CFIO. A product containing Humulus Lupulus (Hops) Extract (0.6% to 1.2%) at 10%.	The IOeq was 2.8 with a MCI of 0.0; the test substance was rated at the lowest irritation level (IOeq = 0 to 15) as a slight ocular irritant. When combining the results of these two *in vitro* HET-CAM/CFIO assays, the author concluded that this cosmetic formulation containing Humulus Lupulus (Hops) Extract (0.6% to 1.2%) was a slight ocular irritant.	95,96
0.5	EpiOcular. A product mixture containing Humulus Lupulus (Hops) Extract at 5% in glycerin/water (50/50) tested at 10%.	Viability at 1, 4, and 24 h was 114%, 90%, and 79%. The ET_{50} was > 1440 min. The test substance has virtually no ocular irritation potential.	98
Approximately 0.18	HET-CAM. A product mixture containing Humulus Lupulus (Hops) Extract (approximately 0.18% in caprylic/capric triglyceride)	Predicted that the test substance was practically non-irritating. No further details were provided.	37
Approximately 0.009, 0.027, 0.045, and 0.09	A product mixture that contains Humulus Lupulus (Hops) Extract at 5%, 15%, 25%, and 50% in paraffin oil was administered to SIRC fibroblastic cells and evaluated for cytotoxicity by the use of the Neutral Red Release method. Paraffin oil was the negative control and sodium dodecyl sulfate (0.01%-0.2%) was the positive control.	Cytotoxicity was not observed at any concentration. Predicted to be non-irritating.	37

CFIO - cornea fibroblast; ET_{50} – time until viability reaches 50%; HET-CAM - hen's egg test-chorion-allantoic membrane; IOeq - ocular irritation index; IP-CAM - primary irritancy index; MCI - mean cytotoxicity index

Table 14. Case reports of sensitization to *Humulus lupulus* (hops).

Presentation	Data, Tests, and Results	Reference
A 57-years-old female farmer presented with occupational airborne dermatitis and hand dermatitis from *Humulus lupulus* (hops).	Disease appeared at the age of 46, after 30 years of working with *Humulus lupulus* (hops) without any health problems. Patient had erythema of the skin of face, neck and upper chest, edema of eyelids, conjunctivitis, as well as acute dermatitis of hands. Symptoms were provoked by exposure to fresh or dried *Humulus lupulus* (hops). Symptoms appeared after 30 min of work and persisted over 1 to 2 days. There were no other skin or allergic problems. Skin tests were conducted with *Humulus lupulus* (hops) leaves (saline extract: prick positive, patch negative; glycerol extract: prick positive, patch negative) and hop strobiles (saline extract: prick positive, patch negative; glycerol extract: prick negative, patch positive after 48 and 72 h). Despite discontinuing work, patient experienced several relapses of her dermatitis. A cream and an herbal sedative, both containing *Humulus lupulus* (hops) extract, were identified as causing her dermatitis. During next *Humulus lupulus* (hops) cultivation period it also turned out that physical proximity to her husband was provoking relapses of the patient's dermatitis. Husband said that sometimes he did not wash thoroughly after working with the plant.	104
An atopic 35-year-old male brewery worker with rhinoconjunctivitis diagnosis due to grass and olea pollen presented with occupational rhinoconjunctivitis after 3 years of exposure to *Humulus lupulus* (hops).	Subject had no symptoms when he was away from his work place. He was able to drink beer without symptoms. An SPT with a common commercial inhalants battery including pollens, mites, animal dander, molds, and latex was performed. Additionally, SPTs were performed using *Humulus lupulus* (hops) and barley extracts. Assays for specific IgE to barley, malt, corn, wheat and hops were also carried out. To demonstrate the patient's symptoms, a nasal challenge with *Humulus lupulus* (hops) extract was performed. SPTs were positive to grass, olive pollen, and *Humulus lupulus* (hops). Specific IgE was positive only to *Humulus lupulus* (hops). Nasal challenge with *Humulus lupulus* (hops) extract reproduced an immediate nasal response. SPTs with *Humulus lupulus* (hops) controls subjects (n = 10) were negative.	105
A 29-year- old male subject, who had three episodes of urticaria–angioedema immediately after ingestion of peanuts, chestnuts, and banana over the last 4 years, the latter requiring emergency treatment. Subject presented with urticaria on both hands while working with ripe dried *Humulus lupulus* (hops), though not with fresh *Humulus lupulus* (hops).	SPTs were negative for common aeroallergens (soy, latex, rapeseed, and the fish nematode Anisakis simplex) and positive for wheat and corn; controls (histamine and normal saline) had expected results. SPTs for banana, chestnut, walnut, almond, kiwi, avocado, and ripe dried *Humulus lupulus* (hops) were positive. Two additional atopic subjects served as controls; they had negative results for ripe dried *Humulus lupulus* (hops). Specific IgE to chestnut was 1.69kU/L, and ripe dried hops: 1.00 kU/L: total IgE: 64 IU/mL. Authors commented that *Humulus lupulus* (hops) rash as skin irritation has been known for several decades, but this subject could not be included in this category. A diagnosis of immunological contact urticaria due to dried *Humulus lupulus* (hops) by was made because: 1) work-related symptoms from handling dried *Humulus lupulus* (hops), but not fresh, 2) positive SPT, and 3) positive specific IgE. Authors hypothesized that *Humulus lupulus* (hops) drying process may transform certain proteins into allergens. Authors were not able to conclude if cross-reactivity between various fruits and dried *Humulus lupulus* (hops) was feasible.	54
A 43-year-old female subject who worked in a laboratory that investigated *Humulus lupulus* (hops), presented with conjunctivitis, rhinitis, bronchitis, and dermatitis of the face.	She had no history of asthma or hay fever or previous dermatitis or inflammation of the mucous membranes. In her workplace, the dried plant strobiles were pulverized in a mill, some of which became airborne; she had no exposure to *Humulus lupulus* (hops) pollen. The results of a patch test of the *Humulus lupulus* (hops) dust was ++ and an intradermal test of 0.1 mL aqueous *Humulus lupulus* (hops) extract was +++. She was able to drink beer with no symptoms.	106
A 28-year-old male subject who was a chemist for a brewery presented with sneezing, itching, hives, closed feeling in his throat, wheezing, shortness of breath, abdominal bloating, watering eyes, and irregular heartbeat.	His job required exposure to *Humulus lupulus* (hops) plants in the field and laboratory. In laboratory, he crushed and rubbed strobiles in his hands and inhaled for aroma. Laboratory also used pure β-myrcene, which is a volatile oil. He had never had hay fever or asthma, but had a former allergy (watering eyes) to Siamese cats. As a child, milk ingestion would produce hives. Walnuts induced a burning feeling in his throat and stomach. Patch tests with crushed, dried *Humulus lupulus* (hops) flowers (two varieties) were negative. A patch test of β-myrcene was positive after 4 h and strongly positive after 48 h. Strongly positive reactions were observed in scratch and intradermal tests to most pollens, house dust, pyrethrum, orris root, and grain dust; moderate reactions were observed to some molds and horse dander. Tests were negative for other molds and other animals. Drinking a beer did not produce symptoms unless he had been exposed to β-myrcene.	11

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2017 VCRP Data for *Humulus lupulus* (Hops)-Derived Ingredients

02A - Bath Oils, Tablets, and Salts	HUMULUS LUPULUS (HOPS) CONE EXTRACT	8
03G - Other Eye Makeup Preparations	HUMULUS LUPULUS (HOPS) CONE EXTRACT	1
10A - Bath Soaps and Detergents	HUMULUS LUPULUS (HOPS) CONE EXTRACT	1
12C - Face and Neck (exc shave)	HUMULUS LUPULUS (HOPS) CONE EXTRACT	1
12D - Body and Hand (exc shave)	HUMULUS LUPULUS (HOPS) CONE EXTRACT	3
12F - Moisturizing	HUMULUS LUPULUS (HOPS) CONE EXTRACT	2
12G - Night	HUMULUS LUPULUS (HOPS) CONE EXTRACT	1
		17

02B - Bubble Baths	HUMULUS LUPULUS (HOPS) EXTRACT	3
02D - Other Bath Preparations	HUMULUS LUPULUS (HOPS) EXTRACT	1
03D - Eye Lotion	HUMULUS LUPULUS (HOPS) EXTRACT	4
03G - Other Eye Makeup Preparations	HUMULUS LUPULUS (HOPS) EXTRACT	5
05A - Hair Conditioner	HUMULUS LUPULUS (HOPS) EXTRACT	14
05B - Hair Spray (aerosol fixatives)	HUMULUS LUPULUS (HOPS) EXTRACT	2
05F - Shampoos (non-coloring)	HUMULUS LUPULUS (HOPS) EXTRACT	19
05G - Tonics, Dressings, and Other Hair Grooming Aids	HUMULUS LUPULUS (HOPS) EXTRACT	18
05I - Other Hair Preparations	HUMULUS LUPULUS (HOPS) EXTRACT	12
07A - Blushers (all types)	HUMULUS LUPULUS (HOPS) EXTRACT	4
07C - Foundations	HUMULUS LUPULUS (HOPS) EXTRACT	1
07I - Other Makeup Preparations	HUMULUS LUPULUS (HOPS) EXTRACT	1
10A - Bath Soaps and Detergents	HUMULUS LUPULUS (HOPS) EXTRACT	2
10B - Deodorants (underarm)	HUMULUS LUPULUS (HOPS) EXTRACT	8
10E - Other Personal Cleanliness Products	HUMULUS LUPULUS (HOPS) EXTRACT	1
12A - Cleansing	HUMULUS LUPULUS (HOPS) EXTRACT	10
12B - Depilatories	HUMULUS LUPULUS (HOPS) EXTRACT	2
12C - Face and Neck (exc shave)	HUMULUS LUPULUS (HOPS) EXTRACT	31
12D - Body and Hand (exc shave)	HUMULUS LUPULUS (HOPS) EXTRACT	58
12F - Moisturizing	HUMULUS LUPULUS (HOPS) EXTRACT	151
12G - Night	HUMULUS LUPULUS (HOPS) EXTRACT	12
12H - Paste Masks (mud packs)	HUMULUS LUPULUS (HOPS) EXTRACT	6
12I - Skin Fresheners	HUMULUS LUPULUS (HOPS) EXTRACT	1
12J - Other Skin Care Preps	HUMULUS LUPULUS (HOPS) EXTRACT	7
13A - Suntan Gels, Creams, and Liquids	HUMULUS LUPULUS (HOPS) EXTRACT	1
13B - Indoor Tanning Preparations	HUMULUS LUPULUS (HOPS) EXTRACT	1
		375

02D - Other Bath Preparations	HUMULUS LUPULUS (HOPS) FLOWER EXTRACT	1
12D - Body and Hand (exc shave)	HUMULUS LUPULUS (HOPS) FLOWER EXTRACT	1
12H - Paste Masks (mud packs)	HUMULUS LUPULUS (HOPS) FLOWER EXTRACT	1
		3

03D - Eye Lotion	HUMULUS LUPULUS (HOPS) STROBILE	1
03F - Mascara	HUMULUS LUPULUS (HOPS) STROBILE	1
05C - Hair Straighteners	HUMULUS LUPULUS (HOPS) STROBILE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	HUMULUS LUPULUS (HOPS) STROBILE	1
07C - Foundations	HUMULUS LUPULUS (HOPS) STROBILE	3
11G - Other Shaving Preparation Products	HUMULUS LUPULUS (HOPS) STROBILE	2
12D - Body and Hand (exc shave)	HUMULUS LUPULUS (HOPS) STROBILE	1
12G - Night	HUMULUS LUPULUS (HOPS) STROBILE	1
12J - Other Skin Care Preps	HUMULUS LUPULUS (HOPS) STROBILE	1
		12

There were no reported uses in 2017 VCRP:
Humulus Lupulus (Hops) Cone Oil
Humulus Lupulus (Hops) Stem Extract

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 4, 2017

SUBJECT: Draft Report: Safety Assessment of *Humulus lupulus* (Hops)-Derived Ingredients as Used In Cosmetics (draft prepared for the April 10-11, 2017 CIR Expert Panel Meeting)

Key Issue

The INCI names for hops-derived ingredients were revised/corrected, not "retired" as stated several places in the CIR report. The deleted and changed names for hops-derived ingredients will be in the list of INCI name changes not with the "retired" names. The following description of the process for retiring an INCI name is from the Introduction of the Dictionary:

> "Beginning in 2013, some INCI names subject to revision that have a long history of usage have been designated as "retired". These INCI names are identified as "retired" in the monograph title, with the new nomenclature, when needed, described in the monograph definition. The "retired" term is intended for descriptive purposes only, and should not be used as part of the INCI name for product ingredient labeling.
>
> Retired INCI names will be retained for publication for an interim period of time. Both the Retired INCI name, and any new INCI name related to the retired name, is available for use for product labeling during this transition period. Additionally, trade names maintain their assignment to retired names, but are also designated by the new nomenclature so that users may update product labels, documentation, and technical literature when economically feasible.
>
> Retired INCI names differ from the names listed in the INCI Name Change Table. Unlike retired INCI names which often relate to "grandfathered" terms, name changes are usually more current (i.e., a change between editions), and relate to ingredient names that were misspelled, misnamed, or reassigned as a result of a name change petition."

Additional Considerations

Introduction, Summary - The Introduction and Summary imply that both the extract and essential oil have all the functions listed. It should be made clear that fragrance is the only function listed for the essential oil. The other functions are only listed for the extract.

Introduction - Please revise: "although toxicity information may be included here" - systemic safety studies are included in this report.

Are references 6-8 really the correct references for the statement: "β-myrcene is reported to be a dermal irritant and possible carcinogen"? The titles of these references suggest that they all concern sensitization rather than irritation, and none suggest that they concern the carcinogenic potential of β-myrcene.

Constituents of Concern - The last paragraph of this section needs to be revised as it mentions Table 11 twice and the last sentence of this paragraph is not complete.

Cosmetic Use - The 48th Amendment to the IFRA standards does not set a limit for hops essential oil. Hops essential oil is included in a table titled "an alphabetical list of other sources (complex synthetic materials or essential oils) for restricted materials having Standards and which must therefore be taken into account for determination of the maximum level". Hops oil is in the list because it contains geraniol (at about 0.2%) for which there is an IFRA standard.

Short-Term - It is not clear what is meant by "There were no effects on the mesenteric and epididymal adipose tissues." How did they determine that were no effects? What was measured/examined?

Subchronic - Please indicate what was studied in the 20-week study in mice. Were histopathological examinations of major organs completed?

Genotoxicity - It should be stated that the material studied in reference 75 was extracted in glycerin/water.

Discussion - The following is not needed as the rest of the Discussion addresses concerns about various constituents in the hops-derived ingredients: "However, concerns about β-myrcene, and possibly other constituents, cannot be addressed fully by the Panel, because the available information is not sufficient to characterize adequately the composition of *Humulus lupulus* (hops)-derived cosmetic ingredients."

It should be stated that it is the oxidation products of limonene and linalool that are considered sensitizers, not limonene and linalool.

Since there is a positive bioassay on β-myrcene, it does not make sense to state: "there do not appear to be any components that could be carcinogenic".

Table 10 - It needs to be made clear that it is the hydroperoxides of limonene and linalool that are the potential sensitizers.

Table 11 - Please state the reason for the limitations (often sensitization). As persons reading CIR reports may not be familiar with IFRA standards, it would be helpful to include a footnote explaining what is meant by "use category".

Table 13 - In the description of the results of the CFIO study, the sentence starting with: "When combining the results of these two *in vitro*.." is presented twice.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: May 10, 2017

SUBJECT: Tentative Report: Safety Assessment of *Humulus lupulus* (Hops)-Extract and Oil as Used In Cosmetics (released May 8, 2017)

Key Issue

Cosmetic Use - The CIR report is not correct when it states: "The International Fragrance Association (IFRA) restricts the concentration of geraniol in *Humulus lupulus* hop oil, to 0.2%."

The 48th Amendment to the IFRA standards (reference 69) does not set a limit for geraniol in hops essential oil. Hops essential oil is included in Annex I to the IFRA Standards - 48th Amendment. The top of the table for Annex I states: "This Annex gives indicative maximum levels of the limited substances in different fragrance materials (e.g. in essential oils). These indicative levels should be taken into account when determining the compliance of a fragrance compound under its conditions of use. However, if reliable analysis has shown that the level of the limited substance in a specific fragrance material is not the same as the indicative level given in this Annex, then the analyzed level can be used instead of the indicative level.." The first page of this table is attached. Hops oil is in the Annex because it contains geraniol (at about 0.2%) for which there is an IFRA standard.

Discussion - The Discussion should note that the extraction solvents reported by suppliers of hops extract used cosmetic ingredients are Water/Propylene Glycol, Water/ethanol, Water/Butylene Glycol and Caprylic/Capric Triglyceride.

The Discussion should not imply that the method of manufacture for hops essential oil is not known. The composition information in the report is for hops essential oil made by steam distillation. For example, the composition information in Tisserand and Young (Table 9, reference 107) came from Malizia et al., 1999. The abstract of this study can easily be found on the internet and it says: "The essential oil from hop cones (*Humulus*

lupulus L.), which was obtained by steam distillation, was analyzed by GC and GC/MS. The major constituents obtained were: myrcene (25.4%), ß-caryophyllene (9.8%), α-humulene (36.7%), α-muurulene (3.0%), γ-cadinene (5.5%) and δ-cadinene (4.1%). Fifteen minor components were also identified. The yield of oil relative to dried hop cones was 0.3%." It is for this essential oil and oils with similar composition that the CIR Expert Panel reached a conclusion of safe when formulated to be non-sensitizing.

Additional Considerations

Abstract - As in the Introduction and Summary, it should also be made clear that the only function listed for hops essential oil is fragrance. The other listed functions are reported for hops extract.

Introduction - It is not clear why the CIR report on phytosterols is relevant to this report. It would be helpful if an example of a phytosterol in hops was identified in the Introduction.

Constituents of Concern - The following at the end of the Constituents of Concern section should be deleted as it is stated in the previous paragraph. "Constituents of *Humulus lupulus* (hops) that have IFRA standars. Table11."

Subchronic Toxicity Studies - Did reference 74 use more than one high fat diet? If so, the differences, e.g., fat source, fat level, should be explained. If only one high fat diet was used in this study, the "s" in "high fat diets" needs to be deleted in several places in this section.

Possible Estrogenic/Endocrine Effects - Please add the word "extract" to the first sentence of the third paragraph.

Case Reports - If all of the case reports found are presented in Table 14, please be more specific and state that there were five case reports (rather than saying there were "multiple case reports"). If these are just examples of case reports in the literature, that should be made clear in the text.

Tables 4 and 5 - As the information in these two tables appears to be similar, please see if they can be combined into one table. For example, a comparison between the two tables of items that just have different names in the two tables are shown below. As reference 2 (Table 5) is a review, perhaps the information in Tables 4 and 5 are actually coming from the same primary reference.

Table 4	**Table 5**
Cellulose + lignin 40.0-50%	Cellulose etc. 43%
Protein 15%	Proteins 15%
Water 8.0-12.0%	Moisture 10%
Minerals 8.0%	Ash 8%
Polyphenols and tannins 3.0-6.0%	Polyphenols (tannins) 4%
Hop oil 0.5-3.0%	Essential oil 0.5-3%

Table 12 - Because of the few uses of the old names and the low use concentrations reported for these ingredients, it is really not necessary to present the information by old name. It would be better to just add the old names with Humulus Lupulus (Hops) Extract and then add a footnote to indicate the total/range for the old names and the number/concentrations of use reported for the old names in the duration of use categories.

Reference 74 - Please correct "ove the long term" in the title of this reference.

Annex I to the IFRA Standards - 48th Amendment

This Annex give indicative maximum levels of the limited substances in different fragrance materials (e.g. in essential oils). These indicative levels should be taken into account when determining the compliance of a fragrance compound under its conditions of use. However, if reliable analysis has shown that the level of the limited substance in a specific fragrance material is not the same as the indicative level given in this Annex, then the analyzed level can be used instead of the indicative level.

The list is intended to be as comprehensive as possible but still remains illustrative only and cannot be regarded as exhaustive.

Part I

Part I is an alphabetical list of the materials that have a standard and for which contibutions from other sources need to be taken into account, listing the sources with indicative values.

CONSTITUENTS			NATURAL RAW MATERIALS					
CAS No.	Principle Name	Level (%)	Essential oil Category	RIFM ID	Principle/Main CAS RIFM DATABASE	ALTERNATIVE/EINECS CAS NO	Principle Name	Botanical/Binomial name
2442-10-6	1-Octen-3-yl acetate	0.2	F2.1	190	8022-15-9	91722-69-9	Lavandin absolute	Lavandula officinalis x Lavendula latifolia
		0.2	F2.7	190	8022-15-9	91722-69-9	Lavandin concrete	Lavandula officinalis x Lavendula latifolia
		0.3	F2.12	5533	8022-15-9	93455-97-1	Lavandin grosso oil	Lavandula x intermedia grosso
		0.7	F2.1	169	8000-28-0	84776-65-8; 90063-37-9; 97722-12-8	Lavender absolute	Lavandula angustifolia Mill.
		0.5	F2.1	169	8000-28-0	84776-65-8 and 90063-37-9	Lavender concrete	Lavandula angustifolia Mill.
		0.9	F2.12	169	8000-28-0	84776-65-8; 90063-37-9; 97722-12-8	Lavender oil	Lavandula officinalis Chaix
		0.5	E2.12	83	68917-15-7	85085-49-0	Mentha citrata oil	Mentha citrata Ehrhart
		0.06	E2.12	771	8008-79-5	84696-51-5	Spearmint oil	Mentha spicata L.
		0.06	E2.13	771	98561-44-5		Spearmint, Mentha spicata crispa, extract	Mentha spicata L. spicata
1504-74-1	o-Methoxycinnamaldehyde	2	C2.13	327	8007-80-5	84961-46-6	Cassia bark extract	Cinnamomum cassia Blume
		4	E2.12	327	8007-80-5	84961-46-6	Cassia oil	Cinnamomum cassia Blume
17369-59-4	3-Propylidenephthalide	0.1	A2.12	813	8016-31-7	84837-06-9	Lovage root oil	*Levisticum officinale* Koch
2883-98-9	trans-Asarone/alpha-Asarone	4	A2.12	576	8015-79-0		Calamus oil	Acorus calamus L.
		0.1	E2.1	776	8024-12-2	85116-63-8	Verbena absolute	Aloysia citrodora Paláu
5273-86-9	cis-Asarone/beta-Asarone	70	A2.12	576	8015-79-0		Calamus oil	Acorus calamus L.
105-13-5	Anisyl alcohol	0.8	F2.1	75	8023-82-3	89958-31-6	Cassie absolute	Vachellia farnesiana (L.) Wild.
		0.2	F2.13	75	8023-82-3	89958-31-6	Cassie extract	Vachellia farnesiana (L.) Wild.
		6.6	G2.1	319	8024-06-4	84650-63-5	Vanilla absolute	Vanilla spp.
		1	G2.21	319	8024-06-4	84650-63-5	Vanilla oleoresin	Vanilla spp.
		1	G2.13	5506	953789-39-47	94167-14-6	Vanilla tahitensis extract	Vanilla tahitensis J.W. Moore
		0.1	G2.31	319	8047-24-3		Vanilla tincture	Vanilla planifolia Jacks. ex Andrews
100-52-7	Benzaldehyde	99	H2.12	778	8013-76-1	90320-35-7	Almond oil, bitter	Prunus spp.
		0.03	K2.9	245	8007-00-9		Balsam oil, Peru	Myroxylon balsamum (L.) Harms var. pereirae (Royle) Harms
		2	C2.13	327	8007-80-5	84961-46-6	Cassia bark extract	Cinnamomum cassia Blume
		4	E2.12	327	8007-80-5	84961-46-6	Cassia oil	Cinnamomum cassia Blume
		0.3	F2.1	75	8023-82-3	89958-31-6	Cassie absolute	Vachellia farnesiana (L.) Wild.
		0.3	F2.13	75	8023-82-3	89958-31-6	Cassie extract	Vachellia farnesiana (L.) Wild.
		99	C2.13	7192	84604-07-9		Cherry Bark, wild, extract	Prunus serotina Ehrh.
		0.1	C2.13	328	8015-91-6	84649-98-9	Cinnamon bark extract	Cinnamomum spp.
		0.26	C2.12	328	8015-91-6	84649-98-9	Cinnamon bark oil	Cinnamomum spp.
		0.5	C2.12		97659-68-2		Cinnamon bark oil, Laos	Cinnamomum loureiroi Nees
		0.16	E2.12	444	8015-91-6	84649-98-9	Cinnamon leaf oil	Cinnamomum zeylanicum Blume
		0.6	F2.1	358	8016-26-0	89997-74-0	Cistus absolute	*Cistus spp.*
		0.4	F2.7	358	8016-26-0	89997-74-0	Cistus concrete	Cistus spp.
		0.9	F2.12	358	8016-26-0	89997-74-0	Cistus oil	Cistus spp.