Safety Assessment of *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
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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 Executive Director is Bart Heldreth, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: November 10, 2017

Subject: *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients

Attached is the Draft Tentative Report of *Hamamelis virginiana* (Witch Hazel)-derived ingredients as used in cosmetics. [*HamVir122017Rep*] These eight ingredients are all derived from part(s) of the *Hamamelis virginiana* (Witch Hazel) plant.

In September 2017, the Panel issued an insufficient data announcement asking for sensitization data on Hamamelis Virginiana (Witch Hazel) Extract at the highest concentration of use and for clarification of the maximum concentration of use for Hamamelis Virginiana (Witch Hazel) Extract in cosmetic formulations.

No new sensitization data have been submitted. However, updated concentration of use data have been submitted that indicate the maximum concentration of use for Hamamelis Virginiana (Witch Hazel) is much lower than previously reported. The highest leave-on concentration of use for Hamamelis Virginiana (Witch Hazel) Extract is 1.8% (down from 86%, which was an OTC product, not a cosmetic). There is currently sensitization data in the report for Hamamelis Virginiana (Witch Hazel) Leaf Extract at 0.45% and Hamamelis Virginiana (Witch Hazel) Water at up to 25.80%. Is this sufficient to address the Panel's needs?

The updated concentration of use data and the Wave 2 and Wave 3 data from September have been incorporated into the report and marked with lines in the margins. These submissions have been included in this packet. [*HamVir122017Data1-4*]

The Council responded to our request to clarify the names and definitions of these ingredients. [*HamVir122017Council*] The Council was asked to address the fact that "witch hazel" is a ubiquitous term and is used generically, along with other terms (e.g., "hamamelis water," "witch hazel extract," "witch hazel oil," and other variations) in the literature. Much of the information in the literature does not clarify the source plant part(s), the solvent(s), and/or

the extraction method(s). To add to the confusion, an additional CAS number has been found in the literature that is not used in the *Dictionary*.

In their reply, the Council stated that there are overlapping definitions/names, and adjustment to the monographs will be made accordingly. However, at the time that the report was prepared, the monographs have not been changed. Therefore, the names have not been changed in this version of the report. It is expected that the monographs for Hamamelis Virginiana (Witch Hazel) **Bark/Twig Extract,** Hamamelis Virginiana (Witch Hazel) **Leaf Water**, and Hamamelis Virginiana (Witch Hazel) **Flower Water** will be proposed for deletion, and that these ingredients will be incorporated under remaining *Hamamelis virginiana* (Witch Hazel)-derived ingredients. Changes to Hamamelis Virginiana (Witch Hazel) **Extract** are pending more information. Hamamelis Virginiana (Witch Hazel) **Water** is currently considered accurate.

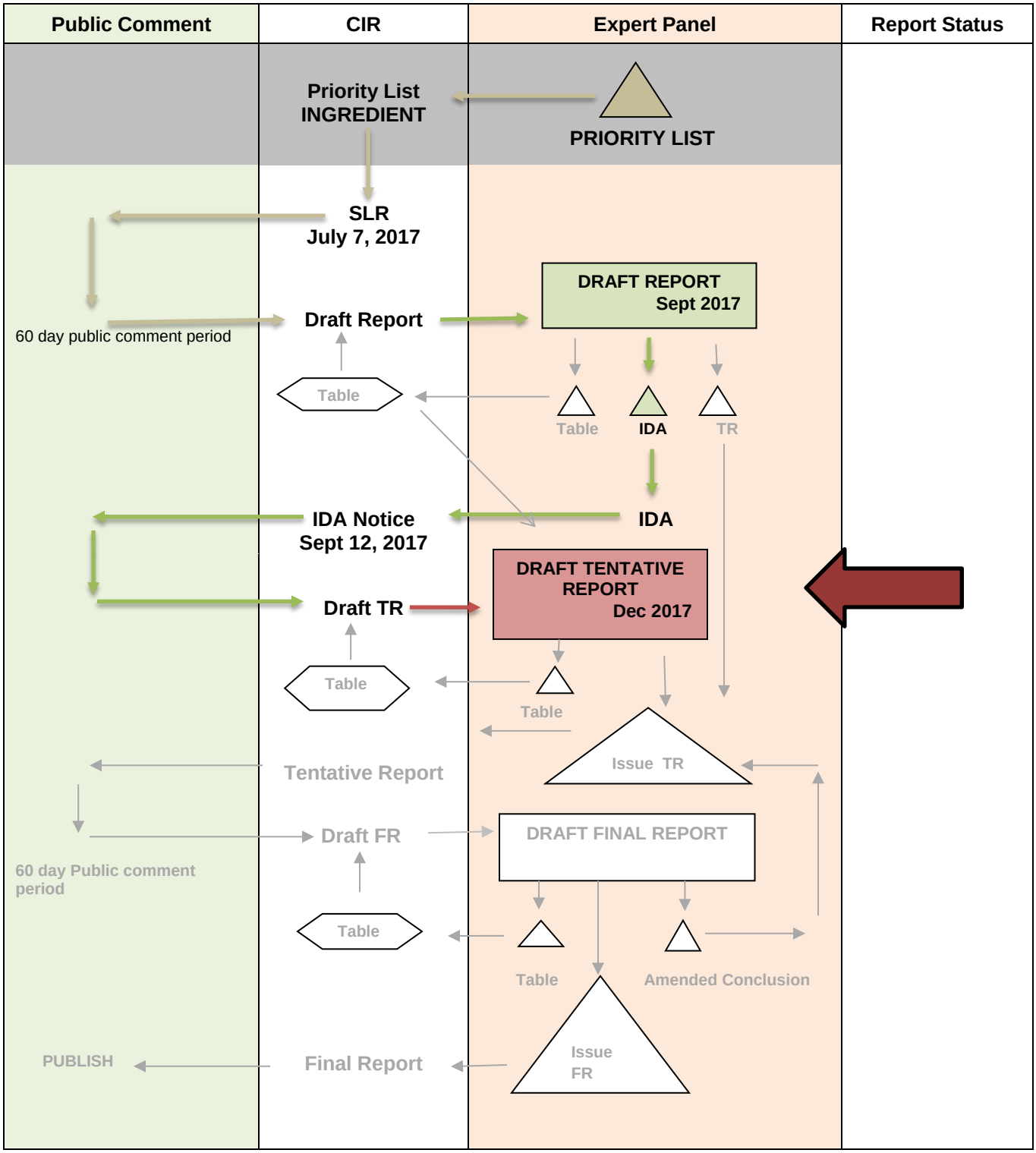
RIFM has been contacted about Hamamelis Virginiana (Witch Hazel) Flower Water, which is reported to be only used as a fragrance ingredient. There has been no reply at the time of the writing of this memo as to whether or not they have or are planning to review this ingredient.

The Panel should come to a conclusion of safety for these ingredients. If the data needs are not satisfied, a split conclusion may be possible. The Panel should develop the basis for the Discussion and issue a Tentative Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY __*Hamamelis virginiana* (witch hazel)-derived ingredients _____

MEETING ___Dec 2017_____



History – *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients

2016 – Included in the priority list

June, 2017 – SLR posted with request for further information including:

- Constituent profiles for each of these ingredients
- Chemical and physical properties
- Method of manufacture
- Impurity data
- Dermal penetration
- Chronic dermal toxicity
- Inhalation toxicity
- Dermal irritation and sensitization

September, 2017 – Panel issued an Insufficient Data Announcement:

The data needs are:

- Sensitization data on Hamamelis Virginiana (Witch Hazel) Extract at the highest concentration of use.
- Clarification of the maximum concentration of use for Hamamelis Virginiana (Witch Hazel) Extract in cosmetic formulations.

The Panel also requested confirmation that the only function of Hamamelis Virginiana (Witch Hazel) Flower Water is fragrance ingredient and whether the Research Institute for Fragrance Materials (RIFM) intends to perform a safety assessment thereon.

September, 2017 – Panel issues a tentative report.

No new sensitization data have been submitted. However, updated concentration of use data have been submitted that indicate the maximum concentration of use for Hamamelis Virginiana (Witch Hazel) is much lower than previously reported. The highest leave-on concentration of use for Hamamelis Virginiana (Witch Hazel) Extract is 1.8% (down from 86%, which was an OTC product, not a cosmetic). There is currently sensitization data in the report for Hamamelis Virginiana (Witch Hazel) Leaf Extract at 0.45% and Hamamelis Virginiana (Witch Hazel) Water at up to 25.80%. Is this sufficient to address the Panel's needs?

New monographs are expected to be issued and it is expected that Hamamelis Virginiana (Witch Hazel) **Bark/Twig Extract,** Hamamelis Virginiana (Witch Hazel) **Leaf Water**, and Hamamelis Virginiana (Witch Hazel) **Flower Water** will be proposed for deletion. Changes to Hamamelis Virginiana (Witch Hazel) **Extract** are pending more information. Hamamelis Virginiana (Witch Hazel) **Water** is currently accurate.

Hamamelis virginiana (Witch Hazel)-derived ingredients Data Profile for ***December*, 2017**. Writer – Lillian Becker

		ADME		Acute toxicity			Repeated dose toxicity			Irritation					Sensitization						
	Use	Log K_{ow}	Dermal Penetration	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Animal	Ocular In Vitro	Dermal Animal	Dermal Human	Dermal In Vitro	Animal	Human	In Vitro	Repro/Devel	Genotoxicity	Carcinogenicity	Phototoxicity
Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract	X																				
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract 84696-19-5											X			X							
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract													X								
Hamamelis Virginiana (Witch Hazel) Extract 84696-19-5	X										X			X							
Hamamelis Virginiana (Witch Hazel) Flower Water	X															X					
Hamamelis Virginiana (Witch Hazel) Leaf Extract	X															X			X		X
Hamamelis Virginiana (Witch Hazel) Leaf Water	X															X					
Hamamelis Virginiana (Witch Hazel) Water	X									X			X						X		
Undefined *Hamamelis virginiana* (Witch Hazel) Extract				X			X						X			X				X	

Ingredient Family Name

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Hamamelis Virginiana (Witch Hazel) Water		Y	N	N	N	N	N	N	N	N	N	N	N	1	N	N	N	Y
Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract		Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	84696-19-5	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract		Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Extract	84696-19-5	Y	N	86/8	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Flower Water		Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Leaf Extract		Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Leaf Water		Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hamamelis virginiana (witch hazel) plant		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y
"Witch hazel"			N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	Y

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
Hamamelis Virginiana (Witch Hazel) Water		N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract		N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract		N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract		N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Extract		N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Flower Water		N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Leaf Extract		N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) Leaf Water		N	N	N	N	N	N
Hamamelis Virginiana (Witch Hazel) plant		Y	Y	Y	N	N	N

Search Terms

"witch hazel" OR Hamamelis virginiana" OR CAS no.

Transcripts – Witch Hazel

September, 2017

Dr. Belsito's Team

DR. BELSITO: Okay. Witch hazel. This is the first time we're looking at this. So, the matches is 86% of the whole plant. And overall, I thought it was pretty good. In terms of skin, I thought we could, you know, formulate it to be non-irritating, clear it. But we don't have sensitization data for anything up to 86%. We have 6% for leaf extract and 6.88% for water. So I thought we needed sensitization at the highest level of leave-on use. And then we don't have any ADME on this. And we don't have RE-PRO. So my question to my team mates was, do we need a 28-day dermal? Where are we going with this in terms of the lack of reproductive toxicity? Are we saying it's been used medicinally for so long we're not concerned about it because there are no reports? How do we get around that?

DR. SNYDER: So, I had a question, going back to the search. Because this is a pretty remarkable how few hits you got on this.

MS. BECKER: Yeah. It's been used so much, nobody is doing anything with it.

DR. SNYDER: I mean there's literally nothing there. And so, hmm. I just thought that was a little problematic. I would have guessed there was more data.

MS. BECKER: That's what I thought too.

DR. LIEBLER: So with respect to Don's question about do we need a 28-day dermal, RE-PRO, and so forth, I lean against needing it for the reason you just indicated. You know, these have been used since antiquity. They're not like grass [GRAS?], you know, food additives, per se. But, I guess I would, that's my two cents worth. Now I'm going to throw it over to, I'll defer to Paul and Kurt on this though.

DR. SNYDER: I did have some concern about the data, because there's not much data and for most of the data that we have is on the leaf extract. And we have virtually very little data on anything else, particularly the extract, which is at the highest concentration of use at 86%.

DR. BELSITO: A lot of the data we have is leaf and bark. It's both. I mean, for safety data, yeah. But for composition data, it looks like it's the same composition. I mean, we got table after table after table of composition data on these. And the only thing we don't have composition on, or any information, is the flower. But we're told that that's a fragrance only ingredient. So I think if we can, I mean, have we, queried RIFIM to see if that in fact is true? Because if we queried RIFIM, doesn't that just go away from this document completely?

MS. FIUME: We have the database of the ingredients that they've looked at. I don't know if we've questioned RIFIM specifically as to whether or not this is only a fragrance only ingredient.

DR. BELSITO: So when the dictionary says it, just lists it as fragrance, do we just assume that's correct, and then dismiss it from the document? Or do we query? I mean, what is the protocol for confirming that it's fragrance only?

MS. FIUME: Typically we've been querying RIFIM.

DR. BELSITO: That's what I thought.

MS. FIUME: So we will need to do that.

DR. BELSITO: And if we do that, does the flower disappear from this report completely? Or do we keep it in and say we didn't review it because it's a fragrance only material?

MS. FIUME: If we confirm it's fragrance only and they are going to review it, then it goes away. The reason it's been…

DR. BELSITO: To my knowledge, it's not on our list, but it probably is.

[laughter]

MS. FIUME: The reason RIFIM fragrance only ingredients go away is to avoid duplication of effort. And lately, they have been telling us, even though we have it listed as fragrance only, if they don't plan on doing a

monograph, we keep it in so that safety is being reviewed somewhere. So that's why we query to see if they are going to review the ingredient.

DR. BELSITO: Okay. So we need to do that. Because otherwise the flower is clearly insufficient. For at least composition. And then depending upon composition, other data. My only concern, I mean, again was, you know, whether we felt we needed RE-PRO because we had no absorption, distribution, metabolism, excretion. And also we clearly, I mean, with the leave-on uses, we can't clear sensitization. I mean, unless you want to go with formulated to be non-sensitizing, but then we could do that for everything, and never look at sensitization data.

DR. ANSELL: The 86% is an OTC application, but we do agree that the highest use of a cosmetic is still greater than the HRIPT, but that's 43% against an HRIPT of 25.8.

DR. BELSITO: So, 86.

DR. ANSELL: This is an OTC regulated drug application.

DR. BELSITO: How do we know that?

MS. FIUME: They told us.

DR. BELSITO: Oh, okay. So then that should go away from this table.

DR. ANSELL: The 86%, yeah.

DR. BELSITO: Yeah. So the highest now would be?

DR. LIEBLER: Water at 43%.

DR. BELSITO: Okay. Yeah. So we would need sensitization for the highest leave-on use concentration. So let me get rid of this 86% here. And the water was forty what, Paul?

DR. SNYDER: Three. 43. And the HRIPT is at 25.8.

DR. BELSITO: I didn't see an HRIPT that high. The highest I saw was six.

DR. SNYDER: Well, we had six, but we already had data at 25.8.

DR. BELSITO: Oh, in the other one?

DR. SNYDER: They gave us, yeah. The regional data we have at 25.8. And then we got new data.

DR. BELSITO: How did I miss that?

DR. SNYDER: At six.

DR. BELSITO: Yeah. 25.8. You're right. Right in front of me. Duh. Okay.

DR. SNYDER: 86% witch hazel extract. Is someone worried about 25, 26 versus 43?

DR. BELSITO: I mean there's nothing. When we go to the tables for composition, I mean, if we go informally.

DR. SNYDER: It's got something there

DR. BELSITO: Right

DR. SNYDER: Geraniol

DR. BELSITO: Geraniol

MS. BECKER: Page 26

DR. LIEBLER: I have a comment that might be relevant right at this spot. Which is, it's not clear to me, since these are provided as, you know, these are provided as solutions in with water, or water alcohol, are we, do we have to deal with the percent active issue with these? In other words, are the tests, what are the actual test concentrations?

DR. BELSITO: Well that's what we discussed at the last meeting.

DR. LIEBLER: Yeah, and it's not clear. I flagged several spots in the report where that could make a big difference.

MS. BECKER: Yes, and where it's clear to me, I've made it clear in the report.

DR. LIEBLER: Right.

DR. BELSITO: So the, water, should they list the extract? I mean, you know what I mean, if. There was one composition for the water, right? Leaves and bark. The vault of fraction the water distilled leaves and bark. I mean, that's still. There doesn't really seem to be anything in there. And we're gonna say when formulated to be non- sensitizing anyway, based upon the fact that, even though they do have low concentrations of IFA [IFRA?] restricted materials, there are some. I think we need to put in non-irritating in there too.

MS. BECKER: Mm hmm.

DR. BELSITO: You know, I mean, it's twice the amount. Again, we need to have that same discussion point that we had in the polyurethane. Looking at what's added to the mixtures that are supplied to the final blenders. Propylene glycol, parabens, things like that. So that same boilerplate. I'm comfortable saying, you know, the flower is insufficient for composition and method of manufacture and purities composition and based upon that additional data may be needed. The others are safe as used when formulated to be non-irritating and non-sensitizing. And then in the discussion, in addition to the non-sensitizing, cumulative exposure to fragrances that have standards, we have to point out that these may be emulsions containing other known sensitizers such as the parabens, propylene glycol. And particularly the parabens since there are limits in Europe on total amounts, and well, we put limits too. So the discussion and the additional components of the mixtures. The fact that we're okay going with sensitization and 46% despite the fact that the HRIPT is somewhere in the twenties. Even the composition material.

DR. SNYDER: So what is the flower, where is the concentration use table? I'm cruising through and I don't see it.

DR. LIEBLER: No reported concentrations, just uses.

DR. SNYDER: Just uses, okay, thank you.

DR. LIEBLER: 43 uses and no concentrations listed. On the flower water.

DR. BELSITO: So, just to be clear, the lack of ADME and reproductive toxicity, we're just saying it's been used forever and there are no reports of issues. That's what we're saying essentially?

DR. LIEBLER: Basically, yeah.

DR. SNYDER: Not absorbed.

DR. BELSITO: We don't have absorption. We don't have any absorption data.

DR. SNYDER: So I had a statement under it that says that the extracts, there's a reference five. Says that witch hazel extracts are not likely to penetrate.

DR. BELSITO: Well, because, they said they're not likely because they vasoconstrict. That's what they said. They don't have any data. They're saying, well, you know, they astringents, they cause constriction, so they're not likely to be absorbed. That's the basis of our absorption data.

DR. LIEBLER: Okay. But that's not data. I mean that's not even as good as

DR. BELSITO: That's like Dan's opinion. [laughter]

DR. LIEBLER: I mean, do you ever see reactions involving witch hazel?

DR. BELSITO: Just irritation.

DR. LIEBLER: Just irritation. Okay. I don't remember if it's this report, but I seem to remember Jim having a comment along those lines when we talked about, well, we haven't talked about this yet?

DR. BELSITO: No.

DR. LIEBLER: Okay. So, never mind. It wasn't this. Bad recall.

DR. BELSITO: But then again, I mean, witch hazel is used, you know, sort of in folk medicine to treat inflammatory skin conditions, so the questions always is, is it the witch hazel that's causing the irritation, or is it just their condition worsening and not responding? So, I mean, it's a little bit of six of one, or half dozen of the other. But, you know, it's a known astringent. So you assume that there's a component of the witch hazel irritation.

DR. SNYDER: We don't have any discussion to look at

DR. BELSITO: Right. So basically, the issues are that we don't have any absorption distribution, metabolism or excretion. But, given the, you know, and we don't have reproductive toxicity, but given the long term historical use of these products without reports, we felt we didn't need them. That we don't have data that would clear the 46% for the leaf water, however, looking at the composition of the leaf water, we are not concerned that if it's not, if there's not sensitization and HRIPT in the twenties, we're not concerned about that in the forties. Plus, we're saying when formulated to be non-sensitizing since they can contain other, they contain potential sensitizers that could be added, additive when included. And also, in addition to the usual fragrance botanical sensitizers, product formulations contain material such as propylene glycol and parabens, which can sensitize, and in particular parabens, along with some of the fragrance materials have restrictions that blenders should be aware of. That would basically be our discussion, right?

MS. FIUME: Can I just ask for a clarification? So, with the new, updated concentration of use, it appears that the

asterisk applies to the 86% being an OTC, but there's a huge range there of 0.5 to 86%. Do we know what the non-OTC concentration of use is for non skin fresheners?

DR. ANSELL: We can ask that question again. But according to my notes, the maximum use concentration of water is 43%.

MS. FIUME: I'm talking about the extract. So, for the new information, the double asterisk said 86% of extract is a skin freshener in an OTC skin astringent. But the range is 0.5 to 86%. So do we know the highest concentration that is not OTC?

MS. LORETZ: We might need to go back. Is the lower number the number, or is there something in between?

DR. BELSITO: Okay. So we need to confirm the highest concentration.

DR. ANSELL: Reference five, which was the generic, doesn't seem to be bad. It actually includes some classic toxicology. We might want to re-open the (inaudible) agency's evaluation. You cite that as number five.

DR. SNYDER: So we just have to have verification that the 43%, our understanding is 43% is the highest max concentration of use.

DR. BELSITO: Yes.

DR. SNYDER: Is that still valid?

DR. BELSITO: And then we'll just have to worry about, what table is it with the concentrations of uses?

DR. SNYDER: Table Nine, page 27

DR. BELSITO: So we're taking out this 86%. Okay.

MS. FIUME: What were you asking about number five, Jay?

DR. ANSELL: Just to look through it because it does include, I was just scanning through it, it includes not only clinical reports and pharmacology, but some toxicology.

MS. FIUME: Like the oral administration single dose?

DR. ANSELL: Yeah.

MS. FIUME: Yeah. I have that in there.

DR. ANSELL: Okay.

DR. SNYDER: So the 86% is listed under inhalation sprays and under dermal contact.

MS. FIUME: Yeah. It can happen in both things. You can spray onto your skin, so it would be both in the table.

DR. BELSITO: So it'd be like a spray-on astringent that goes onto the skin.

MS. FIUME: Or spray-on suntan.

DR. BELSITO: I doubt you'd put witch hazel in sun block.

MS. FIUME: No. But that would be something you would spray and have a derm exposure to.

DR. BELSITO: I see.

MS. FIUME: So then, can I just take the question just one step further? Cause I guess I'm a little confused. So, it's still listed in a concentration of use survey as a cosmetic product then. Because it's listing it as a cosmetic concentration. It wasn't removed from the table. It's just saying that it's an OTC. Do we have the status of that OTC drug? Like is it an approved OTC? Or is it just in an OTC? Do we have? I just don't want to take that highest concentration away when it still should be being considered. Because it's still listed as a cosmetic concentration. And OTCs sometimes have different status. Whether they're approved, you know, grass weed or not. I don't know if we have any information on.

MS. BECKER: Or this could be something that's listed in the non-cosmetic use section, that we know that it's been used at 86%.

DR. ANSELL: Well, did you check the MADRAS for astringents?

MS. BECKER: No. Did you?

DR. ANSELL: Yes. Well, I didn't. Carol tells me.

MS. FIUME: So it's an approved astringent?

DR. ANSELL: Yeah.

MS. FIUME: Thank you.

DR. BELSITO: Okay. Anything else?

Dr. Marks' Team

DR. MARKS: … Okay. Next witch hazel.
SPEAKER: Was that next?
SPEAKER: Mm-hmm.
SPEAKER: Mm-hmm.
DR. MARKS: I hope so.
SPEAKER: It's what it says on my --
DR. MARKS: Either that -- if we aren't, I'm not reading our Agenda correctly there. Okay. This is witch hazel. And I like the last part of the botanical name, hamamelis -- I presume is somewhat how you pronounce it -- virginiana.
MS. BECKER: Virginiana.
DR. MARKS: Virginiana. So that's appropriate with Virginia just across the river. This is the first review of these ingredients and presumably these plants are found just across the river. At any rate, we have 8 ingredients and Ron, Ron, and Tom, do you like -- I can't imagine you don't like these 8 ingredients -- but do you like these ingredients? Is there anything that should be dropped out? Should we drop out a stem or a flower, or should we do it all together?
DR. SLAGA: I like them all.
DR. MARKS: And then obviously then the next question is what needs to we have to proceed?
DR. SLAGA: I have no needs.
DR. SHANK: I had a need for 28 day dermal tox on all of them unless the chemist can identify one of the extracts for read across for all of the others. And we would need it on only one. If there are systemic adverse effects seen in the 20 dermal then we would need developmental and reproductive tox.
DR. EISENMANN: So you didn't consider the NTP bioassay sufficient for systemic data?
DR. HILL: This is the one where they invalidated the study.
DR. EISENMANN: They never -- well, we don't know. If I understand it Dr. Slaga was on the review panel that was the lead reviewer for that material. They don't really clearly say why they didn't ever produce a technical report.
DR. MARKS: Then wait a second. You mean Tom didn't ever say?
DR. EISENMANN: No, in the minutes he said he was concerned about what the dose was because it was evaporated, but I don't know --
DR. SLAGA: Well, I don't have any problem with it. I looked at this a lot of times and I think there's sufficient data for a mixture like this. Some concern that, you know, a lot of the data is related to a water aspect of -- I assume water extract, right?
DR. MARKS: Well, no. They have one --
DR. EISENMANN: Redistillation part.
DR. MARKS: -- undefined witch hazel extract, but I was concerned there's 359 uses of the extract and I assume the extract, when I looked it up, is the entire plant. And it's use is up to 86 percent on a leave on. So my concern was --
DR. EISENMANN: One comment about that use that we (inaudible) that's an OTC astringent that -- a high percent product.
SPEAKER: Which one?
DR. EISENMANN: The 82 percent.
DR. MARKS: 86.
DR. EISENMANN: 86 percent. Yeah, that's an OTC.
DR. MARKS: So what --
DR. SHANK: So that's not a cosmetic?
SPEAKER: Correct.
DR. EISENMANN: So I left it -- I didn't want to just take it away because I thought it would be good to

give - - relative to cosmetics that an OTC astringent is 82 percent.

DR. SHANK: Good information, yes.

MS. BECKER: Carol, I was thinking it would be a good place to move it to the non cosmetic use, but do you know what the next highest thing is? Because you got a range there and we know what the lowest high is, is there another high, or is that other number the next highest.

DR. EISENMANN: I'd have to check for you.

MS. BECKER: Okay. Thank you.

DR. MARKS: So that was my need, was what is the sensitization potential of the extract. And I don't know that. Let me see here, the extract -- we have the water, but again, the water obviously doesn't include everything that would be in the extract.

DR. HILL: So in wave 2 we have the leaf extract at percent, but it's the leaf.

DR. MARKS: Yeah, the leaf extract again, just leaf. And the extract I assume contains the flower. Is there stem in here? Yeah, here's bark, twig, and -- huh?

DR. BERGFELD: Bark, leaf, twig.

DR. MARKS: Yes, exactly. But so the extract presumably if it's from the whole plant would include more than just the leaf. And so do we feel comfortable. And the other thing is do we even have -- that 6 percent, now we have sensitization data for that water at 25 percent is okay, but - -

DR. HILL: Flower water is things that vaporize when you --

DR. MARKS: Exactly.

DR. HILL: -- leave the flower sit there and whatever volatilizes. That's a very different beast I think.

DR. MARKS: And I'd feel comfortable with the water. It's actually used at 43 percent and obviously 25 percent in a sensitization study doesn't cover that, but if we had the extract in somewhere I'd be -- that's why I put in here the 86 percent. But obviously if that's being used for an over the counter drug then -- actually it would be nice if they had sensitization data on that over the counter drug.

DR. HILL: One would guess they would be required to provide that.

DR. MARKS: I don't know. But if we had that then to me I could -- the rest of the ingredients would be fine because it would be components of that. So I'm going to leave it as I need sensitization. You had the 28 dermal tox for all, Ron Shank, but then, Tom, you were not really concerned - -

DR. SLAGA: (Inaudible) carcinogenicity study it was okay. It's with the water.

DR. SHANK: Well, it says the study was considered inadequate and no technical report was prepared. So I figured that didn't offer any information.

DR. SLAGA: Yep.

DR. EISENMANN: Yeah, but then NTP is reporting it in these review things as being negative.

DR. SLAGE: Right.

DR. EISENMANN: So it's kind of they're sending a mixed signal. Yes, they do write it up when they're writing up a whole lot of studies as a study they've completed and is negative.

DR. SHANK: Okay. On some list of something.

DR. SLAGE: Right.

DR. EISENMANN: But they never prepared a technical report and I --

DR. SHANK: Because they thought it was inadequate.

DR. EISENMANN: But I'm not sure why it was inadequate. I mean the one thing that came out in the minutes was the dose was not clear.

MS. BECKER: And this is before everything was put on line, so what I could find is sketchy.

DR. SHANK: Okay. So the last sentence in our report in the dermal carcinogenicity study says the study was considered inadequate. By whom?

DR. EISENMANN: It wasn't the review committee. It was later on. NTP must have made a decision because the minutes don't reflect that the report was -- that the study was inadequate.

MS. BECKER: Yes, the minutes do not. It was in one of the reports that was reporting the results and why there's no technical report to quote, which could have been a personal opinion on that as opposed to --

DR. SLAGA: There's been a lot of discussion about that compound.
DR. SHANK: Okay.
DR. SLAGA: I don't think that anybody was ever concerned with it.
DR. SHANK: Okay.
DR. SLAGA: I mean that's what I understand.
DR. SHANK: Well, the study was negative, but.
DR. SLAGA: I know it was negative, yeah.
DR. SHANK: So, but if you can't -- if it's not valid then it doesn't make a difference. But you say --
DR. SLAGA: Somewhere I read --
DR. SHANK: He was -- okay.
DR. SLAGA: Sometimes NTP, if it doesn't -- if it's experimental and they had 20 animals at 25 they may call that inadequate.
DR. SHANK: I see.
DR. SLAGA: I mean based on NTP standards, but no research group or anything is going to use 50 males and 50 females in every study.
DR. SHANK: Right.
DR. SLAGA: If you're looking at -- depending on what you're looking at.
DR. SHANK: Okay. I would maybe change the wording there then.
DR. MARKS: Right. So do you still have the 28 day dermal tox for all of them.?
DR. SHANK: No.
DR. MARKS: Okay. And we need to address why that is. And, Tom, you said you've studied it a long time. Is this back to professional opinion or do we have enough data in this draft report to substantiate the safety of these --
DR. SLAGA: Well, what's in -- the study, the undefined, the witch hazel extract, there was not HRM.
DR. MARKS: HRIPT?
DR. SLAGA: Or only on the water.
DR. MARKS: Yeah, only the water. And that was 25 percent and was not a sensitizer. The water is actually being used up to 43 percent. I'd be willing to -- okay, perhaps if I knew the extract, that 86 percent was non sensitizing, now I find out that the extract at 86 percent is really not a personal care product, it's an over the counter drug. But it would really be nice even with that if we had sensitization data.
DR. SLAGA: There may be some data.
DR. MARKS: So I'd probably leave -- where I thought I would move would be an insufficient data announcement.
DR. SLAGA: Well, I mean that's okay. This is the first time.
DR. MARKS: I know.
DR. SLAGA: It doesn't (inaudible).
DR. MARKS: But I want to clarify the needs for me. All I want to see is a sensitization data on the extract at 86 percent and then we'll see what we get. Does that sound okay? And we don't have any other needs? Irritation and damaged skin is okay? Not surprising. I mean this is used all the time.
DR. SLAGA: To put it on damaged skin, that's --
DR. MARKS: I know.
DR. SLAGA: Who would normally do that?
DR. MARKS: I know. There's got to be some more sensitization data out there.
DR. HILL: I just want to say if it's approved as an OTC drug, I don't know if only in this country, there's a dossier. I realize that's not all public record, but it's got to be possible to get -- we can do an FOI and table it until we get it, right?
DR. MARKS: I wouldn't table it, I would just put an insufficient data announcement and that's creates I would say more emphasis on let's get some data, rather than tabling it.
DR. HILL: Somewhere I swear I remember reading -- and I can't find it in either the wave 2 or the original -- that there was a question raised that because it was an astringent if it was studied at high concentrations your

dermal toxicology data might not be valid because of the astringent effect. But where did I read that? I don't think I dreamed it.

MS. BECKER: I can't --

DR. HILL: Okay. I must have run off the maps.

MS. BECKER: I'm not remembering right off hand, but you might be looking at the penetration statement in there, the dermal penetration.

DR. HILL: Maybe. I searched under astringent and I couldn't find it, so maybe that's where I went wrong. Or maybe I read something -- one of the cross references. I just remember that was raised as a question mark because if it's approved as an OTC drug, I mean clearly somebody is -- well, I won't say clearly, I would assume somebody has looked at this in pretty close detail.

MS. BECKER: You might be looking at the first full paragraph on page 13 in the PDF.

DR. HILL: All right, let me look there.

MS. BECKER: And then, Dr. Marks, you said 86 percent sensitization data?

DR. MARKS: Right. Right. Either at HRIPT or (inaudible). Something that would indicate -- and actually your wave 2, Lillian, says that the extract in a skin freshener at up 86 percent. A skin freshener, but you say it's really not a skin freshener, this is an OTC drug.

DR. HILL: Here it is.

MS. BECKER: Correct. It's the same thing, it's from hers --

DR. MARKS: Okay. Okay. Tomorrow I'll move that we issue an insufficient data announcement and that we would like to see the sensitization data at the extract at 86 percent. We'll see where that goes. Does that sound good, Ron, Ron, and Tom?

DR. SLAGA: Yeah.

MS. BECKER: Yeah. And I'm just pointing out that the stuff has been used since before the Pilgrims got here, so there could be a reason there's no data because nobody sees any reason to do it.

DR. MARKS: Yeah, we'll see what the Belsito team says tomorrow.

DR. EISENMANN: This one might be where your experience will help.

DR. MARKS: And lack of case reports.

DR. EISENMANN: Mm-hmm.

DR. MARKS: Yeah.

DR. SLAGE: This only grows in a wet (inaudible) along the East Coast.

DR. MARKS: What I can tell you, sometimes -- you've heard the definition of an expert opinion? It's the same wrong conclusion with greater confidence, time after time. (Laughter) And I can remember when topical corticosteroids were felt not to be sensitizers. Indeed they are significant sensitizers. And we have corticosteroids obviously circulating, endogenous ones.

SPEAKER: That's very strange.

DR. MARKS: So even though I agree--

DR. SLAGA: Was it cortisone --

SPEAKER: No, I think (inaudible)the data.

DR. MARKS: -- at least I'd like to --

DR. SLAGA: Because it's misnomered.

DR. MARKS: But anyway --

DR. SLAGA: How they described the steroids. Cortisol is the human version with hydrogen in the 11 position, hydroxy group. Cortisone is a ketone and cortisone is inactive unless it can be converted into the hydroxy. So because it won't bind to the receptor. So there is an enzyme that -- in ever tissue to -- let me back up. Cortisone is the major circulating steroid in a human and that's because in tissues that deal with mineralocorticoids or sodium potassium exchange the cortisol has 80 percent of the binding capacity mineralocorticoid receptor. So colon, placenta, salivary gland, kidneys, all have an enzyme to deactivate the cortisol and that's why most of the circulating is cortisone. But then it has to be in the skin or the liver converted back into the hydroxy group to be able to have activity. So cortisone is really inactive by itself

unless it's converted. But the nomenclature has stayed forever and some people will call cortisone hydrocortisone, which really means cortisol.

DR. HILL: And if you go and buy the OTC drug, it's --

DR. SLAGA: None of that's been changed. There's been big arguments about that.

DR. HILL: If you go buy the OTC drug it's hydrocortisone.

DR. SLAGA: Yeah.

DR. HILL: That's how it's labeled.

DR. SLAGE: Now it has the hydrogen on the --

DR. MARKS: Okay. Any other comments?

DR. SLAGA: A little history.

DR. MARKS: Yeah, thank you, Tom. I wasn't expected elucidation on corticosteroids. But at any rate, so I'll --

MR. GREMILLION: Yeah, I just wanted to go back to the study that was being discussed. Is that related to the sensitization question? Because the sense I got is that there's some uncertainty as to why it wasn't --

DR. MARKS: You mean the NTP?

MR. GREMILLION: Yes, yes.

DR. SHANK: That was a cancer study.

MR. GREMILLION: Yes, and so I just wanted to make sure we're not -- or I wanted to clarify whether that study is being relied upon to reach a conclusion --

DR. MARKS: For all the other (inaudible)?

MR. GREMILLION: Yeah, for -- yeah.

DR. SLAGE: Well, it's non genotoxic, witch hazel. It's non irritating, okay. And to be carcinogenic it either has to be genotoxic or highly -- or a combination of highly irritant or something to cause proliferation. And if you don't have that you don't get cancer. And the levels you have in the skin are generally used in the skin are so low they won't cause cancer, okay.

MR. GREMILLION: So I mean that study is superfluous or is not -- it's not --

DR. MARKS: Oh, I think it's important, it's just --

DR. SLAGE: Well, that particular study -- they say wasn't either done right or however it was stated -- that particular study my recollection had like 20 or 25 animals in it. So to me I would accept data with 10 or 15. With a (inaudible) amount.

DR. MARKS: Actually, I'm going to carry your question a little bit further. The sensitization data isn't related, but the 28 day tox and all those, the reason, Ron Shank, you didn't feel you needed --

DR. SHANK: Because we have no systemic toxicity.

DR. MARKS: No? Okay.

DR. SHANK: But the carcinogenicity study is a systemic toxicity study, so.

DR. MARKS: Okay, gotcha. Does that make sense now?

MR. GREMILLION: So I guess I'm confused. On the one hand there were some questions about why this study is characterized the way it is and it seems like there's -- you know, it wasn't legitimated in the normal what that these studies are. On the other hand there are some conclusions that are relying on that study. Is that a fair characterization?

DR. SLAGA: I really wasn't relying on that. I was taking all of the data together to come up with that it's okay. Some of the 28-day dermal toxicity stats, you don't have 20 animals in those groups. What sometimes, what do you have five.

DR. GREMILLION: Five

DR. SLAGA: Five.

DR. GREMILLION: Sure.

DR. SLAGA: And we accept that data, why would we accept something with 5 and not with 20.

DR. GREMILLION: I guess --

DR. SLAGA: NTP, to be able to call it a carcinogen requires 50 animals, 50 males and females in one study. No normal researcher would do that to prove if that they're looking at it for a different aspect or 28-day

dermal. NTP you once again, they use large numbers of animals for a 28 dermal. Most studies would not meet their standard (inaudible) when they're trying to set a specific compound to do something.

DR. GREMILLION: So is it clear that the number of animals is the reason that the study was classified that way?

DR. SLAGA: What would a five-animal dermal 28-day dermal tell you?

DR. GERMILLION: I just got a sense that there wasn't clarity on why the study was categorized the way it was.

DR. SLAGE: I don't remember, I guess I didn't see --

DR. GERMILLION: And is that a kind of information that you can, like, when you go back and ask for more data. Can you ask for more?

DR. MARKS: Well, I think the important thing is Tom was involved in evaluating this in the data.

DR. SLAGA: Well, I don't want to use that to break that down.

DR. BERGFELD: Just put your name in.

DR. SLAGA: Done a long time ago.

MS. BECKER: I spent a lot of time looking for why they didn't write one up and it's not online anywhere. It's cited in other studies, but it's no details on why it wasn't written up. I found one set of minutes for discussion on it, where he participated in. But other than that, there's no reason why it was not written up.

DR. HILL: So what was your sense again from the minutes? You said something -- what was your sense again from the minutes?

MS. BECKER: My sense from the minutes was that it was fine and they were going on with the accepting the results. But why accepting the results didn't go to writing up the study, I don't know.

MR. HILL: So he's suggesting inadequate number of animals and lack of statistical power for their purposes of carcinogenicity end point.

DR. SLAGA: They don't usually like to include that in.

DR. HILL: Well, yeah, because somebody didn't plan in the study of this case.

DR. SLAGA: Huh.

DR. HILL: They paid for a study that somebody didn't plan to make sure they got the right power.

DR. SLAGA: If I applied for a grant to study Witch Hazel, and I submit it and I said I want to use 50 males and females.

DR. HILL: They all shoot it (inaudible).

DR. SLAGA: They wouldn't even give me money to do it.

DR. HILL: So I did find the statement about the astringency and I searched astringent instead of astringency. And that's why -- and it's exactly where you said at the top of page 13. And that references an herbal committee -- Committee on Herbal Medicine from the EMEA. The European Medicine Agency review of this ingredient in 2009.

DR. SLAGA: But keep in mind NTP has a lot of committees.

DR. HILL: Yeah.

DR. SLAGA: That have to prove things and I've seen compounds or different things take ten years. I mean, it's amazing.

MR. MARKS: Okay. I did have a question on that same page that (inaudible).

MS. BECKER: Uh-huh.

MR. MARKS: It says, ingredients in cosmetics expected to be lower than that from dietary exposure. Do people eat this stuff or is that a mistake?

MS. BECKER: No, there is dietary exposure.

MR. MARKS: Okay. I didn't see anything up in the use section suggesting that it was consumed but...

MS. BECKER: No, it's not actually a dietary I'm sorry take that back. But some people do take it as tinctures and teas and stuff. Even though I've got lots of --

DR. HILL: Okay.

DR. SLAGA: No history of (inaudible).

DR. MARKS: I get it, I gather that that's a (inaudible).

SPEAKER: (Inaudible) if it was a problem that would have been picked up.

SPEAKER: I think.
MR. MARKS: Can we move on to the next ingredient.
DR. HILL: Yeah, yeah.
MR. MARKS: I didn't want to close this before we were done with the --
DR. HILL: Well, it's an interesting thing about that astringency, right? Because if you're using dermal for the toxicology but then at higher concentrations you don't penetrate the skin. Then you've at most U-shaped cure.
SPEAKER: Okay. Fascinating

DAY TWO

DR. BERGFELD: … Moving on to Dr. Marks, witch hazel.
DR. MARKS: So this is a draft report of eight witch hazel derived ingredients. This is the first time we've seen these ingredients. After our team reviewed these, we felt that we would move that an insufficient data notice or announcement be issued and that we need sensitization on the extract. We were told yesterday that 86 percent of the extract was being used in an over-the-counter drug, but we don't know the maximum concentration in personal care products. So that was really our need was to get sensitization data on the extract and concentration of use in personal care products.
DR. BERGFELD: Comment by Belsito team, Don.
DR. BELSITO: Yeah. So we, you know, picked up the exact same thing, that once you got rid of the 86 percent as an OTC, we didn't know the maximum concentration. However, we felt and the final -- and we asked that that data be provided, but we felt that the final conclusion as with all of the botanicals would be "formulated to be non-sensitizing." And so, therefore, that sensitization data would be nice, but it would not change our conclusion.
And we thought we could go ahead with just a request for what the highest concentration of use is, but (inaudible), you know, as a tentative final, that when "formulated to be non-sensitizing and non-irritating."
DR. BERGFELD: Jim?
DR. MARKS: Didn't we just deal with a botanical a few ingredients ago which we will eventually come with that same conclusion, "formulate to be non-sensitizing," but at least we asked for the sensitizing data up front. So, I mean, we could move forward with a tentative report requesting this information. I think that's -- I know where we're going to end, but the intent of "formulate to be non-sensitizing" in my mind was that was aimed at combining botanicals, and we might have a sensitizer in the particular botanical that we are reviewing which is at a low enough concentration we're not worried about. But then, when we add botanicals together, we might get to a level which is sensitizing and not as an escape for clearing the specific botanical ingredient we're reviewing.
DR. BERGFELD: No. It's a first-time review.
DR. BELSITO: I mean, it's the first time we -- I mean, so you're asking specifically for the extract?
DR. MARKS: Yes. Because then the extract could be representative for all the ingredients in this group.
DR. BELSITO: Sensitization for the extract at that highest concentration of use (inaudible).
DR. MARKS: Yeah, 86 percent or whatever the highest --
DR. BELSITO: Well, 86 percent is OTC.
DR. MARKS: Yes. Or whatever the highest concentration it's being used in personal care products.
DR. BELSITO: Yeah.
DR. MARKS: We had water sensitization okay at 25 percent. But again, that doesn't help me for the extract.
DR. BELSITO: Okay. So fine. Insufficient sensitization and --
DR. BERGFELD: So you're seconding --
DR. BELSITO: Yeah.
DR. BERGFELD: -- seconding the motion to go insufficient for sensitization studies and concentration of use? Is

that correct?
DR. BELSITO: Yes.
DR. BERGFELD: Okay.
DR. SHANK: Can you read-across for all of the -- the tox data is pretty thin unless you can read-across all of these, and I --
DR. BELSITO: Well, we addressed the tox data by saying that, yes, it is very thin. But basically, this material has been used since antiquity with no reported tox effects.
DR. SHANK: That's a departure from our usual --
DR. BERGFELD: Behavior?
DR. SHANK: (Inaudible) reviews.
DR. BELSITO: I don't know that it is. You know, I mean, certainly in terms of sensitization, we've said that, you know, the lack of case reports of sensitization. I mean, it's an approved, you know, botanical drug in the EU.
DR. LIEBLER: So we do have -- for acute and short term tox, we do have data. What we are lacking is data for sub-chronic and chronic.
DR. HILL: And that's an interesting case because they concluded that in skin painting where you use the 86 percent, the astringent effect would be so strong that you would essentially preclude absorption of almost anything.
DR. LIEBLER: Well, that sounds like massive --
DR. HILL: Sort of a fascinating --
DR. LIEBLER: -- hand waving to me.
DR. HILL: Yeah.
DR. BERGFELD: Well, since you're going insufficient, would it be (inaudible) just to ask for the genotox studies if available?
DR. SHANK: For a genotox on the water.
DR. BERGFELD: Okay.
DR. SHANK: That's all. So can you use that data for all of the other?
DR. LIEBLER: We've got water and we got the leaf oil.
DR. SLAGA: Well, how about genotox on the extract? Like if we're going to ask for sensitivity, just go ask some more.
DR. LIEBLER: So we have genotox on the water, which would be like a steam distillation product, and then we've got the leaf oil. And actually, those are kind of complementary extracts --
DR. SHANK: Okay.
DR. LIEBLER: -- that will pretty much cover the water front in terms of the composition of what's in there. And those are both in vitro negative genotox.
DR. SHANK: We have genotox only on the water.
DR. LIEBLER: We also have it on the witch hazel leaf oil. It's on PDF 14, right under the water listing. It says leaf oil was not genotoxic in AMES assay in four different strains with or without metabolic activation.
DR. HILL: So the question is whether the water is capturing anything because you know how those waters are typically made. You basically put these things in a steamer and then capture the things that are volatilized. So it wouldn't be the same as steam distilling. I wonder if it is, in fact, capturing everything.
DR. LIEBLER: Oh, it doesn't capture everything. I mean, it emphasizes the volatiles. I thought that they actually -- we have pretty good method of manufacture on these.
DR. HILL: It just struck me that since this has undergone review for OTC use that people have surely looked at the systemic tox issues. We would be inventing the wheel? Or can we get robust summaries of those reviews in some manner?
DR. BERGFELD: They should be public record.
DR. MARKS: So, Lillian, you didn't find anything? If you go back and search, are you going to find that?
MS. BECKER: I did search for these. I can search again, but they're so --

DR. BELSITO: Doesn't the EU have a botanical pharmacopoeia?
DR. HILL: They definitely have an herbal medicines review.
DR. BELSITO: Right. So I mean, this --
MS. BECKER: Right.
DR. BELSITO: I mean, since it's an approved --
MS. BECKER: I do have their -- I believe this is the one I have the EMA on there. (Inaudible)
MR. GREMILLION: I just wanted -- the table on page 5 says "indicated there's not genotoxicity data for the extract" and so it sounds like that's -- there should be an X in the box for the extract.
DR. SHANK: That table's not up to date.
MR. GREMILLION: Yeah. Okay.
SPEAKER: There's some (inaudible) to the data, right, that got --
DR. BERGFELD: Yes.
DR. LIEBLER: That's the extract.
DR. MARKS: So there are different names of these ingredients.
DR. BELSITO: There was also wave two data, so that table does not reflect the wave two data that was obtained.
MS. BECKER: Yes. I got the European (inaudible) -- I do have the European --
DR. HILL: We got six percent data.
DR. BERGFELD: Lillian's speaking.
DR. HILL: Sorry.
MS. BECKER: I do have the European assessment on it as an herbal medicine. It's in there. That's reference 5. And there's some tox data in there, too.
DR. BELSITO: So all the tox data that was in that European herbal medicine has been brought into this report?
MS. BECKER: Yes, it has.
DR. BELSITO: Okay.
DR. BERGFELD: Dr. Marks, do you want to summarize where we are?
DR. MARKS: Well, we've agreed we're going to do an insufficient data announcement. We need sensitization on the extract, the maximum concentration of use in personal care products, and Ron Shank, he wanted some more tox data. Did you want --
DR. SHANK: Well --
DR. MARKS: And we could ask for the extract, also. Do you want to clarify what you wanted?
DR. SHANK: It depends on how much we can read-across with all of these different preparations.
DR. LIEBLER: So based on --
DR. SHANK: Is there one we can use to represent the others?
DR. LIEBLER: I mean, it looks like that the method of manufacture for the extract -- things listed as extract --
DR. SHANK: Yes.
DR. LIEBLER: -- are all pretty equivalent, so any data on those would extend to the others. The waters are a little different because it's a different method and you get a different mixture. I would say the waters are probably a subset of what's in the extracts. So the extract data sets would probably be the most valuable.
DR. SHANK: Okay.
DR. LIEBLER: So if we're going to ask for anything, we should ask for it on the extract.
DR. SHANK: Okay.
DR. BERGFELD: So can you continue what we're going to ask for?
DR. MARKS: Yeah. That's what I was going to -- so, Paul, what were you going to say?
DR. SNYDER: Well, I was just -- a question to Lillian. I raised this yesterday that, I was struck by pages 6 and 7 that have the search and all the N's where there were no data generated. And that's the first time I've ever seen that many N's in a search.
But I just noticed that your search terms were down below -- you said witch hazel or the cast [cas] number. So you didn't search with a plant name or anything like that?
MS. BECKER: Yeah. I used the plant name, witch hazel.

DR. SNYDER: Okay. Because on the bottom --
MS. BECKER: Yeah.
DR. SNYDER: -- I mean at the table there, it says witch hazel or cast number. So you did search with --
MS. BECKER: Yeah. I also used the --
DR. SNYDER: Okay. Thank you.
DR. MARKS: So, Ron Shank, specifically, is there any -- on the extract, any tox data you'd like to see in this insufficient data announcement?
DR. SHANK: Well we have a carcinogenicity study on the leaf extract. That'll probably take care of it.
DR. MARKS: So I think we're just -- the sensitization data for the extract is the insufficient data and the --
DR. BELSITO: And concentration of use.
DR. MARKS: And concentration of use, yeah.
DR. BELSITO: And the other thing is, we need to confirm with RIFM that the flower is, which is listed as a fragrance only, is on their radar to review. Otherwise, if it is, we can drop it from this report.
DR. MARKS: Okay.
DR. BERGFELD: Are you going to second that motion?
DR. BELSITO: Yeah.
DR. BERGFELD: Thank you. Any other discussion before I call the question? Seeing none, I call the question. All those in favor, it is going out as an insufficient data announcement. Thank you. Unanimous.

(The motion passed unanimously.)

Safety Assessment of *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients 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 Executive Director is Bart Heldreth, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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ABSTRACT

This is a safety assessment of 8 *Hamamelis virginiana* (witch hazel)-derived ingredients as used in cosmetics. Many of these ingredients are reported to function as astringents and skin-conditioning agents - miscellaneous in cosmetics. 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. With *Hamamelis virginiana*-derived ingredients, the Panel was concerned about the presence of geraniol and the oxidation products of linalool in cosmetics. Industry should use good manufacturing practices to limit impurities. The Panel concluded that *Hamamelis virginiana* (witch hazel)-derived ingredients were [*To be determined*]

INTRODUCTION

This is a safety assessment of 8 *Hamamelis virginiana* (witch hazel)-derived ingredients as used in cosmetics (Table 1).

Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract	Hamamelis Virginiana (Witch Hazel) Flower Water
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	Hamamelis Virginiana (Witch Hazel) Leaf Extract
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract	Hamamelis Virginiana (Witch Hazel) Leaf Water
Hamamelis Virginiana (Witch Hazel) Extract	Hamamelis Virginiana (Witch Hazel) Water

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*), many of these ingredients are reported to function as astringent and skin-conditioning agent – miscellaneous in cosmetics.[1] However, the only stated function therein for Hamamelis Virginiana (Witch Hazel) Flower Water is fragrance ingredient.

Drug astringent – skin protectant drug is also listed as a function of Hamamelis Virginiana (Witch Hazel) Water. Drug astringent is not a cosmetic function, and the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) does not evaluate non-cosmetic functions.

The names of the ingredients in this report are written in accordance with International Nomenclature Cosmetic Ingredient (INCI) naming conventions, 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., *Hamamelis virginiana*).

Often in the published literature, the information provided is not sufficient to determine how well the tested substance represents the cosmetic ingredient (e.g., "hamamelis water" with the CAS number 68916-39-2); in such cases, the taxonomic name is used unless it is clear that the test substance is similar to a cosmetic ingredient. If the tested substance is a cosmetic ingredient, then the INCI name is used.

Botanicals, such as *Hamamelis virginiana* (witch hazel)-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects. For example, geraniol and linalool are constituents of the *Hamamelis virginiana* (witch hazel) plant; geraniol is a potential dermal sensitizer, as are the oxidation products of linalool.[2-4] In this assessment, CIR is reviewing the potential toxicity of each of the *Hamamelis virginiana* (witch hazel)-derived ingredients as a whole, complex mixture. CIR is not reviewing the potential toxicity of the individual constituents herein.

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.

Pertinent data were discovered in other reports, including reports by the Committee on Herbal Medicinal Products (HMPC), the World Health Organization (WHO), and the European Agency for the Evaluation of Medicinal Products (EMEA), Veterinary Medicines Evaluation Unit.[5-7] Reports by these organizations are cited in this assessment to identify the source of the data obtained from these summaries.

CHEMISTRY

Definition

The definitions of the ingredients in this safety assessment are provided in Table 1.

Plant Identification

Hamamelis virginiana (witch hazel), a member of the family Hamadelidaceae, is indigenous to damp woods on the Atlantic coast of North America, regionally from Florida to Nova Scotia, and may be found as far west as Texas (Figure 1).[5,7-10] The appearance/structure of the plant and leaves vary widely with no consistent pattern of variation or geographic correlation. The plant may be a tall shrub with the branches coming from the base or small tree of up to 4.6 m tall. The leaves are 1 to 5 cm long and may alternate or stipulate, have short petioles, and may be unequilateral or rhomboid-ovate, with an oblique base and sinuate or sinuate-dentate margin. The flowers are golden-yellow and thread-like, and grow in

axillary clusters. *Hamamelis virginiana* (witch hazel) likely reproduces through insect pollination instead of wind pollination. The leaves fall in autumn about the same time as fruits ripen from the flowers of the previous year. The fruit are a 2-beaked, 2-celled, woody capsule each cell containing a single black seed. This plant is unusual in that it has flowers and fruit at the same time.

Photo credit: Lillian Becker

Figure 1. *Hamamelis virginiana* (witch hazel)

Physical and Chemical Properties

Chemical and physical properties of Hamamelis Virginiana (Witch Hazel) Leaf Water and Hamamelis Virginiana (Witch Hazel) Water at 84% to 85% in grain alcohol or ethanol are presented in Table 2.

Method of Manufacture

The definitions of several of the *Hamamelis virginiana* (witch hazel)-derived ingredients in this safety assessment give insight into possible methods of manufacture. For example, the definition for Hamamelis Virginiana (Witch Hazel) Flower Water states that this ingredient is an aqueous solution of the steam distillates obtained from the flowers of *Hamamelis virginiana*.[1]

Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract

A manufacturer reported that the method of manufacture for a product mixture containing Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract (10%) starts with the testing of the collected *Hamamelis virginiana* (witch hazel) plant material.[11] If the materials pass (criteria not specified), the plant matter is mechanically cleaned to remove unnecessary material. The twigs, bark, and leaves are then processed by grinding and milling. An aqueous extraction is performed at a specific pH and temperature for a specified duration (not provided). Phenoxyethanol, tetrasodium ethylenediaminetetraacetic acid (EDTA), methylparaben, ethylparaben, butylparaben, propylparaben, and isobutylparaben are added to the extract. The extract is filtered and the batch is sampled for quality control. Adjustments are made if needed. After the extract is packaged, it is sampled for microbes.

A similar method of manufacture was reported for a product mixture containing Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract (20%).[11] The only difference is that the propylene glycol is added to dilute the mixture after the aqueous extraction is performed, and the EDTA is not added to the extract

Hamamelis Virginiana (Witch Hazel) Extract

A manufacturer reported that the method of manufacture for a product mixture containing Hamamelis Virginiana (Witch Hazel) Extract (5%) starts with grinding and milling the collected *Hamamelis virginiana* (witch hazel) plants.[12] The resulting material is extracted with cyclopentasiloxane at a specific pH and temperature for a specified duration (not provided). The extract is filtered and the batch is sampled for quality control. Adjustments are made if needed. After the extract is packaged, it is sampled for microbes.

Hamamelis Virginiana (Witch Hazel) Leaf Water

A manufacturer reported that one Hamamelis Virginiana (Witch Hazel) Leaf Water product is a distillate prepared from recently harvested and partially dried leaves of *Hamamelis virginiana* (witch hazel).[13] Alcohol is added to the final product at 14%.

Hamamelis Virginiana (Witch Hazel) Water

A manufacturer reports that a Hamamelis Virginiana (Witch Hazel) Water product is a distillate prepared from recently cut and partially dried dormant twigs of *Hamamelis virginiana* (witch hazel).[14] In this product, grain alcohol or

ethanol is added to the final product at 14%.

Composition

Hamamelis virginiana (Witch Hazel) Plant

Polyphenols - The leaves contain up to, but not more than, 3% tannins.[7,15] The cortex/bark of the stems contains up to 12%, but not less than 4%, tannins. Both hydrolysable and condensed tannins are present, with the latter predominating.[7] Leaf tannins are a mixture of gallic acid (10%), hydrolysable hamamelitannin (1.5%) and condensed proanthocyanidins (88.5%). Bark tannins are similar qualitatively, but have a much greater hamamelitannin concentration (up to 65% of a hydroalcoholic extract). Polyphenols, other than tannins, include phenolic acids and flavonoids. At least 27 phenolic constituents have been identified.

Flavonoids – The leaves contain flavonoid galactosides and glucuronides and other flavonoids such as kaempferol, quercetin, quercitrin, and isoquercitrin.[5]

Catechins - Catechins include (+)-catechin, (+)-gallocatechin, (-)-epicatechin gallate(III), and (-)-epigallocatechin gallate(III). Oligomeric procyanidins are also present. [7,15]

Volatile oil – Both bark and leaves contain volatile oil (0.1% and 0.01% to 0.05%, respectively).[6] The composition of the volatile fraction obtained by water distillation from the leaves and bark of *Hamamelis virginiana* (witch hazel), determined by gas chromatography-mass spectrometry (GC-MS), consists of about 175 identified compounds in the leaves and 168 compounds in the bark.[2,5] The dominating substances were represented by a homologous series of alkanes, alkenes, aliphatic alcohols, related aldehydes, ketones, and fatty acid esters. The volatile oil contains hexane-2-ol, hexenol, α- and β-ionones, eugenol, safrole (maximum 0.2% of the volatile oil) and sesquiterpenes. Other constituents include gallic acid. The bark contains significantly higher levels of phenylpropanoids and sesquiterpenoids in the volatile fractions compared to the leaves, which contain higher amounts of monoterpenoids.[5] Other components include kaempferol, quercetin, chlorogenic acid isomers, and hydroxycinnamic acids.[7] The volatile oil contains small amounts of safrole and eugenol as well as numerous other minor components, such as resin, wax, and choline.

The constituents in the volatile fraction of water-distilled (4 h) leaves and bark from freshly harvested *Hamamelis virginiana* (witch hazel) using *n*-hexane as the collector solvent are listed in Table 3. The constituents were identified by GC-MS.[2]

Hamamelis virginiana (Witch Hazel)-Derived Ingredients

The methods of manufacture significantly impact the compositions of *Hamamelis virginiana* (witch hazel)-derived ingredients. For example, distilled ingredients have fewer astringent tannins than a water extract.[16]

Hamamelis Virginiana (Witch Hazel) Water is reported by a manufacturer to be supplied at 85% to 86% with 14% to 15% grain alcohol or ethanol.[17-19] The same manufacturer reports that Hamamelis Virginiana (Witch Hazel) Leaf Water is also supplied at 85% to 86% with 14% to 15% ethanol.[20]

Impurities/Constituents

Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract

One manufacturer reported that Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract is supplied in product mixtures.[21-24] Two product mixtures that include Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract at 10.00% or 20.00%, also contain tetrasodium EDTA (0.1%) or propylene glycol (48%), respectively (Table 4). Both of these product mixtures also contain parabens (0.138%). These product mixtures were certified to not include detectable allergens including amyl cinnamal, citral, coumarin, eugenol, geraniol, and linalool (Table 5). These product mixtures are also certified to not include detectable pesticides including alachlor, diazinon, heptachlor, dichlorodiphenyltrichloroethane (DDT), and parathion. These two product mixtures are also specified to contain < 20 ppm heavy metal, < 10 ppm lead, < 2 ppm arsenic, and < 1 ppm cadmium.[25,26] Microbial content is < 100 colony forming units (CFU)/g with no pathogens, < 100 CFU/g yeast and mold, and 0 CFU/g gram negative bacteria.

Hamamelis Virginiana (Witch Hazel) Extract

One manufacturer reported that Hamamelis Virginiana (Witch Hazel) Extract is supplied as a product mixture of 5.00% Hamamelis Virginiana (Witch Hazel) Extract and 95.00% cyclopentasiloxane.[27,28] This product mixture was certified to not include detectable allergens including amyl cinnamal, citral, coumarin, eugenol, germaniol, and linalool (Table 5). This product mixture was also certified to not include detectable pesticides including alachlor, diazinon, heptachlor, DDT, and parathion. These two product mixtures are also specified to contain < 20 ppm heavy metal, < 10 ppm lead, < 2 ppm arsenic, and < 1 ppm cadmium.[29] Microbial content is < 100 CFU/g with no pathogens, < 100 CFU/g yeast and mold, and 0 CFU/g gram negative bacteria.

Hamamelis Virginiana (Witch Hazel) Leaf Water

Specifications for Hamamelis Virginiana (Witch Hazel) Leaf Water (and 14% grain alcohol) state that this ingredient is to contain < 50 mg/100 mL nonvolatile residue, < 10 CFU/mL yeast and mold, a maximum of 1 CFU/mL gram negative bacteria, and is below the levels of detection for acetone, other ketones, isopropyl alcohol and *t*-butyl alcohol.[13]

Hamamelis Virginiana (Witch Hazel) Water

Specifications for Hamamelis Virginiana (Witch Hazel) Water (and 14% grain alcohol) state that this ingredient is to contain < 25 mg/100 mL nonvolatile residue, < 10 CFU/mL yeast and mold, a maximum of 1 CFU/mL bacteria, and is below the levels of detection for acetone, other ketones, isopropyl alcohol and t-butyl alcohol, and formaldehyde.[14,30,31] Tannins are limited to < 0.03 mg/mL.

Hamamelis virginiana (witch hazel) Plant

Table 6 lists constituents of concerns of *Hamamelis virginiana* (witch hazel) plants. These plants are reported to contain linalool and quercetin.[2,32] Safrole was also found at a level of < 0.2% in *Hamamelis virginiana* (witch hazel) leaf oil.[5] Possible contaminants (e.g., tributylphosphate and dibutyl phthalate) from the volatile fraction of water-distilled leaves and bark are noted in Table 3.

The International Fragrance Association (IFRA) publishes restrictions for fragrance ingredients. Constituents of *Hamamelis virginiana* (witch hazel) that have restrictions established by the International Fragrance Association Standards are listed in Table 7.[33]

During harvest, *Hamamelis virginiana* (witch hazel) plants can be confused with *Coryllus avellana* (hazelnut); this may be a source of impurities.[5] The two plants can be distinguished by anatomical and analytical examination.

UV Absorption

Hamamelis virginiana (Witch Hazel) Plant

In ethanol extracts of dried *Hamamelis virginiana* (witch hazel) plant material (most likely leaves), the light absorbance curves peaked between 250 and 280 nm, depending on the method of extraction.[34] Extracts were prepared by reperculation and microwave assisted extraction, and tested at 3%, 10%, and 40%.

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (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.

According to VCRP survey data received in 2017, Hamamelis Virginiana (Witch Hazel) Water is reported to be used in 386 formulations (255 in leave-on formulations, 122 in rinse-off formulations, and 9 in formulations that are diluted for the bath; Table 8).[35] Hamamelis Virginiana (Witch Hazel) Extract is reported to be used in 359 formulations (266 in leave-on formulations, 91 in rinse-off formulations, and 2 in formulations that are diluted for the bath) and Hamamelis Virginiana (Witch Hazel) Leaf Extract is reported to be used in 218 formulations (138 in leave-on formulations, 73 in rinse-off formulations, and 7 in formulations that are diluted for the bath). All other in-use ingredients are reported to be used in 128 or fewer formulations. The VCRP has entries for "Hamamelis Virginiana Flower Water," which is assumed to be Hamamelis Virginiana (Witch Hazel) Flower Water.

The results of the concentration of use survey conducted by the Council in 2017 indicate Hamamelis Virginiana (Witch Hazel) Water has the highest reported maximum concentration of use; it is used at up to 43% (in the category of other skin care preparations).[36] All other in-use ingredients are reported to be used at up to 4.3% or less.

In some cases, reports of uses were received in the VCRP, but concentration of use data were not provided. For example, Hamamelis Virginiana (Witch Hazel) Flower Water is reported to be used in 43 cosmetic formulations, but no use concentration data were reported. In other cases, no uses were reported in the VCRP, but concentration of use data were received from industry; Hamamelis Virginiana (Witch Hazel) Leaf Water had no reported uses in the VCRP, but use concentrations in paste masks and mud packs were provided in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported.

There were no uses reported to the VCRP and the industry survey for Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Extract and Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract.

Several of these ingredients were reported to be used in formulations used near the eyes (up to 30.6% Hamamelis Virginiana (Witch Hazel) Water in eye lotions and other eye makeup preparations) and in formulations that come in contact with mucous membranes (up to 30.6% Hamamelis Virginiana (Witch Hazel) Water in lipsticks). Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract and Hamamelis Virginiana (Witch Hazel) Water are used in formulations that may be ingested (including lipsticks, mouth washes, and breathe fresheners) at up to 30.6% Hamamelis Virginiana (Witch Hazel) Water (lipsticks), and in formulations for use on babies (no concentrations of use reported).

Additionally, some of the *Hamamelis virginiana* (witch hazel)-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Hamamelis Virginiana (Witch Hazel) Water and Hamamelis Virginiana (Witch Hazel) Extract are used in body and hand spray formulations at up to 25.8% and 0.03%, respectively. 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.[37,38] 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.[39,40] Hamamelis Virginiana (Witch Hazel) Water was reported to be used in face powders at concentrations up to 0.093%. Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400- to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[41-43]

Non-Cosmetic

Hamamelis virginiana (witch hazel), under the name "witch hazel" may be used as an active ingredient as an astringent in over-the-counter (OTC) anorectal drug products at 10% to 50% and OTC skin protectant drug products (as an astringent active ingredient with no limit specified). [21CFR346.18; 21CFR347.12]

Hamamelis Virginiana (Witch Hazel) Extract is used in an OTC skin astringent at 86%.[36]

Hamamelis virginiana (witch hazel) preparations are commonly used for dermatological conditions, including diaper-related dermatitis; however, clinical studies supporting these uses are generally lacking.[5] In Europe, extracts of *Hamamelis virginiana* (witch hazel) folium and/branches are used in teas/poultices (leaf), liquid and dry extracts (leaf 1:1 or 2 with 30% to 60% ethanol; bark 5 to 7:1 with 30% ethanol, respectively), distillates (1:1.12 to 2.08 with ethanol), ointments, creams, tinctures (1:10 with 45% ethanol), suppositories, and liquid extracts to treat hemorrhoids, fever, nose and gum bleeds, lesions, varicose veins, and other minor inflammations of the skin and mucosa. *Hamamelis virginiana* (witch hazel) folium is also used to make eye drops (10%) to treat irritation.

Hamamelis virginiana (witch hazel), 2.5% to 10.8% (w/w) of an extract of the leaves, is used in veterinary medicine as a topical solution, or as an ointment, combined with other herbal extracts, to promote wound-healing of minor injuries to the skin, treatment of skin inflammations, ulcerations, and dermatoses.[6]

TOXICOKINETIC STUDIES

Dermal Penetration

Obtaining data on the toxicokinetics of *Hamamelis virginiana* (witch hazel)-derived ingredients would not be practical because these ingredients are complex mixtures.

A manufacturer reported that *Hamamelis virginiana* (witch hazel) extracts dermally applied in therapeutic amounts do not penetrate into the deeper layers of the skin because of the astringency of their ingredients; thus, they are not absorbed into the blood circulation.[5]

Absorption, Distribution, Metabolism, and Excretion (ADME)

No published ADME studies were discovered and no unpublished data were submitted.

TOXICOLOGICAL STUDIES

Acute Dose Toxicity

No published acute dermal or inhalation toxicity studies were discovered and no unpublished data were submitted.

Oral

The oral administration of a single dose of a *Hamamelis virginiana* (witch hazel) preparation (10 to 20 g; preparation was not specified) showed no toxic effect in mice and rats.[5] No further details were provided.

Anorectal

New Zealand White rabbits (n = 2/sex) were administered suppositories containing *Hamamelis virginiana* (witch hazel) ethanol extract (0, 20, 100, or 300 mg/kg).[44] The extract was characterized as having a minimum of 10% tannins and containing gallic acid. The suppository was comprised of hard fat, white beeswax, and colloidal anhydrous silica. The suppositories were melted and a single dose was administered with a graduated pipette with a plastic tip. The rabbits were observed for 7 h after dosing and then daily for 2 weeks. A local examination of the anorectal region was conducted on days 2, 7 and 14 post-dosing. Blood was sampled on the last day of the observation period. No rabbits died as the result of the experiment. There were no differences in body weights among test groups. There were no changes in liver and kidney functions. There was a non-dose-dependent increase in serum urea content in all treatment rabbits. There were no hematological effects observed. The no-observed-adverse-effects-level (NOAEL) was > 300 mg/kg.

Short-Term Toxicity Studies

No published short-term oral, dermal, or inhalation toxicity studies were discovered and no unpublished data were submitted.

Anorectal

Sprague Dawley rats (n = 5/sex) were administered suppositories containing *Hamamelis virginiana* (witch hazel)

ethanol extract (0, 20, 100, or 300 mg/kg/day) for 28 days.[44] The suppositories were melted and administered with a graduated pipette with a plastic tip. The rats were observed for 1 h after dosing, and then observed and weighed daily. Feed and water consumption was assessed weekly. Blood was sampled by cardiac puncture on the last day of the observation period. The rats were killed and necropsied; the digestive tract was included in the examinations. The liver, kidney, and rectal biopsies were isolated from two rats/sex in the placebo and high-dose groups; these samples were fixed in formaldehyde and examined under light microscope. No rats died as the result of the experiment and no clinical signs were observed. There were no differences in body weight gains among test groups. The observed organs (liver, kidneys, spleen, submandibular salivary glands, heart, testis, and lungs) were similar among placebo and treatment groups. There were no changes in liver and kidney functions without changes in serum lipids and protein profiles. There were no hematological effects observed. The NOAEL was > 300 mg/kg/day.

Subchronic

No published dermal or inhalation subchronic toxicity studies were discovered and no unpublished data were submitted.

Oral

Hamamelis virginiana (witch hazel) at 100 mg/kg/day was orally administered to rats for three months. There were no abnormalities reported. No further information was available.[5]

Chronic Toxicity Studies

No published chronic toxicity studies were discovered and no unpublished data were submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

No published reproductive or developmental toxicity studies were discovered and no unpublished data were submitted.

GENOTOXICITY STUDIES

In Vitro

Genotoxicity studies are summarized in Table 9.

An Ames assay of a product containing Hamamelis Virginiana Leaf Extract (6%; tested at up to 3100 µg/plate Hamamelis Virginiana Leaf Extract) was negative. [48] Hamamelis Virginiana (Witch Hazel) Water (concentration not specified) was not genotoxic in a *Salmonella* mammalian microsome assay, with and without metabolic activation.[5] A sister chromatid exchange (SCE) and a chromosome aberration test were performed on Hamamelis Virginiana (Witch Hazel) Water with negative result at up to 5000 µg/mL.[49] Hamamelis Virginiana (Witch Hazel) Water (up to 5000 µg/mL) was tested for mutagenic potential in the L5178Y tk+/- mouse lymphoma cell forward mutation assay, with and without metabolic activation, and was not identified as a mutagen.[5,50]

Hamamelis virginiana (witch hazel) leaf oil (under the CAS number 68916-39-2) (100 to 10,000 µg/plate) was not genotoxic in an Ames assay using *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537), with and without metabolic activation.[51]

In Vivo

No published in vivo genotoxicity studies were discovered and no unpublished data were submitted.

CARCINOGENICITY STUDIES

No published oral or inhalation carcinogenicity studies were discovered and no unpublished carcinogenicity data for these routes of exposure were submitted.

Dermal

In a skin painting study, a *Hamamelis virginiana* (witch hazel)-derived substance (50% in deionized water and at 100%; under the name "Hamamelis water" with the CAS number 68916-39-2) was dermally administered to male and female F344 rats and $B6C3F_1$ mice, 5 days per week for 2 years, in a National Toxicology Program (NTP) experiment.[45-47] There was a trend for increased tumors, fibromas or fibrosarcomas noted in the male rats and alveolar/bronchiolar adenomas or carcinomas in female mice, but none of these observations were statistically-significant. There were no other signs of carcinogenicity in either species at either concentration. No further details were provided. A technical report number was assigned to the chronic study of this test article. It was not clear why no technical report was prepared.

Subcutaneous

An aqueous *Hamamelis virginiana* (witch hazel) leaf extract (10 mg in saline; 0.5 mL) was subcutaneously injected into the flanks of NIH Black rats once per week for up to 78 weeks.[52] Saline was the control. The extract was made from

wild collected leaves that were powdered and extracted with hot water, and lyophilized. The dose was based on preliminary studies to find the amount of plant material that did not produce any systemic toxicity or local necrosis and sloughing (this dose did cause some swelling, which disappeared within 1 to 2 weeks). Injections were conducted for 78 weeks or until a tumor was detected. The detected tumor was allowed to grow to sufficient size, and then the rat was killed and necropsied. Rats that lived through treatment were observed for an addition 12-week period, and then they were killed and necropsied. Tumor tissue and organs (including regional lymph nodes, lungs, liver, spleen, and kidneys) were examined. No tumors were detected in the control group. Three males in the treatment group had tumors that were discovered in weeks 72 to 73. No tumors were observed in the female rats. Two males (weeks 24 and 57) and one female (week 59) died of lung infections. The number of treated rats with tumors was not significantly greater than that of the controls.

OTHER RELEVANT STUDIES

Comedogenicity

A 4-week use study was conducted of a sunless tanner that contained Hamamelis Virginiana (Witch Hazel) Water (6.02%).[56] Female subjects (n = 19) were examined before and after the test period for comedogenicity/clogged pores. The test material did not increase the number of acnegenic lesions over the test period. [See Irritation for dermal results and Ocular Irritation Studies for ophthalmic results]

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

In Vitro

EpiDerm™ assays of two product mixtures that contains Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract (5% and 10%) were negative (Table 10). [53,54] An EpiDerm™ assay of Hamamelis Virginiana (Witch Hazel) Extract (5%) was negative for predicting dermal irritation.

In Vivo

Hamamelis Virginiana (Witch Hazel) Water

A patch test of a face product containing Hamamelis Virginiana (Witch Hazel) Water (8.5%; 25 µL) was conducted.[55] The test substance was applied to the scapular area of subjects (n = 11) under occlusion using Finn chambers for 48 h. The test sites were observed at 30 min and 24 h after removal. The test substance was found to be a nonirritant.

A 4-week use study was conducted of a sunless tanner that contained Hamamelis Virginiana (Witch Hazel) Water (6.02%).[56] Female subjects (n = 19) were examined before and after the test period for erythema, edema, and dryness as well as non-inflammatory and inflammatory lesions. One subject reported "tingling" for 5 min after application on the last two days of the test. There were no signs of irritation with dermal examination. [See Ocular Irritation Studies for ophthalmic results and Comedogenicity for comedogenic effects]

Sensitization

Hamamelis Virginiana (Witch Hazel) Leaf Extract

A human repeated insult patch test (HRIPT; n = 108) of a trade name mixture that contains Hamamelis Virginiana (Witch Hazel) Leaf Extract (6% diluted in water to 7.5% for final concentration of 0.45%) was conducted.[48] The test material was applied to the upper back under semi-occlusion for 24 h for a total of 9 applications. After a two-week rest period, the challenge patch was applied to a naive site for 24 h and the test site was examined for signs of irritation or sensitization. The results were negative for irritation and sensitization

Hamamelis Virginiana (Witch Hazel) Water

A HRIPT (n = 105) was performed on a product containing Hamamelis Virginiana (Witch Hazel) Water (25.80%).[57] Induction patches were applied neat to the upper back three times per week for three weeks. The test sites were wiped with 70% isopropyl alcohol prior to placement of the patches. Patches were in place for 24 h. The test sites were examined prior to the application of the next patch. After approximately 2 weeks rest, the challenge patch was applied for 24 h. The challenge site was examined upon removal, and at 48 and 72 h. If there was a reaction, the challenge site was examined again at 96 h. There were no reactions at any time during this test demonstrating no potential for irritation or sensitization of this test material.

A HRIPT (n = 199) was performed on a product containing Hamamelis Virginiana (Witch Hazel) Water (6.88%).[58] The test material was applied neat to the upper back under semi-occlusion for 24 h for a total of 9 applications. After a 10- to 15-day rest period, the challenge patch was applied to a naive site for 24 h and the test site was examined for signs of irritation or sensitization. The results were negative for sensitization.

A HRIPT (n = 107) was performed on a product containing Hamamelis Virginiana (Witch Hazel) Water (6.02%).[59] Patches containing the test material were applied neat to the upper back after wiping the test site with isopropyl alcohol for 24 h for a total of 9 applications. After an approximately 2-week rest period, the challenge patch was applied to a naive site for 24 h and the test site was examined for signs of irritation or sensitization at 24 and 72 h. The results were negative for irritation and sensitization.

Photosensitization/Phototoxicity

An *in vitro* phototoxicity assay of a trade name mixture that contains Hamamelis Virginiana (Witch Hazel) Leaf Extract (6%) was conducted.[48] The test substance (up to 17,000 µg/mL; 1020 µg/mL Hamamelis Virginiana (Witch Hazel) Leaf Extract) was exposed to Balb/c 3T3 cells with and without a UVA dose of 5 J/cm^2. No cytotoxicity was observed at any concentration tested with or without UVA irradiation.

OCULAR IRRITATION STUDIES

In Vitro

EpiOcular™ assays of two product mixtures that contains Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract (5% and 10%) were negative for predicting ocular irritation (Table 11). [53,54] An EpiOcular™ assay of Hamamelis Virginiana (Witch Hazel) Extract (5%) was negative for predicting ocular irritation.

In Vivo

A 4-week use study was conducted of a sunless tanner that contained Hamamelis Virginiana (Witch Hazel) Water (6.02%).[56] Female subjects (n = 10 that did not wear contact lenses, 9 that wore contact lenses) were examined before and after the test period with a slit lamp. They were also examined for signs of ocular irritation such as stinging, burning, itching, dryness, and foreign body sensation. The eyelids and the conjunctivae were also examined. The cornea was examined for inflammation, edema, infiltration, neovascularization, opacities, and/or epithelial defects. Soft contact lenses were examined for deposits and color change; rigid gas permeable contact lenses were examined for deposits and scratches. One subject had an increase in redness of the palpebral conjunctivae, which was deemed not related to the test material. There were no other differences in the eye examinations before and after the use period. [See Irritation for dermal results and Comedogenicity for comedogenic effects.]

CLINICAL STUDIES

Retrospective and Multicenter Studies

In a multicenter, prospective pediatric cohort study, subjects of different age groups (27 days to 1 year; 1 to 5 years; 6 to 11 years of age) suffering from superficial skin lesions, diaper skin rash, or other local inflammations of skin and mucous membranes were treated in a randomized manner with either an ointment containing *Hamamelis virginiana* (witch hazel; concentration, composition, and source not specified; n = 231) or dexpanthenol, a documented therapy used for the control (n = 78).[5,60] The recommended individual observation periods were 7 to 10 days; dosage was based on the recommendations of the treating physician. Tolerability of the ointment containing *Hamamelis virginiana* (witch hazel) was assessed as excellent or good by 99.1% of the doctors and 98.2% of the parents (dexpanthenol: 97.4% and 92.3%, respectively). Twelve of 231 subjects experienced adverse events, which included confusion, head lice, cough/allergic reaction, fungal infection/deterioration, otitis, increase in erythema, rhinopharyngitis, burning sensation, super-infection, diaper candidiasis, and obstructive bronchitis. The authors considered only two adverse events as potentially *Hamamelis virginiana* (witch hazel)-related (i.e. erythema and burning sensation), which were resolved by the end of the treatment period.

Subjects (n = 12) that were confirmed to be sensitized to chamomile (thus, Compositae-sensitive) were administered patch tests for other plant-derived extracts, including an aqueous-alcoholic *Hamamelis virginiana* (witch hazel) distillate (concentration and method of extraction not specified).[61] One subject had a positive reaction the *Hamamelis virginiana* (witch hazel) distillate.

Subjects (n = 1032) that were in clinics to be patch tested for allergens were administered additional patch tests for ointments that contain botanical extracts, including one that contained *Hamamelis virginiana* (witch hazel) extract (25%).[62] A total of four subjects had positive results to the ointment containing *Hamamelis virginiana* (witch hazel) extract. Two of these subjects also had reactions to other ointments and to "wool fat," one of the ingredients in the ointments.

Damaged Skin

Studies on the use of *Hamamelis virginiana* (witch hazel)-derived substances on damaged skin are summarized in Table 12.

There were no reported adverse effects when a cream containing Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract (10%) was applied to skin damaged by UVB light.[63]

There were no reported adverse effects from an oil/water (o/w) emulsion containing *Hamamelis virginiana* (witch hazel) distillate (up to 0.00256% *Hamamelis* ketone) applied to skin damaged by UVB light or tape stripping.[64] There were no reported adverse effects from three O/W emulsions containing *Hamamelis virginiana* (witch hazel) distillates (10% *Hamamelis* ketone) from different suppliers applied to skin damaged by UVB light.[65]

There were no adverse events attributed to a cream containing *Hamamelis virginiana* (witch hazel) distillate (up to 0.00064%) when applied to subjects with moderately severe atopic eczema for 14 days.[66]

Case Reports

A 31-year-old non-atopic woman started to use a new eye gel that contained "witch hazel distillate," after which edema developed around the eyes within 1 week.[67] At the same time, she was treated with 1% hydrocortisone-17-butyrate for dermatitis of the lower limbs. She stopped using the eye gel, but instead started to use alternative remedies (not specified). Over the following days, edema spread to the rest of the face and neck and then presented as eczema. She was treated systemically with corticosteroid and told not to use any cosmetics or other treatments. The dermatitis resolved and did not relapse. A patch test of the eye cream and its components was conducted. At the readings on day 3, the patch test had positive results for the eye cream (+) and for "witch hazel distillate" in a concentration-dependent manner (1%, -; 5%, +?; 10%, +; 50%, ++; 100%, ++).

SUMMARY

This is a safety assessment of 8 *Hamamelis virginiana* (witch hazel)-derived ingredients as used in cosmetics. According to the wINCI *Dictionary*, the functions of these ingredients include cosmetic astringent and skin-conditioning agent – miscellaneous.

Hamamelis virginiana (witch hazel), a member of the family Hamadelidaceae, is indigenous to damp woods on the Atlantic coast of North America ranging from Florida to Nova Scotia.

In ethanol extracts of dried *Hamamelis virginiana* (witch hazel) plant material (most likely leaves), the light absorbance curves peaked between 250 and 280 nm, with variations depending on the method of extraction.

According to VCRP survey data received in 2017, Hamamelis Virginiana (Witch Hazel) Water is reported to be used in 386 formulations (255 in leave-on formulations, 122 in rinse-off formulations, and 9 in formulations that are diluted for the bath). Hamamelis Virginiana (Witch Hazel) Extract is reported to be used in 359 formulations and Hamamelis Virginiana (Witch Hazel) Leaf Extract is reported to be used in 218 formulations. All other in-use ingredients are reported to be used in 128 or fewer formulations.

The results of the concentration of use survey conducted by the Council in 2017 indicate Hamamelis Virginiana (Witch Hazel) Water has the highest reported maximum concentration of use; it is used at up to 43% (in the category of other skin care preparations). All other in-use ingredients are reported to be used at up to 4.3% or less.

In the United States, *Hamamelis virginiana* (witch hazel), under the name "witch hazel" may be used as an active ingredient as an astringent in OTC anorectal drug products at 10% to 50% and in OTC skin protectant drug products (no limit specified).

The oral administration of a single dose of a *Hamamelis virginiana* (witch hazel) preparation (10 to 20 g; preparation was not specified) showed no toxic effect in mice and rats.

In an experiment where *Hamamelis virginiana* (witch hazel) ethanol extract was administered to rabbits in a suppository in a single dose, no rabbits died as the result of the experiment. There were no differences in body weights among test groups. There were no changes in liver and kidney functions. There were no hematological effects observed. The NOAEL was > 300 mg/kg.

In an experiment where *Hamamelis virginiana* (witch hazel) ethanol extract was administered to rats in a suppository for 28 days, no rats died as the result of the experiment. There were no differences in body weights among test groups. There were no changes in liver and kidney functions. There were no hematological effects observed. The NOAEL was > 300 mg/kg.

There were no abnormalities reported when *Hamamelis virginiana* (witch hazel) at 100 mg/kg/day was orally administered to rats for three months.

Hamamelis Virginiana Leaf Extract and Hamamelis Virginiana (Witch Hazel) Water were not genotoxic in various assays. An Ames assay of a product containing Hamamelis Virginiana Leaf Extract (6%; tested at up to 3100 µg/plate Hamamelis Virginiana Leaf Extract) was negative. Hamamelis Virginiana (Witch Hazel) Water was not genotoxic in a *Salmonella* mammalian microsome assay, a SCE assay, a chromosome aberration test (up to 5000 µg/mL), and a L5178Y tk+/- mouse lymphoma cell forward mutation assay.

In a skin painting study, a *Hamamelis virginiana* (witch hazel)-derived substance (50% in deionized water and at 100%) was dermally administered to male and female rats and mice for 2 years in a NTP study. There were no significant signs of carcinogenicity in either species at either concentration.

The number of treated rats with tumors was not significantly greater than that of the controls when an aqueous *Hamamelis virginiana* (witch hazel) leaf extract (10 mg in saline) was subcutaneously injected into the flanks of rats once per week for up to 78 weeks.

EpiDerm™ assays of two product mixtures that contain Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract (5% and 10%) were negative for predicting dermal irritation. An EpiDerm™ assay of Hamamelis Virginiana (Witch Hazel) Extract (5%) was negative for predicting dermal irritation.

A face product containing Hamamelis Virginiana (Witch Hazel) Water (8.5%) was found to be a non-irritant in a patch test. There were no signs of dermal irritation from a sunless tanner that contained Hamamelis Virginiana (Witch Hazel) Water (6.02%) in a 4-week use test.

No irritation or sensitization was reported in HRIPTs of products containing Hamamelis Virginiana (Witch Hazel) Water at 6.02%, 6.88%, or 25.80%.

EpiOcular™ assays of two product mixtures that contain Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract (5% and 10%) were predictive of no ocular irritation. An EpiOcular™ assay of Hamamelis Virginiana (Witch Hazel) Extract (5%) was predictive of no ocular irritation. There were no signs of ocular irritation from a sunless tanner that contained Hamamelis Virginiana (Witch Hazel) Water (6.02%) in a 4-week use test.

In a multicenter, prospective pediatric cohort study, subjects suffering from superficial skin lesions, diaper skin rash, or other local inflammations of skin and mucous membranes were treated with either an ointment containing either *Hamamelis virginiana* (witch hazel; concentration, composition, and source not specified) or dexpanthenol (control). Only two adverse events were potentially related to the *Hamamelis virginiana* (witch hazel; i.e.: erythema and burning sensation), which were resolved by the end of the treatment period.

One of 12 subjects that were confirmed to be sensitized to chamomile (thus, Compositae-sensitive) had a positive reaction to *Hamamelis virginiana* (witch hazel) distillate in a patch test. Four of 1032 subjects had positive results to an ointment containing *Hamamelis virginiana* (witch hazel) extract in a patch test.

There were no reported adverse effects when a cream containing Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract (10%) was applied to skin damaged by UVB light.

There were no reported adverse effects from an o/w emulsion containing *Hamamelis virginiana* (witch hazel) distillate (up to 0.00256% *Hamamelis* ketone) applied to skin damaged by UVB light or tape stripping. There were no reported adverse effects from o/w emulsions containing *Hamamelis virginiana* (witch hazel) distillates (10% *Hamamelis* ketone) from different suppliers applied to skin damaged by UVB light.

There were no adverse events attributed to a cream containing *Hamamelis virginiana* (witch hazel) distillate (up to 0.00064%) when applied to subjects with moderately severe atopic eczema for 14 days.

DRAFT DISCUSSION

[*To be further developed*]

The Panel examined the oral toxicity, genotoxicity, carcinogenicity, dermal irritation, and sensitization studies of *Hamamelis virginiana* (witch hazel)-derived ingredients and substances. The lack of irritation and sensitization were noted.

These ingredients are reported to be supplied as product mixtures that may include sensitizers such as parabens (e.g., Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Cosmetics manufacturers and formulators are advised to be aware of the presence of potentially sensitizing constituents in these ingredients, as supplied, and to avoid reaching levels of potential sensitizers that may be hazardous to consumers, especially when combining these ingredients with other ingredients that may contain sensitizers.

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 *Hamamelis virginiana* (witch hazel)-derived ingredients, the Panel's concerns included the presence of geraniol and the oxidation products of linalool in cosmetics, which could result in potential dermal sensitization, as well as other constituents of concern. The Panel noted that IFRA standards to avoid adverse effect have been published for several *Hamamelis virginiana* (witch hazel) constituents (Table 7). 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.

The Panel expressed concern about pesticide residues, heavy metals, and substances from plants of other species (weeds) that may be present in botanical ingredients. To address these concerns, the cosmetics industry should continue to use cGMPs to limit impurities.

The Panel discussed the issue of incidental inhalation exposure from aerosol and pump hair sprays. There were no inhalation toxicity data available. These ingredients are reportedly used at concentrations up to 25.8% in cosmetic products that may be aerosolized and up to 0.05% 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 *Hamamelis virginiana* (witch hazel)-derived ingredients to cause toxicity, genotoxicity, irritation, and sensitization. They noted the lack of systemic toxicity, genotoxicity, irritation, and sensitization at relevant doses by *Hamamelis virginiana* (witch hazel)-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 that the following ingredients are *[To be developed.]*:

Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract*
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract*
Hamamelis Virginiana (Witch Hazel) Extract
Hamamelis Virginiana (Witch Hazel) Flower Water
Hamamelis Virginiana (Witch Hazel) Leaf Extract
Hamamelis Virginiana (Witch Hazel) Leaf Water
Hamamelis Virginiana (Witch Hazel) Water

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

TABLES

Table 1. Definitions and functions of the *Hamamelis virginiana* (Witch Hazel)-derived ingredients.[1]

Ingredient	Definition	Functions
Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract [84696-19-5 (generic)]	Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract is the extract of the bark and leaves of *Hamamelis virginiana.*	Cosmetic astringent; skin-conditioning agent – miscellaneous
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract 84696-19-5 [(generic)]	Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract is the extract of the bark, leaves and twigs of *Hamamelis virginiana.*	Cosmetic astringent; skin-conditioning agent – miscellaneous
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract [84696-19-5 (generic)]	Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract is the extract of the bark and twigs of *Hamamelis virginiana.*	Cosmetic astringent; skin-conditioning agent – miscellaneous
Hamamelis Virginiana (Witch Hazel) Extract 84696-19-5 [(generic)]	Hamamelis Virginiana (Witch Hazel) Extract is the extract of the whole plant, *Hamamelis virginiana*	Cosmetic astringent; skin-conditioning agent – miscellaneous
Hamamelis Virginiana (Witch Hazel) Flower Water [84696-19-5 (generic)]	Hamamelis Virginiana (Witch Hazel) Flower Water is an aqueous solution of the steam distillate obtained from the flowers of *Hamamelis virginiana.*	Fragrance ingredient
Hamamelis Virginiana (Witch Hazel) Leaf Extract [84696-19-5 (generic)]	Hamamelis Virginiana (Witch Hazel) Leaf Extract is the extract of the leaves of *Hamamelis virginiana.*	Cosmetic astringent; skin-conditioning agent – miscellaneous
Hamamelis Virginiana (Witch Hazel) Leaf Water [84696-19-5 (generic)]	Hamamelis Virginiana (Witch Hazel) Leaf Water is an aqueous solution of the steam distillates obtained from the leaves of *Hamamelis virginiana.*	Cosmetic astringent; skin-conditioning agent – miscellaneous
Hamamelis Virginiana (Witch Hazel) Water [84696-19-5 (generic)]	Hamamelis Virginiana (Witch Hazel) Water is an aqueous solution containing natural volatile oils obtained by the distillation of twigs, bark and leaves of *Hamamelis virginiana.*	Drug astringent – skin protectant drugs; skin-conditioning agent - miscellaneous

Table 2. Chemical and physical properties of *Hamamelis virginiana* (witch hazel)-derived ingredients.

Property	Value	Reference
Hamamelis Virginiana (Witch Hazel) Leaf Water[a]		
Physical Form	Liquid	13,20
Color	Clear Colorless to slight yellow	20 13
Odor	Characteristic Characteristic with slight green note	20 13
Specific Gravity @ 20°C @ 25°C	0.976 - 0.982 0.979 - 0.983	13,20 13,20
Vapor pressure mmHg@ 20°C	18.75	20
Vapor Density mmHg	1.03	20
Melting Point °C	-8	20
Boiling Point °C	88	20
Water Solubility	Very soluble	20
Hamamelis Virginiana (Witch Hazel) Water[a]		
Physical Form	Liquid	14,17-19,30,31
Color	Clear	14,17-19,30,31
Odor	Characteristic Mild	14,17-19,30,31 31
Specific Gravity @ 20°C @ 25°C	0.976 - 0.982 0.979 - 0.983	17-19,30,31 17-19,30,31
Vapor pressure mmHg @ 20°C	18.75	18,19
Vapor Density mmHg	1.03	18,19
Melting Point °C	-8	18,19
Boiling Point °C	88	18,19
Water Solubility g/L	Very soluble	18,19

[a] These values are for Hamamelis Virginiana (Witch Hazel) Leaf Water and Hamamelis Virginiana (Witch Hazel) Water at 84%-85% in ethanol.

Table 3. The constituents in the volatile fraction of water distilled (4 h) leaves and bark from freshly harvested *Hamamelis virginiana* (witch hazel) using *n*-hexane as the collector solvent identified by GC-MS.[2]

Compound	Leaf (%)	Bark (%)
Hydrocarbons		
Alkanes, alkenes		
Octane	0.59	1.47
Nonane	0.01	0.02
Decane	0.01	0.04
Undecane	-	0.02
4,8-Dimethyl-1,3,7-nonatriene	-	0.07
Dodecane	0.03	0.1
Tridecane	0.54	trace
Tetradecane	0.23	0.2
3-Methyltetradecane	0.27	-
Pentadecane	0.1	minor
4,8,12-Trimethyl-1,3,7-tridecatetraene	0.23	0.13
Hexadecane	0.07	0.39
Not identified	0.13	-
1-Hexadecyne	0.16	-
Heptadecadiene	-	0.78
1-Heptadecene	-	0.05
Heptadecane	0.31	0.5
1-Octadecene	-	0.14
Octadecane	0.12	0.71
1-Nonadecene	-	0.31
Nonadecane	0.78	1.64
Eicosane	0.6	1.14
1-Heneicosene	-	0.14
Heneicosane	trace	4.78
2-Methylheneicosane	0.02	-
3-Methylheneicosane	0.01	-
1-Docosene	-	0.05
Docosane	1.27	0.87
Methyldocosane	0.05	0.04
2-Methyldocosane	0.02	0.04
Tricosane	10.38	3.14
Methyltricosane	0.02	-
Not identified	0.35	-
5-Methyltricosane	-	0.04
1-Tetracosene	0.08	0.06
Tetracosane	2.59	1,64
Methyltetracosane	0.03	-
Methyltetracosane	0.07	0.05
Methyltetracosane	0.01	-
4-Methyltetracosane	0.02	-
Methyltetracosane	0.07	-
Pentacosane	10.99	3.56
4-Methylpentacosane	0.05	-
2-Methylpentacosane	0.18	-
3-Methylpentacosane	0.15	-
1-Hexacosene	-	0.07
Hexacosane	2.27	1.92
Methylhexacosane	0.05	-
2-Methylhexacosane	0.22	0.15
3-Methylhexacosane	0.04	-
Heptacosane	16.12	5.45
3-Methylheptacosane	0.08	0.07
Ethyltetracosanoate	0.09	-
Octacosane	1.75	1.65
Methyloctacosane	0.03	-
2-Methylhexacosane	0.22	0.15
3-Methylhexacosane	0.04	-
Heptacosane	16.12	5.45
3-Methylheptacosane	0.08	0.07
Ethyltetracosanoate	0.09	-
Octacosane	1.75	1.65
Methyloctacosane	0.03	-

Table 3. The constituents in the volatile fraction of water distilled (4 h) leaves and bark from freshly harvested *Hamamelis virginiana* (witch hazel) using *n*-hexane as the collector solvent identified by GC-MS.[2]

Compound	Leaf (%)	Bark (%)
2-Methyloctacosane	0.07	-
3-Methyloctacosane	0.08	-
Nonacosane	7.12	6.86
Methylnonacosane	0.09	0.18
Triacontane	1.14	1.96
2-Methyltriacontane	0.13	-
3-Methyltriacontane	0.04	-
Hentriacontane	1.14	2.24
Methylhentriacontane	0.06	-
Dotriacontane	0.69	0.98
Triatriacontane	0.68	1.01
Tetratriacontane	0.3	0.76
Sum	62.85	45.42
Alcohols		
cis-3-Hexenol	0.19	0.1
1-Hexanol	0.13	1.33
1-Heptanol	-	0.32
1-Octen-3-ol	0.03	1.16
3-Octanol	-	0.11
1-Octanol	Minor	-
1-Nonanol	0.09	0.6
1-Pentadecanol	-	0.05
1-Hexadecanol	0.1	0.05
1-Octadecanol	Minor	0.34
Eicosanol	0.02	1.25
Not identified	0.09	-
1-Docosanol	0.21	-
Sum	0.86	5.31
Aldehydes		
Octanal	0.03	-
Nonanal	0.62	2.72
2,6-Nonadienal	-	0.05
2-Nonenal (*cis* or *trans*)	-	0.01
Decanal	0.03	0.67
Undecanal	0.42	0.36
trans-2-Undecenal	0.03	0.36
Dodecanal	0.2	0.14
Tridecanal	0.24	0.41
Tetradecanal	0.05	0.07
Pentadecanal	0.13	0.12
Hexadecanal	0.15	0.15
Nonadecanal	0.03	0.09
Eicosanal	Trace	0.1
Heneicosanal	-	0.02
Docosanal	0.28	0.3
Tetracosanal	0.39	0.28
Hexacosanal	0.91	0.17
Octacosanal	0.28	0.12
Sum	3.79	6.14

Table 3. The constituents in the volatile fraction of water distilled (4 h) leaves and bark from freshly harvested *Hamamelis virginiana* (witch hazel) using *n*-hexane as the collector solvent identified by GC-MS.[2]

Compound	Leaf (%)	Bark (%)
Ketones		
2-Undecanone	-	0.02
γ-Nonalactone	-	0.03
2-Tridecanone	0.04	0.01
6-Methyl-5-(3-methylphenyl)-2-hepanone	-	Minor
5,9-Dimethyl-2-decanone	-	0.03
2-Pentadecanone	0.04	0.02
2-Hexadecanone	-	0.03
6,10,14-Trimethylpentadecan-2-one	0.7	0.68
2-Heptadecanone	0.05	0.08
γ-Hexadecalactone	-	0.04
2-Octadecanone	-	0.05
2-Nonadecanone	-	0.19
2-Eicosanone	-	0.02
2-Heneicosanone	-	0.29
2-Tricosanone	-	0.06
Sum	0.83	1.55
Esters		
Methyl salicylate	-	0.02
cis-3-Hexenyl butyrate	Trace	-
trans-2-Hexenyl butyrate	0.14	-
cis-3-Hexenyl 2- or 3-methylbutyrate	0.15	0.24
cis-3-Hexenyl tiglate or angelate	0.06	0.02
Hexyl tiglate	Trace	0.02
Butyl benzoate	Trace	-
cis-3-Hexenyl hexanoate	0.23	-
trans-2-Hexenyl hexanoate	0.03	-
cis-3-Hexenyl *trans*-2-hexenoate	Trace	-
2-Methyl- or 3-methyl butylbenzoate	-	0.02
trans-2-Hexenyl *trans*-2-hexenoate	0.02	-
cis-3-Hexenyl benzoate	0.3	Trace
Hexyl benzoate	-	Trace
cis-3-Hexenyl octanoate	Trace	-
cis-3-Hexenyl salicylate	0.01	-
Benzyl benzoate	0.01	0.06
2-Phenylethyl benzoate	-	0.21
Sum	0.95	0.59
Terpenoids		
Monoterpenes		
cis-Linalool oxide (furanoid)	0.31	1.89
trans-Linalool oxide (furanoid)	0.12	0.5
Linalool	3.71	2.03
Hotrienol	Trace	Trace
Myrcenol	0.04	-
trans-Pinocarveol	-	0.06
Not identified	0.03	-
Nerol oxide	0.09	-
Not identified	0.12	-
Isoborneol	-	0.38
4-Terpineol	-	Minor
p-Cymen-8-ol	Trace	Trace
α-Terpineol	1.06	0.44
Myrtenol	-	0.3
Nerol	0.03	0.39
Isobornyl formate	-	Trace
Geraniol	1.74	1.21
Not identified	-	0.53
Geranyl formate	0.01	-
Geranylacetone	0.07	0.61
Sum	7.36	8.34

Table 3. The constituents in the volatile fraction of water distilled (4 h) leaves and bark from freshly harvested *Hamamelis virginiana* (witch hazel) using *n*-hexane as the collector solvent identified by GC-MS.[2]

Compound	Leaf (%)	Bark (%)
Sesquiterpene hydrocarbons		
Cyclosativene	0.07	Trace
α-Ylangene	-	11.1
Sesquiterpene hydrocarbon	-	0.8
Sesquiterpene hydrocarbon	0.07	-
β-Caryophyllene	0.21	-
Sesquiterpene hydrocarbon	-	Trace
cis-α-Bergamotene	-	0.18
α-Humulene	0.05	-
α-Himachalene	-	0.04
Sesquiterpene hydrocarbon	-	0.03
β-Santalene	0.03	-
(*E*)-β-Farnesene	-	0.06
α-Amorphene	-	2.02
α-Curcument	-	Minor
α-Fanesene	0.08	-
Germacrene-D	-	0.16
(*E*,*E*)-α-Farnesene	1.47	-
β-Bisabolene	-	Minor
(*Z*)-γ-Bisabolene	-	1.08
δ-Calacorene	-	0.25
β-Calacorene	-	Minor
Cadalene	0.05	0.35
Sum	2.07	15.35
Oxygenated sesquiterpenes		
Not identified	-	0.15
trans-Nerolidol	0.17	2.73
Oxygenated sesquiterpene	-	0.08
Viridiflorol or ledol	0.21	-
α-Eudesmol	0.05	1.32
γ-Eudesmol	0.02	-
Gossonorol	-	0.23
α-Turnerone	0.8	-
τ-Muurolol	-	0.16
Not identified	-	0.16
Not identified	-	Trace
Sum	1.25	4.83
Diterpenes		
Manoyl oxide	0.03	0.93
Geranyl linalool-isomer-4[a]	0.47	-
Kaurene	0.02	-
Manool	0.1	-
Sum	0.62	0.99
Compounds with 13 carbons		
Vitispirane (*cis* and *trans*)	0.09	0.29
Rieslingacetal	Trace	Trace
1,1,6-Trimethyl-1,2-dihydronaphthalene	0.21	-
1,1,6-Trimethyl-1,2,3,4-tetrahydronaphthalene	0.01	-
trans-β-Damascenone	Trace	-
Hydroxydihydroedulan-1[a]	Trace	0.19
Sum	0.31	0.48
Phenylpropanoids		
Estragol	-	1.63
trans-Anethole	-	3.3
Eugenol	-	2.41
Methyleugenol	-	0.12
trans-Methylisoeugenol	-	Minor
Sum	-	7.46

Table 3. The constituents in the volatile fraction of water distilled (4 h) leaves and bark from freshly harvested *Hamamelis virginiana* (witch hazel) using *n*-hexane as the collector solvent identified by GC-MS.[2]

Compound	Leaf (%)	Bark (%)
Fatty acids and fatty acid esters		
Nonanoic acid	0.11	0.09
Methyl tetradecanoate	0.03	0.01
Ethyl tetradecanoate	0.01	-
Isopropyl tetradecanoate	0.07	-
Methyl hexadecanoate	0.33	0.05
Hexadecanoic acid	1.62	0.03
Ethyl hexadecanoate	0.16	0.02
Methyl linolate	0.09	-
Methyl linolenate	0.47	Trace
Methyl oleate	0.13	-
Ethyl linolate	0.14	-
Ethyl linolenate	0.05	-
Methyl eicosanoate	0.04	-
Methyl docosanoate	0.11	-
Methyl tetracosanoate	0.15	-
Sum	3.57	0.20
Miscellaneous compounds		
2-Phenylacetaldehyde	-	0.02
1,4-Dimethyoxybenzene	-	Trace
Not identified	0.36	-
Not identified	0.02	0.45
Not identified	0.18	0.04
Dimethylnaphthalene[b]	-	0.06
Not identified	Trace	-
Butylhydroxytolene[b]	-	0.04
β-ionone	0.08	0.07
Not identified	0.25	-
Not identified	0.26	-
Tributylphosphate[b]	-	0.15
Phenanthrene[b]	0.01	0.19
Diisobutyl phthalate	0.01	0.01
Methylanthracene or Methylphenanthrene[b]	-	0.01
Dibutyl phthalate[b]	0.07	0.33
Fluoranthene or Pyrene[b]	-	0.05
Isophytol	0.68	0.05
trans-Phytol	9.79	-
Not identified	0.34	0.03
Not identified	0.18	-
Not identified	0.06	-
Not identified	0.14	0.28
Dioctyl phthalate[b]	-	Trace
Not identified	0.23	-
Not identified	0.16	0.05
Not identified	0.71	-
Not identified	0.33	-
Squalene	0.09	0.31
Sum	14.03	2.14
Total	98.48	98.8

[a] No further information was provided on the chemical
[b] Compound is probably a contaminant.
GC-MS = Gas chromatography-mass spectrometry; Minor = minor component of a peak comprised of more than one compound as estimated by MS; Trace = < 0.01%

Table 4. The contents of two product mixtures that contain Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract.[21-24]

	A	B
Mixture constituent	%	%
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	10.00	20.00
Water	89.40	31.50
Propylene glycol	0	48.00
Phenoxyethanol	0.362	0.362
Tetrasodium EDTA	0.10	0
Methylparaben	0.078	0.078
Ethylparaben	0.02	0.02
Butylparaben	0.02	0.02
Propylparaben	0.01	0.01
Isobutylparaben	0.01	0.01

Table 5. Allergens certified to not be present in product mixtures containing 10% or 20% Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig or 5.00% Hamamelis Virginiana (Witch Hazel) Extract. [21,23,27]

Allergen	**Limit of Detection (ppm)**
α-Isomethyl ionone	< 0.02
Amyl cinnamal	< 0.10
Amylcinnamyl alcohol	< 1.00
Anise alcohol	< 0.00
Benzyl alcohol	< 0.01
Benzyl benzoate	< 0.09
Benzyl cinnamate	< 0.30
Benzyl salicylate	< 0.06
Butylphenyl methylpropional	< 0.50
Cinnamal	< 0.01
Cinnamyl alcohol	< 0.30
Citral	< 1.00
Citronellol	< 1.00
Coumarin	< 0.00
Eugenol	< 0.70
Farnesol	< 0.04
Geraniol	< 0.08
Hexyl cinnamal	< 0.40
Hydroxycitronellal	< 1.00
Hydroxymethylpentyl 3-cyclohexene carboxaldehyde	< 0.30
Isoeugenol	< 0.06
Limonene	< 0.05
Linalool	< 0.00
Methyl 2 octynoate	< 0.02
Evernia furfuracea	< 0.00

Table 6. Constituents of concern found in *Hamamelis virginiana* (witch hazel)

Constituent	Concern	Reference
Afzelin	Cytotoxic, promoted death of neutrophils	68
Geraniol	Potential dermal sensitizer	4
Linalool	Hydroperoxides are potential dermal sensitizers. Safe at up to 4.3% (20% in a consumer fragrance)	3
Phenol	Toxic by ingestion, inhalation, and dermal absorption. Strong dermal irritant. May induce cardiac arrhythmia and is toxic to the liver and kidneys.	69,70
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	71,72
Safrole	Liver cancer (hepatocellular carcinoma, adenoma) in male mice; liver cancer and other tumors in rats.	73

Table 7. Constituents of *Hamamelis virginiana* (witch hazel) that have IFRA standards.[33]

Constituent	Standard Limits
2-Phenylacetaldehyde	Limited to 0.01% - 2.9%, depending on use category due to sensitization.*
Benzyl benzoate	Limited to 2% - 42.8%, depending on use category due to sensitization.*
trans-β-Damascenone	Limited to 0.2% in fragrances and Eau de Toilette; 0.01% in other leave-on and rinse-off products; and 0.2% in non-skin, and incidental skin contact products due to carcinogenicity.
Estragol	Limited to 0.2% - 4.3%, depending on use category due to sensitization.*
Eugenol	Limited to 0.2% - 4.3%, depending on use category due to sensitization.*
Geraniol	Limited to 0.03% - 8.6%, depending on use category due to sensitization.*
Ionone (mixed isomers)	Limited to 2% - 50.72%, depending on use category 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.
Phenylacetaldehyde	Limited to 0.02% - 3%, depending on use category due to sensitization.*
Safrole	Not to be used as a fragrance ingredient. Essential oils containing safrole are not to exceed 0.01% in consumer products.

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 8. Frequency of use according to duration and exposure of *Hamamelis virginiana* (witch hazel)-derived ingredients.[35,36]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract		**Hamamelis Virginiana (Witch Hazel) Extract**		**Hamamelis Virginiana (Witch Hazel) Flower Water**		**Hamamelis Virginiana (Witch Hazel) Leaf Water**	
Total/range	**128**	**0.00005-4.3**	**359**	**0.000013-1.8**	**43[f]**	**NR**	**NR**	**0.67-4.1**
Duration of use								
Leave-on	90	0.00005-4.3	266	0.00003-1.8	21	NR	NR	NR
Rinse-off	37	0.00005-0.072	91	0.000013-1.8	21	NR	NR	0.67-4.1
Diluted for (bath) use	1	NR	2	0.000013-0.0001	1	NR	NR	NR
Exposure type								
Eye area	14	NR	12	0.1	3	NR	NR	NR
Incidental ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	23[a];26[b]	0.18[a]	2; 79[a]; 128[b]	0.00003-0.03; 0.0013[a]	6[a]; 6[b]	NR	NR	NR
Incidental inhalation-powders	26[b]	0.004-4.3[c]	1; 128[b]	0.0001-1.8[c]	6[b]	NR	NR	NR
Dermal contact	122	0.00005-4.3	349	0.000013-1.8	43	NR	NR	4.1-5
Deodorant (underarm)	2[a]	NR	3[a]	0.0013[d]; 0.0013[e]	NR	NR	NR	NR
Hair-noncoloring	3	NR	7	0.0001-0.3	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	2	NR	2	NR	NR	NR	NR	NR
Mucous Membrane	6	NR	13	0.000013-1	8	NR	NR	NR
Baby	1	NR	NR	NR	NR	NR	NR	NR

	Hamamelis Virginiana (Witch Hazel) Leaf Extract		**Hamamelis Virginiana (Witch Hazel) Water**	
Total/range	**218**	**0.00018-0.011**	**386**	**0.00008-43**
Duration of use				
Leave-on	138	0.00018-0.011	255	0.00008-43
Rinse-off	73	0.00035-0.01	122	0.00066-33.3
Diluted for (bath) use	7	NR	9	0.43
Exposure type				
Eye area	9	NR	21	0.04-30.6
Incidental ingestion	NR	NR	5	0.1-30.6
Incidental Inhalation-sprays	1; 44[a]; 65[b]	0.00035[a]	92[a]; 81[b]	0.00008-25.8; 0.00086-6.1[a]; 0.0086[b]
Incidental inhalation-powders	1; 65[b]	0.0018-0.011[c]	2[c]; 81[b]	0.043-0.093; 0.00066-8.5[c]; 0.0086[b]
Dermal contact	195	0.00018-0.011	354	0.00008-43
Deodorant (underarm)	6[a]	0.00018[d]	14[a]	0.086-5.2[d]
Hair-noncoloring	23	0.00035-0.00042	24	0.26-2.5
Hair-coloring	NR	NR	NR	NR
Nail	NR	NR	1	4.3
Mucous Membrane	24	NR	45	0.0086-30.6
Baby	NR	NR	4	NR

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.
[a] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[c] It is possible these products may be powders, but it is not specified whether the reported uses are powders.
[d] Not spray.
[e] Spray
[f] VCRP lists this ingredient as Hamamelis Virginiana Flower Water.

Table 9. In vitro genotoxicity assays of *Hamamelis virginiana* (witch hazel)-derived ingredients and substances.

Ingredient/Test Substance	Concentration	Assay	Results	Reference
Product containing Hamamelis Virginiana Leaf Extract (6%)	Product: 333 – 66,666 µg/plate (0.06 – 3100 µg/plate Hamamelis Virginiana Leaf Extract) in water	Ames assay using *S. typhimurium* (TA98, TA00 [sic], TA1535, TA1537) and E. coli (WP2 uvrA)	Weak toxic effects were occasionally observed at approximately 33,333 µg/plate. No increase in the number of revertant colonies at any concentration for any strain with or without metabolic activation.	48
Hamamelis Virginiana (Witch Hazel) Water	Concentration not specified	*Salmonella* mammalian microsome assay (stains TA97, TA98, TA100, and TA1535)	Not genotoxic with and without metabolic activation	5
Hamamelis Virginiana (Witch Hazel) Water	Up to 5000 µg/mL	SCE	Negative with and without metabolic activation	49
Hamamelis Virginiana (Witch Hazel) Water	Up to 5000 µg/mL	Chromosome aberration test	Negative with and without metabolic activation	49
Hamamelis Virginiana (Witch Hazel) Water	Up to 5000 µg/mL	L5178Y tk+/- mouse lymphoma cell forward mutation assay. Cultures were exposed to test substance for 4 h, and cultured for 2 days before plating in soft agar with or without TFT(3 µg/mL). Negative control was distilled water; positive controls were methyl methanesulphonate without metabolic activation and ethyl methanesulphonate with metabolic activation. Test substance was tested at least twice.	Not a mutagen	5,50
Hamamelis virginiana (witch hazel) leaf oil (under the CAS number 68916-39-2)	100 to 10,000 µg/plate	Ames assay using *S. typhimurium* (stains TA98, TA100, TA1535, and TA1537)	Negative with and without metabolic activation	51

SCE = Sister chromatid exchange; TFT = Trifluorothymidine

Table 10. In vitro dermal irritation assays of *Hamamelis virginiana* (Witch Hazel)-derived ingredients

Ingredient	Concentration	Assay	Results	Reference
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	10% (product mixture)	EpiDerm™	Not predicted to be a dermal irritant. Controls had the expected results.	53
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	20% (product mixture)	EpiDerm™	Not predicted to be a dermal irritant. Controls had the expected results.	54
Hamamelis Virginiana (Witch Hazel) Extract	5% in cyclopentasiloxane	EpiDerm™	Not predicted to be a dermal irritant. Controls had the expected results.	74

Table 11. In vitro ocular irritation assays of *Hamamelis virginiana* (Witch Hazel)-derived ingredients

Ingredient	Concentration	Assay	Results	Reference
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	10% (product mixture)	EpiOcular™	Not predicted to be an ocular irritant. Controls had the expected results.	53
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	20% (product mixture)	EpiOcular™	Not predicted to be an ocular irritant. Controls had the expected results.	54
Hamamelis Virginiana (Witch Hazel) Extract	5% in cyclopentasiloxane	EpiOcular™	Not predicted to be an ocular irritant. Controls had the expected results.	74

Table 12. *Hamamelis virginiana* (witch hazel)-derived ingredients administered to damaged skin.

Ingredient	Dose, vehicle	Procedure/notes	Results	Reference
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract	Creams with and without Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract (10%)	Skin on subjects' backs (n = 28; skin types I, II, or III) was exposed to 800 UV light (mainly in the UVB range with a small amount of UVA and visible light) at 1, 1.25, 1.6, and 2 MED. Test substances were administered using 18-mm Finn chambers immediately after and at 7 and 24 h after irradiation. Test sites were observed at 7, 24 and 48 h after irradiation.	There were no adverse events reported at any time during the experiment.	63
Hamamelis virginiana (witch hazel) distillate (plant parts not specified)	0.00064% (0.64 mg *Hamamelis* ketone/100 g; 75 µL applied) o/w emulsion with and without PC; 0.00256% (2.56 mg *Hamamelis* ketone/100 g; 75 µL applied). Controls were the vehicles and an untreated area.	Randomized, double-blind studies. EXPERIMENT 1: Skin on subjects' backs (n=24) was exposed to 800 UV light (mainly in the UVB range with a small amount of UVA and visible light) at 1.5 MED then test substances were applied. Test sites were observed at 24 and 48 h. EXPERIMENT 2: Skin subjects' backs (n=12) was tape stripped. The low-dose (0.00064% without PC) emulsion and the vehicle (control) were applied. Skin on another group of subjects backs (n=12) was tape stripped. The low- and high-dose (0.00064% and 0.00256% with PC) emulsions were applied. Vehicles were the controls. Test sites were observed at 4, 8 and 24 h.	There were no adverse effects observed in any group during the experiments.	64
Hamamelis virginiana (witch hazel) distillates (plant parts and composition not specified) from three different suppliers	O/W emulsions containing a *Hamamelis virginiana* (witch hazel) distillate (10%) from three different suppliers	Double-blind study. Skin on light-skinned subjects backs (n = 40) was exposed to a sun simulator (UVA:UVB, 16:1; 4 mW/cm^2 UVB) at 1.2, 1.4, and 1.7 MED. Test substances (250 µL) were administered using 18-cm Finn chambers immediately after and at 24 and 48 h after irradiation. Test sites were observed at 24, 48, and 72 h after irradiation.	There were no adverse events reported at any time during the experiment.	65
Hamamelis virginiana (witch hazel) distillate (plant parts not specified)	Creams containing *Hamamelis virginiana* (witch hazel) distillate (0.00064%; 0.64 mg *Hamamelis* ketone/100 g) with and without 0.5% hydrocortisone or just the vehicle	Randomized, double-blind study. Subjects (n = 72) with moderately severe atopic eczema applied a cream containing *Hamamelis virginiana* (witch hazel) distillate on one side of the body and either the same cream with hydrocortisone or the vehicle to lesions on the other side of the body twice per day for 14 days. Blood samples were collected before and after the experiment period at the discretion of a physician.	Self and physician scores of tolerability were similar to controls. Five subjects had itching, erythema, stinging, lichenification/dry skin from using the vehicle. One subject had signs of skin irritation from both the cream containing *Hamamelis virginiana* (witch hazel) distillate and the vehicle control. There were no adverse effects connected to the application of *Hamamelis virginiana* distillate.	66

MED = minimal erythema doses; o/w= oil/water; PC = phosphatidylcholine

REFERENCES

1. Nikitakis, J and Lange B (eds). web-based International Cosmetic Ingredient Dictionary and Hanbook (wINCI). http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC. Last Updated 2017. Date Accessed 5-2-2017.

2. Engel R, Gutmann M, Hartisch C, Kolodziej H, and Nahrstedt A. Study on the composition of the volatile fraction of *Hamamelis virginiana*. *Planta Medica*. 1998;64(3):251-258.

3. Bickers D, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, Sipes IG Smith RL, and Tagami H. A toxicologic and dermatologic assessment of linalool and realated esters when used as fragrance ingredients. *Food and Chemical Toxicology*. 2003;41(7):919-942.

4. Nijkamp MM, Bokkers BG, Bakker MI, Exendam J, and Delmaar JE. Quantitiative risk assessment of the aggregate dermal exposure to the sensitizing fragrance geraniol in personal care products and household cleaning products. *Regulatory Toxicology and Pharmacology*. 2015;73(1):9-18.

5. Committee on Herbal Medicinal Products (HMPC). Assessment report on *Hamamelis virginiana* L., cortex *Hamamelis virginiana* L., folium *Hamamelis virginiana* L., folium et cortex aut ramunculus destillatum. Canary Wharf, London, European Medicines Agency (EMA). 2009. http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2010/04/WC500089242.pdf. Report No. EMA/HMPC/114585/2008. pp. 1-47.

6. European Agency for the Evaluation of Medicinal Products (EMEA), Veterinary Medicines Evaluation Unit. Hamamelis virginiana summary report (1). Canary Wharf, London, European Medicines Agency. 1998. http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500014389.pdf. Report No. EMEA/MRL/358/98-FINAL. pp. 1-2.

7. World Health Organization (WHO). Folium et Cortex Hamamelidis. In: *WHO Monographs on Selected Medicinal Plants - Volume 2*. Vol. 2. Geneva: 2002:124-136.

8. Weber, RW. Allergen of the month - Witch hazel. *Annals of Allergy, Asthma, & Immunology*. 2012;109(5):A17

9. Anderson GJ and Hill JD. Many to flower, few to fruit: The reproductive biology of *Hamamelis virginiana* (Hamamelidaceae). *Amercian Jounal of Botony*. 2002;89(1):67-78.

10. eFloras. Flora in North America: Hamamelis Linnaeus. *eFloras*. 2017. Missouri Botanical Garden, St.Louis, MO & Harvard University Herbiaraia, Cambridge, MA. http://www.efloras.org/florataxon.aspx?flora_id=1&taxon_id=114541Date Accessed 6-1-2017

11. Active Concepts. 2017. Manufacturing flow chart ABS Witch Hazel Extract (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

12. Active Concepts. 2017. Manufacturing flow chart ABS Witch Hazel Extract Sil (Hamamelis Virginiana (Witch Hazel) Extract). Unpublished data submitted by Personal Care Products Council.

13. American Distilling Inc. Specifications: Certified organic witch hazel leaf extract [pamphlet]. East Hampton, CT: American Distilling Inc; 2012.

14. American Distilling Inc.. Specifications: Distilled witch hazel (14% natural grain alcohol) [pamphlet]. East Hampton, CT: American Distilling Inc.; 2012.

15. PDR for herbal medicines. 4 *ed*. Montvale, NJ: Thomson Healthcare, Inc., 2017.

16. Elias, J and Masline, SR. The A to Z Guid to Healing Herbal Remedies. 1 *ed*. New York: Lynn Sonberg Book Associates, 1995.

17. American Distilling Inc.. Material safety data sheet: Distilled witch hazel (14% standard alcohol) [pamphlet]. East Hampton, CT: American Distilling Inc; 2011.

18. American Distilling Inc.. Material safety data sheet: Distilled witch hazel, AVF [pamphlet]. East Hampton, CT: American Distilling Inc; 2011.

19. American Distilling Inc.. Material safety data sheet: Distilled witch hazel 14% natural grain alcohol [pamphlet]. East Hampton, CT: American Distilling Inc.; 2011.

20. American Distilling Inc.. Material safety data sheet: Certified organic witch hazel leaf extract [pamphlet]. East Hampton, CT: American Distilling Inc; 2011.

21. Active Concepts. 2017. Compositional breakdown ABS Witch Hazel Extract (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

22. Active Concepts. 2017. Certificate of origin ABS Witch Hazel Extract (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

23. Active Concepts. 2017. Compositional breakdown ABS Witch Hazel Extract NS (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

24. Active Concepts. 2017. Certificate of origin ABS Witch Hazel Extract NS (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

25. Active Concepts. 2017. Product specification ABS Witch Hazel Extract (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

26. Active Concepts. 2017. Product specification ABS Witch Hazel Extract NS (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

27. Active Concepts. 2017. Compositional breakdown ABS Witch Hazel Extract Sil (Hamamelis Virginiana (Witch Hazel) Extract). Unpublished data submitted by Personal Care Products Council.

28. Active Concepts. 2017. Certificate of origin ABS Witch Hazel Extract Sil (Hamamelis Virginiana (Witch Hazel) Extract). Unpublished data submitted by Personal Care Products Council.

29. Active Concepts. 2017. Product specification ABS Witch Hazel Extract Sil (Hamamelis Virginiana (Witch Hazel) Extract). Unpublished data submitted by Personal Care Products Council.

30. American Distilling Inc. Specifications: Distilled witch hazel (14% standard alcohol) [pamphlet]. East Hampton, CT: American Distilling Inc.; 2011.

31. American Distilling Inc. Specifications: Distilled witch hazel, AVF [pamphlet]. East Hampton, CT: American Distilling Inc.; 2011.

32. Duke JA. Handbook of phytochmical constituents of GRAS herbs and other economic plants. Boca Raton, FL: CRC Press, 1992.

33. International Fragrance Association (IFRA). IFRA Standards. 2017. http://www.ifraorg.org/en-us/standards-library. Date Accessed 1-30-2017.

34. Ramos MFS, Santos EP, Bizarri CHB, Mattos HA, Padilha MRS, and Duarte HM. Preliminary studies towards utilization of various plant extracts as antisolar agents. *International Journal of Cosmetic Science*. 1996;18(3):87-101.

35. U.S. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients; *FDA Database*. Washington, DC, FDA. 2017.

36. Personal Care Products Council. 10-16-2017. Updated Concentration of Use by FDA Product Category: Witch Hazel-Derived Ingredients. Unpublished data submitted by Personal Care Products Council.

37. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27. http://www.spraytechnology.com/index.mv?screen=backissues.

38. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.

39. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

40. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 8-28-2011;205(2):97-104. PM:21669261.

41. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 11-3-2015. Cosmetic Powder Exposure. Unpublished data submitted by the Personal Care Products Council.

42. Aylott RI, Byrne GA, Middleton, J, and Roberts ME. Normal use levels of respirable cosmetic talc: preliminary study. *Int J Cosmet Sci*. 1979;1(3):177-186. PM:19467066.

43. Russell RS, Merz RD, Sherman WT, and Sivertson JN. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol*. 1979;17(2):117-122. PM:478394.

44. Qinna NA. Safety profile of suppository *Hemamelis virginiana* leaf extract. *Journal of Medicinal Plants Research*. 2013;7(36):2669-2679.

45. Board of Scientific Counselors, National Toxicology Program (NTP). Summary minutes from peer reviews of draft technical reports of long-term toxicology and carcinogenesis studies by the Technical Reports Review Subcommittee and Pane of Experts. Washington, DC, National Toxicology Program (NTP). 3-23-1984. pp. 1-11.

46. Haseman JK, Crawford DD, Huff JE, Boorman GA, and McConnell EE. Results from 86 two-year carcinogenicity studies conducted by the National Toxicology Program. *Journal of Toxicology and Environmental Health*. 1984;14:621-639.

47. Haseman JK, Huff JE, Zeiger E, and McConnell EE. Comparative results of 327 chemical carcinogenicity studies. *Environmental Health Perspectives*. 1987;74:229-235.

48. BASF. 2015. Information on toxicological data for a trade name mixture containing Hamamelis Virginiana Leaf Extract. Unpublished data submitted by Personal Care Products Council.

49. Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin BH, Resnick MA, Anderson B, and Zeiger E. Chrmosome aberrations and sister chrmatid exchages in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environmental and Molecular Mutagenesis*. 1987;10(Supplement 10):1-175.

50. McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, and Caspary WJ. Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay II; 18 coded chemicals. *Environmental and Molecular Mutagenesis*. 1988;11(1):91-118.

51. Mortelmans, K, Haworth, S, Lawlor, T, Speck, W, Tainer, B, and Zeiger E. Salmonella mutagenicty tests: II. Results from the testing of 270 chemicals. *Environmental Mutagenesis*. 1986;8(Suppl. 7):1-119.

52. Kapadia GJ, Chung EB, Ghosh B, Shukla YN, Basak SP, Morton JF, and Pradhan SN. Carcinogenicity of some folk medicinal herbs in rats. *Journal of the National Cancer Institute*. 1978;60(3):683-686.

53. Active Concepts. 2017. Dermal and ocular irritation tests ABS Witch Hazel Extract NS (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

54. Active Concepts. 2017. Dermal and ocular irritation tests ABS Witch Hazel Extract (Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract). Unpublished data submitted by Personal Care Products Council.

55. Anonymous. 2015. Summary of study of acute compatibility of a test item: 48-hours occlusive patch test of a face tonic with 8.5% Hamamelis Virginiana (Witch Hazel) Water. Unpublished data submitted by Personal Care Products Council.

56. Clinical Research Laboratories Inc. 2006. Safety-in-use study to determine the ocular and dermal irritation potential and comedogenic-acnegenic potential of a cosmetic product (sunless tanner containing 6.02% Hamamelis Virginiana (Witch Hazel) Water). Unpublished data submitted by Personal Care Products Council.

57. Clinical Research Laboratories Inc. 2011. Repeated insult patch test of a soothing spray containing 25.80% Hamamelis Virginiana (Witch Hazel) Water. Unpublished data submitted by Personal Care Products Council.

58. TKL Research Inc. 2013. Repeated insult patch test of a toner containing 6.88% Hamamelis Virginiana (Witch Hazel) Water. Unpublished data submitted by Personal Care Products Council.

59. Clinical Research Laboratories Inc. 2006. Repeated insult patch test of a tanning spray containing 6.02% Hamamelis Virginiana (Witch Hazel) Water. Unpublished data submitted by Personal Care Products Council.

60. Wolff HH and Kieser M. Hamamelis in children with skin disorders and skin injuries: results of an observational study. *European Journal of Pediatrics*. 2007;166(9):943-948.

61. Paulsen E, Christensen LP, and Andersen KE. Cosmetics and herbal remedies with Compositae plant extracts - are they tolerated by Compositae-allergic patients? *Contact Dermatitis*. 2008;58(1):15-23.

62. Bruynzeel DP, van Ketel WG, Young E, van Joost T, and Smeenk G. Contact sensitization by alternative topical medicaments containing plant extracts. *Contact Dermatitis*. 1992;27(4):278-279.

63. Hughes-Formella BJ, Bohnsack K, Rippke F, Benner G, Rudolph M, Tausch I, and Gassmueller J. Anti-inflammatory effect of Hamamelis lotion in a UVB erythema test. *Dermatology*. 1998;196(3):316-322.

64. Korting HC, Schäfer-Korting M, Hart H, Laux P, and Schmid M. Anti-inflammatory activity of hamamelis distillate applied topically to the skin. *European Journal of Clinical Pharmacology*. 1993;44(4):315-318.

65. Hughes-Formella BJ, Filbry A, Gassmueller J, and Rippke F. Anti-inflammatory efficacy of topical preparations with 10% hamamelis distillate in a UV erythema test. *Skin Pharmacology and Applied Skin Physiology*. 2002;15(2):125-132.

66. Korting HC, Schäfer-Korting M, Klõvekorn W, Klõvekorn G, Martin C, and Laux P. Comparative effeicacy of hamamelis distillate and hydrocortisone cream in atopic eczema. *European Journal of Clinical Pharmacology*. 1995;48(6):461-465.

67. Granlund H. Contact allergy to witch hazel. *Contact Dermatitis*. 1994;31(3):195

68. Vellosa JC, Regasini LO, Belló C, Schemberger JA, Khalil NM, deAraújo Morandim-Giannetti A, daSilva Bolzani V, Brunetti IL, and de Faria Oliveria OM. Preliminary in vitro and ex vivo evaluation of afzelin, daempferitrin, and pterogynoside action over free radicals and reactive oxygen species. *Archives of Pharmcal Research*. 2015;38(6):1168-1177.

69. Hawley's Condensed Chemical Dictionary. 15 *ed*. Hoboken, NJ: John Wiley & Sons, Inc., 2007.

70. Lover CW. Chemexfoliation--indications and cautions. *Journal of the American Academy of Dermatology*. 1987;17(1):109-112.

71. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, and Lines TC. A critical review of the data related to the safety of quercetin and lack of evidene of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. *Food and Chemical Toxicology*. 2007;45(11):2179-2205.

72. Poginsky B, Westendorf N, Prosenc N, Kuppe M, and Marquardt H. St. John's wort (*Hypericum perforatum* L.). Genotoxicity induced by quercetin content. *Deutsche Apotheker Zeitung*. 1988;128:13464-13466.

73. National Toxicology Program (NTP). 14th report on carcinogens (RoC) - Safrole CAS No. 94-59-7. Triangle Park, NC, National Institute of Environmental Health Sciences. 2016. http://ntp.niehs.nih.gov/ntp/roc/content/profiles/safrole.pdf. pp. 1-2.

74. Active Concepts. 2017. Dermal and ocular irritation tests ABS Witch Hazel Extract Sil (Hamamelis Virginiana (Witch Hazel) Extract). Unpublished data submitted by Personal Care Products Council.

2017 VCRP Data – *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients

01A - Baby Shampoos	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
02B - Bubble Baths	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
03D - Eye Lotion	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	7
03E - Eye Makeup Remover	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
03G - Other Eye Makeup Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	6
05A - Hair Conditioner	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
05I - Other Hair Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
07C - Foundations	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
07E - Lipstick	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
07F - Makeup Bases	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
07I - Other Makeup Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
08B - Cuticle Softeners	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
08G - Other Manicuring Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
10B - Deodorants (underarm)	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	2
10E - Other Personal Cleanliness Products	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	4
11A - Aftershave Lotion	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	2
11E - Shaving Cream	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	3
12A - Cleansing	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	15
12B - Depilatories	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	1
12C - Face and Neck (exc shave)	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	23
12D - Body and Hand (exc shave)	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	3
12F - Moisturizing	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	11
12G - Night	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	2
12H - Paste Masks (mud packs)	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	11
12I - Skin Fresheners	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	7
12J - Other Skin Care Preps	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	17
13B - Indoor Tanning Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) BARK/LEAF/TWIG EXTRACT	3
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02C - Bath Capsules	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	2
03D - Eye Lotion	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	6
03E - Eye Makeup Remover	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
03F - Mascara	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
03G - Other Eye Makeup Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	4
04C - Powders (dusting and talcum, excluding aftershave talc)	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
04E - Other Fragrance Preparation	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
05A - Hair Conditioner	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
05B - Hair Spray (aerosol fixatives)	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
05F - Shampoos (non-coloring)	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	2
07C - Foundations	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	4
07F - Makeup Bases	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
07I - Other Makeup Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
08G - Other Manicuring Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	2
10A - Bath Soaps and Detergents	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	8
10B - Deodorants (underarm)	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	3
10E - Other Personal Cleanliness Products	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	3
11A - Aftershave Lotion	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	6
11E - Shaving Cream	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	1
11G - Other Shaving Preparation Products	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	4
12A - Cleansing	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	47
12B - Depilatories	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	8
12C - Face and Neck (exc shave)	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	119
12D - Body and Hand (exc shave)	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	9
12F - Moisturizing	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	56
12G - Night	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	5
12H - Paste Masks (mud packs)	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	15
12I - Skin Fresheners	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	11
12J - Other Skin Care Preps	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	28
13B - Indoor Tanning Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) EXTRACT	5
		359

02B - Bubble Baths	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	5
02D - Other Bath Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	2
03D - Eye Lotion	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	5
03G - Other Eye Makeup Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	4
05A - Hair Conditioner	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	8
05B - Hair Spray (aerosol fixatives)	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	1
05F - Shampoos (non-coloring)	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	12
05G - Tonics, Dressings, and Other Hair Grooming Aids	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	1
05I - Other Hair Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	1
07B - Face Powders	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	1
10A - Bath Soaps and Detergents	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	13
10B - Deodorants (underarm)	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	6
10E - Other Personal Cleanliness Products	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	4
11A - Aftershave Lotion	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	3
11E - Shaving Cream	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	4
12A - Cleansing	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	23
12C - Face and Neck (exc shave)	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	48
12D - Body and Hand (exc shave)	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	17
12F - Moisturizing	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	21
12G - Night	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	3
12H - Paste Masks (mud packs)	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	5
12I - Skin Fresheners	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	16
12J - Other Skin Care Preps	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	12
13B - Indoor Tanning Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) LEAF EXTRACT	3
		218

01A - Baby Shampoos	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	1
01B - Baby Lotions, Oils, Powders, and Creams	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	2
01C - Other Baby Products	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	1
02A - Bath Oils, Tablets, and Salts	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	1
02B - Bubble Baths	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	5
02D - Other Bath Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	3

03D - Eye Lotion	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	7
03E - Eye Makeup Remover	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	3
03F - Mascara	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	2
03G - Other Eye Makeup Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	9
05A - Hair Conditioner	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	4
05C - Hair Straighteners	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	2
05D - Permanent Waves	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	2
05F - Shampoos (non-coloring)	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	9
05G - Tonics, Dressings, and Other Hair Grooming Aids	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	4
05I - Other Hair Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	2
07F - Makeup Bases	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	1
07H - Makeup Fixatives	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	1
07I - Other Makeup Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	3
08B - Cuticle Softeners	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	1
09B - Mouthwashes and Breath Fresheners	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	5
10A - Bath Soaps and Detergents	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	26
10B - Deodorants (underarm)	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	14
10E - Other Personal Cleanliness Products	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	5
11A - Aftershave Lotion	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	19
12A - Cleansing	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	54
12C - Face and Neck (exc shave)	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	60
12D - Body and Hand (exc shave)	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	21
12F - Moisturizing	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	34
12G - Night	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	7
12H - Paste Masks (mud packs)	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	11
12I - Skin Fresheners	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	32
12J - Other Skin Care Preps	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	25
13A - Suntan Gels, Creams, and Liquids	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	1
13B - Indoor Tanning Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	7
13C - Other Suntan Preparations	HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER	2
		386

02A - Bath Oils, Tablets, and Salts	HAMAMELIS VIRGINIANA FLOWER WATER	1
03D - Eye Lotion	HAMAMELIS VIRGINIANA FLOWER WATER	2
03G - Other Eye Makeup Preparations	HAMAMELIS VIRGINIANA FLOWER WATER	1
07A - Blushers (all types)	HAMAMELIS VIRGINIANA FLOWER WATER	1
07C - Foundations	HAMAMELIS VIRGINIANA FLOWER WATER	1
07I - Other Makeup Preparations	HAMAMELIS VIRGINIANA FLOWER WATER	1
10A - Bath Soaps and Detergents	HAMAMELIS VIRGINIANA FLOWER WATER	7
12A - Cleansing	HAMAMELIS VIRGINIANA FLOWER WATER	11
12C - Face and Neck (exc shave)	HAMAMELIS VIRGINIANA FLOWER WATER	3
12D - Body and Hand (exc shave)	HAMAMELIS VIRGINIANA FLOWER WATER	3
12F - Moisturizing	HAMAMELIS VIRGINIANA FLOWER WATER	5
12G - Night	HAMAMELIS VIRGINIANA FLOWER WATER	1
12H - Paste Masks (mud packs)	HAMAMELIS VIRGINIANA FLOWER WATER	3
12J - Other Skin Care Preps	HAMAMELIS VIRGINIANA FLOWER WATER	3
		43

There were no reported uses in the 2017 VCRP for:
Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract
Hamamelis Virginiana (Witch Hazel) Bark Twig Extract
Hamamelis Virginiana (Witch Hazel) Leaf Water

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D., Interim Director
COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: September 5, 2017

SUBJECT: Hamamelis Virginiana (Witch Hazel) Water

Anonymous. 2015. Summary of study of acute compatibility of a test item: 48-hours occlusive patch test of a face tonic with 8.5% Hamamelis Virginiana (Witch Hazel) Water.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Study title	**STUDY OF ACUTE SKIN COMPATIBILITY OF A TEST ITEM: 48-HOURS OCCLUSIVE PATCH-TEST**
Product	***FACE TONIC LOTION WITH 8.5% OF HAMAMELIS VIRGINIANA (WITCH HAZEL) WATER***
Study dates	From September 29 to October 2, 2015
Objective of study	Assess the irritant potential of the studied test item after its unique application, maintained for 48 hours in contact with the skin, with the help of an occlusive patch.
Application conditions	Single application of 25 µl of the studied test item pure, on the scapular part of the back, maintained for 48 hours in contact with the skin, with the help of an occlusive patch (Finn Chamber).
Assessment methods	The clinical quotation is made 30 minutes after the patch removal and 24 hours later. It takes in account the erythema and oedema. According to their intensity, the quotation is spread out from 0 to 3. The total sum of the scores, divided by the number of readings and then the number of subjects, defines the Mean Cumulative Irritation Index (MCII), which allows to classify arbitrarily the test item according the following scale: - MCII < 0,25 : non irritating - 0,25 ≤ MCII < 0,50 : very slightly irritating - 0,50 ≤ MCII < 1 : slightly irritating - 1 ≤ MCII < 2 : moderately irritating - MCII ≥ 2 : irritating
Volunteers' characteristics	11 volunteers of the female or male sex, from 23 to 68 years old, with phototype I to III, without any cutaneous pathology on the experimental area, were analyzed.
Results	Mean Cumulative Irritation Index (MCII) of the test item : 0.00
Conclusion	The test item applied pure, can be considered as **non irritant** after an application with the help of an occlusive patch (Finn Chambers) for 48 consecutive hours on 11 volunteers.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D., Interim Director
COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: September 7, 2017

SUBJECT: Hamamelis Virginiana (Witch Hazel) Water

Clinical Research Laboratories, Inc. 2006. Repeated insult patch test of a tanning spray containing 6.02% Hamamelis Virginiana (Witch Hazel) Water.

Clinical Research Laboratories, Inc. 2006. Safety-in-use study to determine the ocular and dermal irritation potential and comedogenic-acnegenic potential of a cosmetic product (sunless tanner containing 6.02% Hamamelis Virginiana (Witch Hazel) Water).

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Clinical Research Laboratories, Inc.

Final Report

Repeated Insult Patch Test

CLIENT: [redacted]

ATTENTION: Manager Product Safety - Toxicology

TEST MATERIAL: 2006.573.001 Tanning Spray
contains 6.02% Hamamelis Virginiana (Witch Hazel) Water

CRL STUDY NUMBER: CRL132406-1

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

George J. Neumaier, M.D.
Diplomate American Board of Dermatology

REPORT DATE: December 29, 2006

371 Hoes Lane • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Good Clinical Practice Quality Assurance Audit Statement

Clinical Study Number: CRL132406-1

Start Date: November 8, 2006

Completion Date: December 15, 2006

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted, as indicated below.

Signature of QA Auditor

12/29/06
Date

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by [redacted] and was received by Clinical Research Laboratories, Inc. on November 6, 2006:

Test Material	Test Condition	Patch Type
2006.573.001 Tanning Spray	Test as received	Occlusive*

The test material was coded with the following CRL identification number:

CRL132406-1

STUDY DATES

This study was initiated on November 8, 2006 and was completed on December 15, 2006.

* Occlusive Strip with Flexcon® (TruMed Technologies Inc., Burnsville, Minnesota)

PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix 1). Subjects who met the following criteria were impaneled:

- Male and female panelists between the ages of 18 and 70;
- Subjects who have completed a Panelist Profile/Medical History;
- Subjects who are in general good health as determined by a Panelist Profile/Medical History;
- Subjects who do not exhibit any skin diseases that might be confused with a skin reaction from the test material;
- Subjects willing to sign an Informed Consent Form in conformance with 21 CFR Part 50: "Protection of Human Subjects";
- Subjects who have completed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164;
- Females who are not pregnant or lactating;
- Subjects who demonstrate dependability and intelligence in following directions;
- Subjects who are not currently using any systemic or topical corticosteroids, anti-inflammatory drugs or antihistamines.

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

TEST METHOD (Continued)

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0 No visible skin reaction
± Barely perceptible erythema
1+ Mild erythema
2+ Well defined erythema
3+ Erythema and edema
4+ Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

RESULTS

This study was initiated with 112 subjects. Five subjects discontinued study participation for reasons unrelated to the test material. A total of 107 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table 1.

CONCLUSION

Based on the test population of 107 subjects and under the conditions of this study, the test material identified as 2006.573.001 Tanning Spray did not demonstrate a clinically significant potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedure 30.6C, unless designated otherwise by the Sponsor.

TABLE I

Summary of Dermal Scores

Test Material:	2006.573.001 Tanning Spray

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	±	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	Discontinued										
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	±	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	±	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	±	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	2006.573.001 Tanning Spray

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	±	±	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	±	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	±	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	±	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	Discontinued									

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	2006.573.001 Tanning Spray

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	±	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	±	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	±	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	±	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	2006.573.001 Tanning Spray

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	Discontinued										
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	±	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	Discontinued										
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	±	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	±	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	2006.573.001 Tanning Spray

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	Discontinued									
106	0	0	0	±	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	±	0	0	0	0	0	0
111	0	0	0	0	0	0	0	0	0	0	0	0
112	0	0	0	0	0	0	0	0	0	0	0	0

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1	DF	16692	44	F
2	DR	13607	53	F
3	NP	16915	39	M
4	DL	16927	40	F
5	JP	15332	28	F
6	AR	13392	62	F
7	CS	03643	50	F
8	MK	11942	30	F
9	RN	14458	30	F
10	LM	13745	58	F
11	RK	15853	58	M
12	DM	15498	56	F
13	SF	16570	37	F
14	JL	16904	20	F
15	KT	06277	47	F
16	BW	01644	62	F
17	BA	00164	43	F
18	JH	14416	70	F
19	VS	04571	34	F
20	RF	10436	69	F
21	GB	16920	62	F
22	NB	16907	50	M
23	FJ	06137	57	F
24	KM	16945	18	M
25	AL	13686	24	F
26	NG	15376	48	F
27	KB	16908	33	F
28	AG	15019	23	M

Subject Number	Subject Initials	CRL ID #	Age	Sex
29	JM	16167	45	F
30	AM	03950	43	F
31	AJ	06417	23	M
32	SR	15278	37	F
33	TW	16946	26	F
34	CL	14050	37	F
35	PL	16070	50	M
36	HV	16925	33	F
37	BT	16924	33	F
38	TS	16923	33	F
39	TD	16941	26	F
40	RM	16898	39	M
41	SV	14673	42	F
42	EW	00641	47	F
43	MM	15443	41	F
44	CC	16466	37	F
45	JB	07118	56	F
46	MD	05390	42	F
47	EA	16434	52	M
48	ME	01155	40	F
49	JB	16948	19	F
50	JB	16949	22	F
51	CP	16909	40	F
52	BG	16881	18	F
53	EM	15780	43	F
54	IC	16936	23	F
55	DD	16939	44	F
56	KL	16938	45	F

Appendix I
(Continued)

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
57	ML	04505	60	F
58	AS	16835	18	F
59	RP	16277	36	M
60	JR	13614	40	M
61	MM	13272	46	M
62	ML	10358	67	F
63	EP	15970	37	M
64	ML	15969	36	F
65	MH	16578	26	F
66	HP	16952	44	F
67	MH	01132	64	F
68	DP	16953	44	F
69	CW	10921	48	F
70	SB	16902	43	F
71	BR	16931	39	F
72	SD	16061	54	F
73	AR	16601	50	M
74	JM	10420	32	F
75	TN	15013	21	F
76	CK	08194	43	F
77	PC	10458	40	F
78	SB	02933	50	F
79	DH	14887	28	F
80	RS	05543	36	M
81	RS	05432	66	M
82	VD	12265	42	F
83	JB	11594	49	M
84	SB	11593	55	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
85	SC	16517	35	F
86	JR	16507	31	F
87	MH	16961	28	M
88	JR	16569	59	F
89	WP	06629	37	F
90	PS	16963	28	F
91	LP	16472	56	M
92	VM	16964	40	F
93	CD	16965	19	F
94	AS	16567	30	F
95	MT	16967	44	F
96	BL	16966	31	F
97	LJ	11123	28	F
98	HP	16504	51	F
99	RS	09790	52	F
100	LR	16971	42	F
101	KK	16166	35	F
102	CL	14646	67	F
103	WS	15796	44	F
104	WS	16976	24	M
105	JW	16916	42	F
106	FH	05729	35	F
107	CM	16628	42	F
108	DH	16337	44	F
109	LB	09989	45	M
110	MS	13316	34	F
111	JN	16977	36	F
112	BA	16158	63	F

Clinical Research Laboratories, Inc.

Final Report

Safety In-Use Study to Determine the Ocular and Dermal Irritation Potential and Comedogenic-Acnegenic Potential of a Cosmetic Product

CLIENT: [redacted]

ATTENTION: Manager, Product Safety Toxicology

TEST MATERIAL: Sunless Tanner 2005.425.003
contains 6.02% Hamamelis Virginiana (Witch Hazel) Water

CRL STUDY NUMBER: CRL132205

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
Ophthalmic Investigator
Diplomate American Board of Ophthalmology
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

Yang Gao, M.D.
Senior Medical Research
Scientist/Ophthalmologist

George J. Neumaier, M.D.
Diplomate American Board
of Dermatology

REPORT DATE: February 14, 2006

371 Hoes Lane • Piscataway, N.J. 08854 • (732) 981-1616 • FAX (732) 981-0520

Good Clinical Practice Quality Assurance Audit Statement

Clinical Study Number: CRL132205

Start Date: January 4, 2006

Completion Date: January 30, 2006

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted, as indicated below.

Signature of QA Auditor

Date

FINAL REPORT

Safety In-Use Study to Determine the Ocular and Dermal Irritation Potential and Comedogenic-Acnegenic Potential of a Cosmetic Product

PURPOSE

The purpose of this study was to evaluate the ocular and dermal irritation potential and comedogenic-acnegenic potential of Sunless Tanner 2005.425.003. The ocular evaluation included subjective ocular irritation responses including stinging, burning, itching, dryness, and foreign body sensation. In addition, this study assessed objective ophthalmic findings including lacrimation, eyelid integrity, palpebral and bulbar conjunctival irritation, corneal tissue involvement and contact lens changes during 4 weeks of use in contact lens wearers and normal eye non-contact lens wearers. A dermal examination included an evaluation of facial skin for erythema, edema, and dryness. Facial skin was examined for the presence of non-inflammatory and inflammatory lesions to assess the potential of the test material for comedogenicity-acnegenicity/pore clogging.

INVESTIGATORS

Bruce E. Kanengiser, M.D.
Diplomate American Board of Ophthalmology
President/Medical Director

Yang Gao, M.D.
Senior Medical Research Scientist/Ophthalmologist

George Neumaier, M.D.
Diplomate American Board of Dermatology

Clinical Research Laboratories, Inc.
371 Hoes Lane
Piscataway, New Jersey 08854
732-981-1616

SPONSOR

[redacted]

TEST MATERIAL

The following test material was provided by [redacted] and was received by Clinical Research Laboratories, Inc. on December 21, 2005:

Sunless Tanner 2005.425.003

The test material containers were weighed prior to distribution and at the end of the 4-week use period (Appendix II – Test Material Assignment and Weights).

STUDY DATES

This study was initiated on January 4, 2006 and was completed on January 30, 2006.

STUDY POPULATION

A total of 20 female subjects, ranging in age from to 18 to 59 years old and in general good health, were selected for the study (Panelist Demographics – Appendix I). Ten subjects (50%) wore contact lenses and 10 subjects (50%) were non-contact lens wearers. Each subject was assigned a permanent CRL Identification Number. All panelists signed an Informed Consent Form in conformance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164. All subjects completed a Panelist Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to study enrollment. Subjects who met the following criteria were impaneled for this study.

Subject Inclusion Criteria:

- Subject is female between 18 and 55 years of age [See STUDY RELATED COMMENT];
- Subject is free from any ocular or dermal disorders which may affect test results;
- Subject is willing to replace their normal moisturizer product with the test material and not to introduce any new cosmetic or personal care products;
- Subject has signed an Informed Consent Contract in compliance with 21 CFR Part 50: "Protection of Human Subjects";
- Subject is dependable and able to follow directions;
- Subject has completed a Panelist Profile/Medical History;
- Subject has completed a "HIPAA Authorization Form";
- Approximately one half of the panel will consist of contact lens wearers, which may include daily soft contact lenses, disposable soft contact lenses, extended wear soft contact lenses, hard contact lenses, and rigid gas permeable contact lenses;

STUDY POPULATION (Continued)

Subject Inclusion Criteria (Continued)

- Subjects must have a subjective ocular irritation score of 0 at the baseline examination. Subjective irritation is determined by ascertaining from the subject any experiences of ophthalmic irritation (i.e. stinging, burning, itching, dryness, and/or foreign body sensation) at the baseline visit. All subjects must have baseline lacrimation, eyelid, contact lens, and corneal scores of 0. Subjects may exhibit slight or mild [level 1 or 2] irritation of the palpebral and/or bulbar conjunctivae at the baseline examination. This latitude is permitted to allow for those subjects who normally exhibit slight or mild irritation as a result of their contact lens wear, and/or environmental and seasonal factors.

Subject Exclusion Criteria:

- Subject reports being pregnant or nursing;
- Subject has received treatment with sympathomimetics, antihistamines, vasoconstrictors, non-steroidal anti-inflammatory agents, and/or systemic or topical corticosteroids within one week prior to initiation of the study;
- Subject has known allergies to eye area products, cosmetics, sunscreens, or moisturizers;
- Subject has participated in an ocular or dermal study within one week of study initiation;
- Subject has participated in investigational systemic drug studies within 14 days of study initiation;
- Subject has a history of acute or chronic dermatologic, medical, physical, and/or ophthalmologic conditions (i.e. external ocular disease or infection of the eye and/or eyelids, history of recurrent erosion of the cornea) which would preclude application of the test material and/or could influence the outcome of the study;
- Subject is currently using any OTC ophthalmic preparations, excluding artificial tears and contact lens solutions, rewetting solutions, contact lens disinfectants, and lubricants.

METHOD

All subjects were instructed to arrive at Clinical Research Laboratories, Inc. not wearing any facial or eye make-up for their pre-test qualifying ophthalmic and dermal examinations. Prior to enrollment, all Inclusion/Exclusion Criteria were verified and an Informed Consent Form was obtained. Each subject was given baseline ophthalmic, dermal and comedogenic/acnegenic examinations. As each subject was accepted onto the panel, the subject was assigned the test material, which was labeled with CRL identification and subject numbers (Test Material Assignment and Weights - Appendix II).

METHOD (Continued)

Each subject was instructed to apply the test material according to the Sponsor's instructions (Appendix IV). Subjects were instructed not to introduce any new eye or facial products other than the assigned test material. Subjects were to continue with their normal cosmetic regimen, and to replace their usual sunless tanner with the test product. The subjects were instructed to record the dates of use and any other comments on the Daily Diary. The subjects were instructed to discontinue use and to call Clinical Research Laboratories, Inc. if they experienced any discomfort while using the assigned test product.

EXAMINATIONS

Ophthalmic Examinations

At the initial examination, all subjects were tested for baseline visual acuity using a Snellen Eye Chart. An ophthalmologist examined all subjects with a Haag-Streit Bern Model No. Z 2982A Slit Lamp Biomicroscope prior to inclusion on this panel. All subjective and objective ophthalmologic scores were recorded on an ocular examination form. Subjective irritation was determined by ascertaining from the subject if they were experiencing any ophthalmic irritation (i.e. stinging, burning, itching, dryness, and/or foreign body sensation) at the time of the specified visit. The ophthalmologist then examined each subject for evidence of excessive lacrimation. Each subject's upper and lower eyelids, specifically the eyelid margins and meibomian gland orifices, were examined for evidence of redness, scaling, swelling, and/or excessive meibomian secretions. The palpebral and bulbar conjunctivae were examined and scored for redness, follicular and/or papillary reactions using the Ophtbalmic Scoring Scale (Appendix III). The cornea was examined for evidence of any inflammation, edema, infiltrates, neovascularization, opacities, and/or epithelial defects. Soft contact lenses were evaluated for deposits and change in color. Rigid gas permeable contact lenses were examined for deposits and scratches.

Comedogenic/Dermal Examinations

On the first day of the study, facial skin was examined for erythema, edema, and dryness. In addition, facial skin was evaluated for non-inflammatory and inflammatory lesions and the number of each type of lesion was recorded for each of six areas of the face.

Final Examination

After approximately 4 weeks of product use, each subject's visual acuity was assessed using a Snellen Eye Chart. Subjective irritation status was once again determined, and ophthalmic, dermal, and comedogenic/acnegenic examinations were performed in the same manner as described for the baseline visit. Subjects completed a final questionnaire regarding product performance. Unused portions of the test materials were returned along with the Daily Diaries to Clinical Research Laboratories, Inc. at the final visit.

STUDY RELATED COMMENT

One subject (#4) exceeded the age inclusion range. The subject met all other qualification criteria and was allowed to participate. In the opinion of the Investigator, inclusion of this subject did not affect the integrity of the study.

TEST RESULTS

A total of 19 subjects completed the study. One subject (#1) discontinued study participation for reasons unrelated to test material use. Ophthalmic and dermal examination results appear in Tables I and II, respectively. Individual comedogenic examination results and statistical analysis of lesion counts appear in Tables III and IV, respectively. Questionnaire responses appear in Table V.

Daily Diaries

Comments recorded on the Daily Diary that were related to reactions or symptoms perceived during use of the test material included a report from subject #16 of "tingling" of facial skin, which lasted five minutes, following the last two test material applications. The subject completed the study with no modification to the schedule of application. There were no increases in ocular or dermal irritation or lesion counts at the final examination.

CONCLUSION

The ophthalmic evaluation of Sunless Tanner 2005.425.003 over a 4-week use period demonstrated trace increases in redness of the palpebral conjunctivae in only 1 subject. In the opinion of the Investigator, these findings were not related to the use of Sunless Tanner 2005.425.003 and were most probably caused by external factors such as hair products, mechanical factors, environmental and/or seasonal factors. There were no reports of subjective irritation at the final examination. There were no increases in lacrimation, eyelid inflammation, or bulbar conjunctival irritation. No changes in visual acuity, corneal tissue integrity, or contact lenses were observed.

The dermal evaluation of Sunless Tanner 2005.425.003 over a 4-week use period revealed no evidence of erythema, edema, or dryness of the face. No statistically significant change in facial lesions was observed following the 4 week use period.

Based on the test results of the subjective and objective ophthalmic and dermal evaluations following the 4-week use period, it was determined that the test material, Sunless Tanner 2005.425.003, did not demonstrate a potential for eliciting ophthalmic or dermal irritation. The test material did not elicit an increase in the number of acnegenic lesions. Therefore, the test material does not demonstrate a potential for comedogenicity/clogging pores. In this limited test population, the test material is clinically safe for use by normal eye non-contact lens wearers and contact lens wearers.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedure 30.6C, unless designated otherwise by the Sponsor.

Table I

Ophthalmic Examination Results

Maximum Increase from Baseline Examination

Subject Number	Subjective Irritation		Lacrimation		Eyelid Irritation (Upper/Lower)		Palpebral Conjunctival Irritation (Upper/Lower)		Bulbar Conjunctival Irritation		Cornea		Contact Lenses	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L
1	Discontinued Study Participation													
2	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
3	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
4	0	0	0	0	0/0	0/0	0/1	0/1	0	0	0	0	0	0
5	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
6	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
7	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
8	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
9	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
10	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
11	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
12	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
13	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
14	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
15	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
16	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
17	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
18	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
19	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
20	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA

The scoring scale for ophthalmic examinations appears in Appendix III
NA= Not Applicable. Subject is not a contact lens wearer.

R = Right Eye
L = Left Eye

Table II

Dermal Examination Results

Subject Number	Baseline Examination			Final Examination		
	Erythema	Edema	Dryness	Erythema	Edema	Dryness
1	Discontinued Study Participation					
2	1	1	1	1	1	1
3	1	1	1	1	1	1
4	1	1	1	1	1	1
5	1	1	1	1	1	1
6	1	1	1	1	1	1
7	1	1	1	1	1	1
8	1	1	1	1	1	1
9	1	1	1	1	1	1
10	1	1	1	1	1	1
11	1	1	1	1	1	1
12	1	1	1	1	1	1
13	1	1	1	1	1	1
14	1	1	1	1	1	1
15	1	1	1	1	1	1
16	1	1	1	1	1	1
17	1	1	1	1	1	1
18	1	1	1	1	1	1
19	1	1	1	1	1	1
20	1	1	1	1	1	1

Dermal Scoring Scale:(Erythema/Edema/Dryness)

1 = None
2 = Mild
3 = Moderate
4 = Severe

Table III

Comedogenic Examination Results

Subject Number	Total Lesion Count		Difference from Baseline
	Baseline	Final	
1	Discontinued Study Participation		
2	4	4	0
3	9	9	0
4	0	2	2
5	1	0	-1
6	2	6	4
7	3	3	0
8	5	2	-3
9	1	2	1
10	3	3	0
11	4	3	-1
12	2	4	2
13	5	2	-3
14	6	8	2
15	3	0	-3
16	6	5	-1
17	4	4	0
18	4	5	1
19	27	15	-12
20	2	2	0
Mean	**4.8**	**4.2**	**-0.6**
St. Dev.	**5.8**	**3.5**	**3.3**

Table IV

Statistical Analysis of Comedogenic Examination Results

	Average Total Lesion Count	
	Baseline	*Final*
Mean	4.8	4.2
Variance	33.4	12.4
Observations	19	19
Pearson Correlation	0.86	
Hypothesized Mean Difference	0	
df	18	
t Stat	0.83	
P(T<=t) one-tail	0.21	
t Critical one-tail	1.73	
P(T<=t) two-tail	0.42	
t Critical two-tail	2.10	

Appendix I

Panelist Demographics

Subject Number	Subject Initials	CRL ID #	Eye Type	Age	Sex
1	SW	20430	NCLW	36	F
2	SL	19734	NCLW	32	F
3	MG	12004	NCLW	35	F
4	RM	20441	DISP	57	F
5	JW	16392	NCLW	39	F
6	DC	19109	NCLW	45	F
7	PH	01487	NCLW	40	F
8	AK	07712	NCLW	46	F
9	KL	17225	NCLW	29	F
10	SL	08078	DISP	42	F
11	DK	18318	DISP	33	F
12	VP	09263	RGP	50	F
13	ME	01693	DSCL	50	F
14	TB	09913	DISP	37	F
15	BT	14310	DISP	49	F
16	LK	12338	DISP	46	F
17	RA	20421	NCLW	48	F
18	SB	20325	DISP	19	F
19	LL	07781	DSCL	18	F
20	MG	14013	NCLW	36	F

Eye Type:
DISP = Disposable Soft Contact Lenses
DSCL = Daily Soft Contact Lenses
RGP = Rigid Gas Permeable
NCLW = Normal Eye Non-Contact Lens Wearer

Appendix II

Test Material Assignment and Weights

Subject Number	Subject Initials	CRL ID #	Baseline (grams)	Final (grams)	Difference (grams)
1	SW	20430	133.0	Discontinued	
2	SL	19734	133.1	100.3	32.8
3	MG	12004	134.4	116.6	17.8
4	RM	20441	132.3	90.2	42.1
5	JW	16392	133.9	118.8	15.1
6	DC	19109	133.4	113.9	19.5
7	PH	01487	132.5	110.4	22.1
8	AK	07712	134.1	124.6	9.5
9	KL	17225	132.9	123.9	9.0
10	SL	08078	132.8	102.7	30.1
11	DK	18318	131.9	90.9	41.0
12	VP	09263	132.4	120.1	12.3
13	ME	01693	132.5	123.3	9.2
14	TB	09913	133.5	124.5	9.0
15	BT	14310	134.6	89.0	45.6
16	LK	12338	132.6	111.2	21.4
17	RA	20421	132.7	114.7	18.0
18	SB	20325	133.0	107.1	25.9
19	LL	07781	133.2	124.5	8.7
20	MG	14013	132.5	110.6	21.9

Appendix III
Ophthalmic Scoring Scales

Subjective Ophthalmic Scoring Scale

Subjective Irritation (stinging, burning, itching, dryness, and/or foreign body sensation)

0 = None
1 = Slight
2 = Mild
3 = Moderate
4 = Severe

Objective Ophthalmic Scoring Scale (Slit Lamp Biomicroscope Examination)

Lacrimation
0 = Normal tear production (no excess wetness)
1 = Trace increase in wetness
2 = Mild increase in wetness (no distinct formed tears)
3 = A few formed tears (contained within the cul de sac and on surface of globe)
4 = Intense tearing (leaving cul de sac and globe, wetting lids and face)

Eyelids (redness, scaling, swelling, and/or meibomian secretions)
0 = No evidence of inflammation
1 = Trace inflammation
2 = Mild inflammation
3 = Moderate inflammation
4 = Severe inflammation

Palpebral Conjunctival Irritation
0 = No evidence of inflammation
1 = Trace redness (very mild inflammation)
2 = Mild redness (mild inflammation)
3 = Moderate redness (moderate inflammation)
4 = Marked, intense redness (severe inflammation)

Bulbar Conjunctival Irritation
0 = No evidence of inflammation
1 = Trace redness (very mild inflammation)
2 = Mild redness (mild inflammation)
3 = Moderate redness, some dilation of blood vessels (moderate inflammation)
4 = Marked, intense redness several dilated blood vessels (severe inflammation)

Cornea (opacities, edema, infiltrates, neovascularization, and/or epithelial defects)
0 = Normal, no abnormality
1 = Trace, very mild abnormality
2 = Mild abnormality
3 = Moderate abnormality
4 = Severe abnormality

Contact Lens Evaluation

Scratches
0 = None
1 = Slight
2 = Mild
3 = Moderate
4 = Severe

Deposits
0 = None
1 = Slight
2 = Mild
3 = Moderate
4 = Severe

Color
0 = No change in color
1 = Slight change in color
2 = Mild change in color
3 = Moderate change in color
4 = Severe change in color

Appendix IV

Test Material Instructions

Apply the product at least once a day, only on days of use indicated on diary (for a total of 8 uses) for four weeks. After cleansing and exfoliating as you normally would, shake can well and hold it 6 inches from face. Close eyes, and spray with even sweeps across the entire face, for even application. Allow to dry before applying your usual cosmetics, if applicable. Wait at least 1 hour before washing, showering or swimming. Avoid spraying directly into eyes. If eye irritation occurs, rinse thoroughly with water.

Memorandum

TO: Bart Heldreth, Ph.D., Executive Director
COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: October 16, 2017

SUBJECT: Updated Concentration of Use by FDA Product Category: Witch Hazel-Derived Ingredients

Concentration of Use by FDA Product Category – *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients*

Hamamelis Virginiana (Witch Hazel) Water
Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract
Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract
Hamamelis Virginiana (Witch Hazel) Extract
Hamamelis Virginiana (Witch Hazel) Flower Water
Hamamelis Virginiana (Witch Hazel) Leaf Extract
Hamamelis Virginiana (Witch Hazel) Leaf Water

Ingredient	Product Category	Maximum Concentration of Use
Hamamelis Virginiana (Witch Hazel) Water	Bubble baths	0.43%
Hamamelis Virginiana (Witch Hazel) Water	Eye lotions	1.4-30.6%
Hamamelis Virginiana (Witch Hazel) Water	Eye makeup removers	2%
Hamamelis Virginiana (Witch Hazel) Water	Other eye makeup preparations	0.04%
Hamamelis Virginiana (Witch Hazel) Water	Colognes and toilet waters	0.00008-0.43%
Hamamelis Virginiana (Witch Hazel) Water	Hair conditioners	0.26%
Hamamelis Virginiana (Witch Hazel) Water	Shampoos (noncoloring)	0.86-2.5%
Hamamelis Virginiana (Witch Hazel) Water	Face powders	0.043-0.093%
Hamamelis Virginiana (Witch Hazel) Water	Foundations	0.0013-0.043%
Hamamelis Virginiana (Witch Hazel) Water	Lipstick	0.1-30.6%
Hamamelis Virginiana (Witch Hazel) Water	Other manicuring preparations	4.3%
Hamamelis Virginiana (Witch Hazel) Water	Bath soaps and detergents	0.1-0.89%
Hamamelis Virginiana (Witch Hazel) Water	Deodorants Not spray	 0.086-5.2%
Hamamelis Virginiana (Witch Hazel) Water	Feminine hygiene deodorants	0.0086%
Hamamelis Virginiana (Witch Hazel) Water	Other personal cleanliness products	0.0086-1.5%
Hamamelis Virginiana (Witch Hazel) Water	Aftershave lotions	0.0024-4.3%
Hamamelis Virginiana (Witch Hazel) Water	Shaving cream	0.0074-0.45%
Hamamelis Virginiana (Witch Hazel) Water	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0013-33.3%
Hamamelis Virginiana (Witch Hazel) Water	Face and neck products Not spray	 0.00066-8.5%
Hamamelis Virginiana (Witch Hazel) Water	Body and hand products Not spray Spray	 0.0013-4.3% 4.3-25.8%
Hamamelis Virginiana (Witch Hazel) Water	Paste masks and mud packs	0.00066-5%
Hamamelis Virginiana (Witch Hazel) Water	Skin fresheners	0.00086-1%
Hamamelis Virginiana (Witch Hazel) Water	Other skin care preparations	0.0013-43%
Hamamelis Virginiana (Witch Hazel) Water	Suntan products Pump spray	 8.9%
Hamamelis Virginiana (Witch Hazel) Water	Indoor tanning preparation	6.1%
Hamamelis Virginiana (Witch Hazel)	Shaving cream	0.0035%

Bark/Leaf/Twig Extract		
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0005-0.072%
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	Face and neck products Not spray	 0.004-4.3%
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	Moisturizing products Not spray	 0.072%
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	Night products Not spray	 0.00005%
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	Paste masks and mud packs	0.00005%
Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract	Skin fresheners	0.18%
Hamamelis Virginiana (Witch Hazel) Extract	Bath oils, tablets and salts	0.000013-0.0001%
Hamamelis Virginiana (Witch Hazel) Extract	Other bath preparations	0.000013%
Hamamelis Virginiana (Witch Hazel) Extract	Eye lotions	0.1%
Hamamelis Virginiana (Witch Hazel) Extract	Colognes and toilet waters	0.00003%
Hamamelis Virginiana (Witch Hazel) Extract	Hair conditioners	0.3%
Hamamelis Virginiana (Witch Hazel) Extract	Hair sprays Pump spray	 0.0001%
Hamamelis Virginiana (Witch Hazel) Extract	Foundations	0.003-0.02%
Hamamelis Virginiana (Witch Hazel) Extract	Bath soaps and detergents	1%
Hamamelis Virginiana (Witch Hazel) Extract	Deodorants Not spray Aerosol	 0.0013% 0.0013%
Hamamelis Virginiana (Witch Hazel) Extract	Aftershave lotions	0.0026-0.3%
Hamamelis Virginiana (Witch Hazel) Extract	Other shaving preparations	0.0013%
Hamamelis Virginiana (Witch Hazel) Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0001-1.8%
Hamamelis Virginiana (Witch Hazel) Extract	Depilatories	0.000013%
Hamamelis Virginiana (Witch Hazel) Extract	Face and neck products Not spray	 0.0001-1.8%
Hamamelis Virginiana (Witch Hazel) Extract	Body and hand products Not spray Spray	 0.0001-0.5% 0.03%
Hamamelis Virginiana (Witch Hazel) Extract	Moisturizing products Not spray	 0.0013-0.0034%
Hamamelis Virginiana (Witch Hazel) Extract	Night products Not spray	 0.12%
Hamamelis Virginiana (Witch Hazel) Extract	Paste masks and mud packs	0.0034%
Hamamelis Virginiana (Witch Hazel) Extract	Skin fresheners	0.5% (86%**)
Hamamelis Virginiana (Witch Hazel) Extract	Other skin care preparations	0.0013-1.1%
Hamamelis Virginiana (Witch Hazel) Extract	Indoor tanning preparations	0.0013%
Hamamelis Virginiana (Witch Hazel) Leaf	Hair conditioners	0.00042%

Extract		
Hamamelis Virginiana (Witch Hazel) Leaf Extract	Shampoos (noncoloring)	0.00035%
Hamamelis Virginiana (Witch Hazel) Leaf Extract	Tonics, dressings and other hair grooming aids	0.00035%
Hamamelis Virginiana (Witch Hazel) Leaf Extract	Deodorants Not spray	0.00018%
Hamamelis Virginiana (Witch Hazel) Leaf Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00035-0.01%
Hamamelis Virginiana (Witch Hazel) Leaf Extract	Face and neck products Not spray	0.0018%
Hamamelis Virginiana (Witch Hazel) Leaf Extract	Body and hand products Not spray	0.011%
Hamamelis Virginiana (Witch Hazel) Leaf Water	Paste masks and mud packs	0.67-4.1%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

**86% Hamamelis Virginiana (Witch Hazel) Extract skin freshener is an OTC skin astringent.

Information collected in 2016-2017

Table prepared: February 1, 2017

Revised August 17, 2017: Hamamelis Virginiana (Witch Hazel) Water in non-spray deodorants changed from 5.2% from 6%; added ** for 86% Hamamelis Virginiana (Witch Hazel) Extract product; Hamamelis Virginiana (Witch Hazel) Leaf Water paste masks and mud packs concentration range changed from 4.1-5% to 0.67 to 4.1%

Updated September 20, 2017: Hamamelis Virginiana (Witch Hazel) Water: Foundations changed from 4.3% to 0.0013%; Aftershave lotions changed from 0.9-8% to 0.0024-4.3%; skin cleansing low concentration changed from 0.01% to 0.0013%; face and neck products high concentration changed from 12.9% to 8.5%; body and hand products low concentration changed from 0.1% to 0.0013%; other skin care products low concentration changed from 0.5% to 0.0013%; Hamamelis Virginiana (Witch Hazel) Extract skin fresheners in addition to the 86% OTC product only one other concentration was reported for skin fresheners, 0.5%; Hamamelis Virginiana (Witch Hazel) Extract 6.1% in Indoor tanning preparation was actually Hamamelis Virginiana (Witch Hazel) Water.

Updated October 16, 2017: multiple changes resulting from a company miscoding Hamamelis Virginiana (Witch Hazel) Water as Hamamelis Virginiana (Witch Hazel) Extract and indicating the concentration as 100% Extract when it contains 85.5% of the Water.

Tue 10/3/2017

Hi Bart,

Attached is a summary of the witch hazel outcome based on supplier feedback. Aside from some minor name assignment changes (e.g., from g/s bark/leaf/twig extract to g/s leaf/extract), the proposed actions are:

1. Hamamelis Virginiana (Witch Hazel) Water is accurate (name and definition).
2. Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract will be proposed for deletion.
3. Hamamelis Virginiana (Witch Hazel) Leaf Water will be proposed for deletion.
4. Hamamelis Virginiana (Witch Hazel) Flower Water will be proposed for deletion.
5. Hamamelis Virginiana (Witch Hazel) Extract (name and definition) is pending reconfirmation of plant part.
6. CAS 84696-19-5 and CAS 68916-39-2 will be added to all witch hazel monographs as generic entries.

Let me know if you have any Qs, and when we hear back from the single supplier who indicates their extract is from the “whole” plant, I will let you know.

Joanne

Witch Hazel

Summary
In conjunction with the CIR review of witch hazel ingredients, suppliers were contacted to clarify the plant part(s) and preparation type for their products listed in the INCI monographs below. Responses were received for about 40% of the commercial materials.

Extracts:

- Hamamelis Virginiana (Witch Hazel) Extract
- Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract
- Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract
- Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract
- Hamamelis Virginiana (Witch Hazel) Leaf Extract

Waters:

- Hamamelis Virginiana (Witch Hazel) Flower Water
- Hamamelis Virginiana (Witch Hazel) Leaf Water
- Hamamelis Virginiana (Witch Hazel) Water

Conclusions

- The names assigned as Hamamelis Virginiana (Witch Hazel) Water are accurate based on the INCI monograph definition which includes the bark, twig and/or leaf.
- One product assigned as Hamamelis Virginiana (Witch Hazel) Leaf Water will be changed to Hamamelis Virginiana (Witch Hazel) Leaf Extract based on supplier information about process.
- The INCI names for the extract monographs are accurate with regard to plant part and preparation, with the exception of the single product named as Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract; it is prepared through distillation and will be re-assigned as Hamamelis Virginiana (Witch Hazel) Water. Consequently, Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract will be proposed for deletion because when the aforementioned reassignment is completed, the monograph will have no suppliers listed.

Recommendations

- The monograph for Hamamelis Virginiana (Witch Hazel) Leaf Water should be deleted and the corresponding name assignments be amended as Hamamelis Virginiana (Witch Hazel) Water, since the latter includes leaf by definition.
- CAS 84696-19-5 and CAS 68916-39-2 should be included for all the witch hazel monographs as generic entries.

Other considerations

- Hamamelis Virginiana (Witch Hazel) Flower Water should be proposed for deletion. Only one supplier is listed in this monograph, and the supplier did not respond to the info request. Furthermore, no suppliers indicated they were using “flower” as a plant part for any of the preparations.
- The supplier related to the monograph Hamamelis Virginiana (Witch Hazel) Extract will be contacted again to re-confirm the entire plant is used for the extract.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Interim Director - COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: September 7, 2017

SUBJECT: Draft Report: Safety Assessment of *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients as Used in Cosmetics (draft prepared for the September 11-12, 2017 CIR Expert Panel Meeting)

Data Profile - The Use column still needs to be completed.
Impurities/Constituents - Please correct "courmarin"
Cosmetic Use, Summary - It should be stated that the product containing 86% Hamamelis Virginiana (Witch Hazel) Extract is actually an OTC astringent. This is indicated in the updated use information provided in Wave 2 (there is a footnote ** that says that this is an OTC product) - but is not mentioned in the Wave 2 memo.
Dermal Penetration - Although witch hazel may be available as a tea, for the average person, it is unlikely that dietary exposure to preparations from this plant is greater than dermal exposure. Are concentrations in cosmetics up to 43% really considered "very low concentrations"?
Subchronic - The oral study was from a 1972 published report[1]. Was an attempt made to obtain this paper? It is not clear why it states: "No further information was provided." If it is not possible to get the primary reference, it should state: "No further information was available."
Genotoxicity, In Vitro - Please correct: "stains"
Carcinogenicity - Did the minutes of the report review panel, or the publications in which the NTP study is mentioned, indicate why the NTP study was considered inadequate to prepare a technical report?

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[1]Bernard P, Balansard P, Balansard G, Bovis A. 1972. Valeur pharmacodynamique toniveineuse des préparations galéniques à base de feuilles d'hamamélis. [Venitonic pharmacodynamic value of galenic preparations with a base of Hamamelis leaves]. *J Pharm Belg*, 27(4): 505-512.

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Table 7 - Please include some indication of a dose or concentration at which the reported adverse effects occurred. These substances are generally at relatively low concentrations in plant preparations and so it is not possible to determine if the effects mentioned are really relevant without some indication of the effective dose/concentration. As safrole is listed in the NTP Report on Carcinogens (RoC) (reference 68), the conclusion should be stated: "reasonably anticipated to be a human carcinogen". It should also be noted that although other plants/spices are listed as sources of exposure in the RoC monograph on safrole, witch hazel is not listed.