Safety Assessment of Honey-Derived Ingredients as Used in Cosmetics

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

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

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Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer, CIR
Date: May 15, 2020
Subject: Draft Final Report on Honey Derived-Ingredients

Enclosed is the Draft Final Report on 7 honey-derived ingredients (identified by *honey062020rep* in the pdf document). The Panel reviewed this report for the first time at the December 2019 meeting, and concluded that these honey ingredients are safe in the present practices of use and concentration described in the safety assessment. The safety of these ingredients is further supported by frequent use in medical wound dressings and historical food use.

Comments on the Draft and Tentative Report were submitted by Council, and have been addressed (*honey062020pcpc1* and *honey062020pcpc2*, respectively). Other documents in this packet include history (*honey062020hist*), flow chart (*honey062020flow*), search strategy (*honey062020strat*), minutes from previous meetings (*honey062020min*), and data profile (*honey062020prof*). Updated 2020 VCRP data have also been included (*honey062020fda*), no significant changes from 2019 VCRP data were apparent.

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

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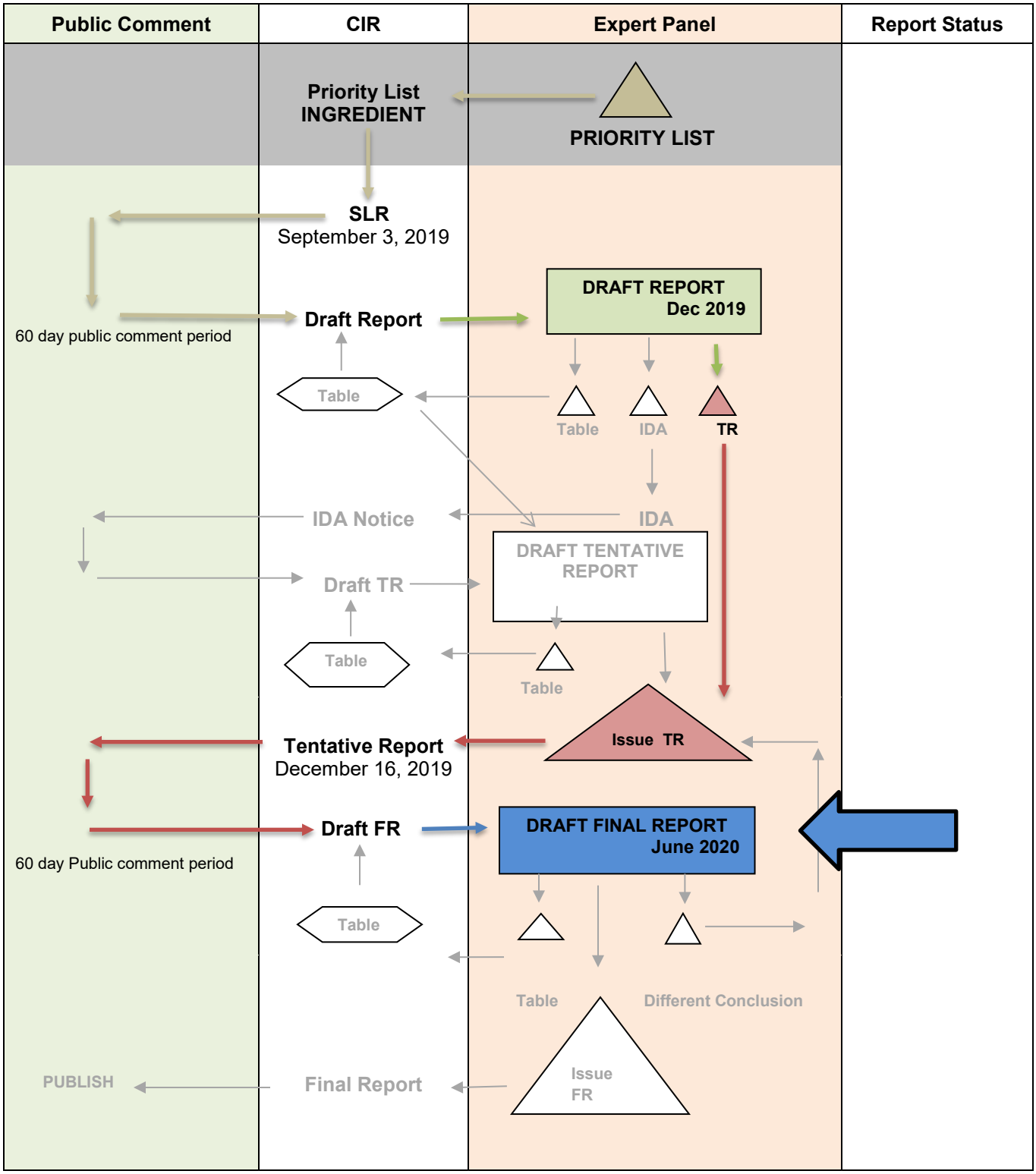
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Honey-derived ingredients

MEETING June 2020



CIR History of:

Honey ingredients

October 2018
-Concentration of use data submitted by Council

February 2019
-FDA frequency of use data obtained

September 2019
-Honey ingredients SLR posted on the CIR website
-The following unpublished data was submitted by Council:

- Manufacturing data on a trade name mixture containing 10.6% Honey Extract, 82.9% water, 4.4% propylene glycol dicaprylate/dicaprate, 1.5% phenoxyethanol, 0.3% xanthan gum, and 0.3% potassium sorbate
- Manufacturing data on a trade name mixture containing 16.5% Honey, 27.6% water, and 55.9% propylene glycol
- An HRIPT performed on 112 subjects using a test substance containing 7% Honey Extract. No signs of sensitization or irritation were reported in this study.

December 2019
-The Draft Report is reviewed by the Panel.
-The Panel issues a Tentative Report for public comment

January 2020
-Comments on the Tentative Report are received from Council
-2020 VCRP data received

June 2020
-The Draft Final Report is reviewed by the Panel

Honey Data Profile* – June 2020 – Writer, Priya Cherian																																
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Honey	X		X											X														X	X
Honey Cocoates	X																												
Honey Powders	X	X																											
Honey Extract	X	X	X																					X					
Hydrogenated Honey	X																												
Hydrolyzed Honey																													
Hydrolyzed Honey Protein																													

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

[Honey – March 2020 – Priya Cherian]

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Honey	8028-66-8	X	X		X	X													X
Honey Cocoates		X				X													
Honey Powder		X				X													X
Honey Extract	91052-95-5	X				X													
Hydrogenated Honey		X				X													
Hydrolyzed Honey		X				X													
Hydrolyzed Honey Protein		X				X													

X = Useful hits were found

Search Strategy

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

Key Words: dermal, irritation, sensitization, inhalation, metabolism, toxicity, phototoxicity, medicine, penetration

LINKS

Search Engines

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

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

Pertinent Websites

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

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

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

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

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

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

Botanical Websites, if applicable

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

Fragrance Websites, if applicable

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

DECEMBER 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – December 9, 2019

DR. BELSITO: Okay. So, this is the first time we're looking at these honey and honey-derived ingredients. So, we've got some Wave 2 on this with an HRIPT at 0.1, but the maximum leave-on is seven.

DR. SNYDER: We already had HRIPT at seven.

DR. BELSITO: Yeah.

DR. SNYDER: I don't know why they gave us -- they had it at a way, way lower concentration, but.

DR. BELSITO: So, we have dermal irritation and sensitization for the extract, and I wasn't certain that we needed it for other components. The extract had the highest leave-on use at seven percent. Only issue I had was -- did you see any mention of a material called propolis? Propolis is bee's glue.

MS. CHERIAN: Yeah, that's in there. We were talking about that upstairs too.

DR. BELSITO: And that can be a sensitizer.

MS. CHERIAN: Right.

DR. BELSITO: And I didn't see anything about any -- for composition, I didn't see propolis, but it wouldn't be a composition of honey, it would be like an impurity. We didn't see any mentions of that?

And then I imagine it would be in very low levels, because it would be more of a solid, sticky. It would not make the honey very palatable.

So, pesticides and heavy metals need to go in the discussion inhalation boilerplate. I thought we could go safe as used for this.

DR. SNYDER: I agree.

DR. LIEBLER: Yeah, I was in the same place.

DR. KLAASSEN: Yes.

DR. LIEBLER: Do you think the sensitization would clear the powder? The thing about the powder is it indicates there were a number of different fillers used to make the powder under a method of manufacture. And I didn't know if the fillers that are used could be sensitizing. And that's why I just want to ask you, Don. They include starch, carboxymethyl cellulose, gum arabic, maltodextrin, and gelatin; any of those a concern?

DR. BELSITO: No.

DR. LIEBLER: None? Okay.

DR. BELSITO: Yeah, so safe as used.

DR. LIEBLER: Yeah, I thought it was a really excellent data package, overall.

DR. BELSITO: Yeah.

DR. BERGFELD: I'm glad to have this. My husband has eight beehives. I'm going to put this in a document for a Christmas present.

DR. LIEBLER: So, if it's non-sensitizing, why do they call it hives anyway? Why do they call it hives?

DR. BELSITO: And then I think in the discussion just something about the damaged skin. And then the fact that it's used as a wound treatment, which sort of mitigate concerns about use on damaged skin that was at some point. I guess it was on Page 13.

DR. SNYDER: On 15 and 16, yeah.

DR. BELSITO: Yeah. But it was on page 13 with contamination by clostridium botulinum spores, not -- the neurotoxins are able to penetrate the skin.

DR. SNYDER: Well, that's the only concern I had about the effect on damaged pediatric skin, was whether or not those -- because if it's damage, there's no -- I mean, they're not absorbed, toxins are not absorbed. But just on clinical assessment, there's a clinical study where the effect on damaged pediatric skin --

DR. BELSITO: Yeah, but you shouldn't have clostridium botulinum in your honey.

DR. SNYDER: Well, no, but it could be an impurity or a contaminant, correct? I mean, that's what happens. But I mean -- but they refer here to medical grade honey. So I didn't know if that meant that it was screened for that like we screen for -- I'm drawing a blank. (Inaudible) endotoxin. I just didn't know what medical grade honey meant, 20 percent medical grade honey.

DR. BERGFELD: They use it for wounds in the hospitals, especially --

DR. BELSITO: Yeah, but that was not the problem. The problem with botulinum was, although rare infant botulism has been reported after ingestion of honey, due to clostridium.

One would assume that the preservative systems put into a cosmetic would not allow for clostridium. I have to presume that this was, someone fed their kids honey.

DR. SNYDER: Well, you're not supposed to -- no babies are not supposed to get honey in any form because of botulinum.

DR. BERGFELD: Infants --

DR. SNYDER: Infants, yeah.

DR. KLAASSEN: Young mothers know that, which I was surprised. Last week I went over and I asked my daughter, well, do you feed my -- my granddaughter I asked her if you could feed my great-grandson honey. She says, oh, no, I can't do that for another month yet. He hasn't turned one.

MS. FIUME: Until they're two.

DR. BELSITO: I never knew that. When did that come out?

MS. DEWAN: That was a long time ago.

MS. FIUME: That was then. It used to be two. You don't give kids honey under the age of two.

DR. KLAASSEN: That was news to me.

DR. SNYDER: No, I knew it.

DR. KLAASSEN: It corresponded with what I was reading. And so, I said, well, I just learned that. And she says, well, no, we all know that.

DR. BELSITO: But then it's used as wound dressings.

DR. KLAASSEN: But it's a pharmaceutical grade.

DR. BELSITO: Okay. So, then do we need to --

DR. BERGFELD: I think it was interesting, to everything that we would ask for, genotoxicity, except all the toxicology tests, these are called anti-tests. And it just showed that they weren't any of those things.

DR. BELSITO: Um hmm.

DR. BERGFELD: I thought -- is that a title we would keep if all those tests were negative? Or are -- actually improved the situation, anti-carcinogenicity.

MS. FIUME: I know anti-carcinogenicity --

DR. BERGFELD: Anti-tumor.

MS. FIUME: -- specifically, that has been discussed when we were developing the report format; and it was stated that that should be a separate heading, which is why it is.

DR. BELSITO: Right.

DR. BERGFELD: Yeah. I think that should go into the discussion, that it has some positive effects. I mean, are positive, even maybe not related, but still.

DR. BELSITO: Okay. Anything else? So heavy metals, pesticides.

MS. FIUME: Do you want anything about the fillers in that -- some of them are ingredients that have been reviewed and found safe, and those that haven't don't pose concern?

DR. BELSITO: Yeah, sure.

DR. LIEBLER: Yeah, it would be good to add that in the discussion, yeah.

DR. BELSITO: Anything else in the discussion? So, how do we deal with this clostridium issue in the discussion? Do we?

DR. KLAASSEN: I don't think so.

DR. BELSITO: Okay. Paul, Dan, you're fine with not dealing with it.

DR. LIEBLER: That's fine.

DR. BELSITO: Okay.

MS. FIUME: Can we just get clarification on what should go in the discussion about use on damaged skin?

DR. BELSITO: Nothing is what we just said.

MS. FIUME: Okay. So I didn't know if that was also a separate issue on its own.

DR. BELSITO: Yeah.

DR. SNYDER: No, I just raised it because it had the medical grade, and just with it being damaged skin. I know that the dermal application has no relevance for the botulinum toxin because it doesn't penetrate. But if the skin is damaged --

DR. BELSITO: But then it's used in wound dressings all the time.

DR. SNYDER: In pediatrics?

DR. LIEBLER: Yeah.

DR. SNYDER: I mean, there was one clinical thing. I think it was eight months to whatever it was. The one study that -- the youngest was eight months, I noted.

MS. FIUME: Would one possibility be --

DR. BELSITO: A honey-based ointment was used as part of a treatment of damaged skin in eight children. No adverse effects or allergic reactions were reported. I mean, it's just oral. We're fine.

MS. FIUME: I was going to suggest one possibility in the pesticide heavy metal boilerplate, you could also add no bacterial contamination.

DR. BERGFELD: That's a great idea.

DR. BELSITO: Yeah, okay.

MS. EISENMANN: I don't think no is -- I would see if you could find what is a spec for medical grade honey. And not say that necessarily you should be using it, but just so that that information is in the report. There probably is a micro-spec on honey. Just to say no, is not going to be of help.

DR. SNYDER: Yeah. I'm going to guess it has no endotoxin -- no toxins.

MS. FIUME: And it's within -- following good manufacturing practices, is what our statement usually is. I'm just going to add that as a third caveat.

MS. EISENMANN: Right, right. That's fine, good manufacturing -- but no; don't say, no.

MS. FIUME: Sorry, that was just my shortcut. Sorry.

DR. BELSITO: Okay. Anything else for the discussion? Okay. We're done honey. That was sweet.

Okay, next on the hit list, soy. There's an endocrine disruptor if I ever saw it.

Marks Team – December 9, 2019

DR. MARKS: Next I have is honey. And this is -- Priya, you're up again?

MS. CHERIAN: Yup.

DR. MARKS: This is the first review of the seven honey ingredients. And as I always do, I first ask -- when it's a first review, it's hard, unless it's chemically dissimilar. I always ask, are the ingredients okay, just to be certain that Priya didn't sneak in some honey ingredient that doesn't belong here. But Ron, Tom, Lisa, ingredients okay?

DR. SHANK: Yeah.

DR. SLAGA: Yes.

DR. MARKS: Yup. Okay. Let me go back up here. So, obviously a next thing is what do we need. Since we went over read across, what can we read across?

We did get W2, or Wave 2 info. Was that HRIPT on a very dilute test in honey at 0.0001 percent extract, honey extract. That was fine, not surprising, that dilute. Okay. Tom, Ron, comments? And, Lisa, you can weigh in after they have.

DR. SHANK: The only comment I had is on sensitization. On Page 16, honey extract was tested, 7 percent, but there's no mention of a challenge concentration. Usually we have that information. And this was negative. I don't know if that would cover the extract, if the extract would concentrate something.

DR. MARKS: I have my notes that the extract was okay. The HRIPT of the extract was okay.

DR. SHANK: It was at 3 percent.

DR. MARKS: Yeah. What page is that? I have the 7 percent was okay. The 3 percent on honey there was no sensitization data. And as I mentioned, Wave 2 had an HRIPT, but that was no big --

DR. SHANK: It was too little.

DR. MARKS: Yeah. Too little is exactly right. Which page is that, again, Ron?

DR. SHANK: Well, the discussion is Page 18.

DR. MARKS: But the actual -- I may go --

DR. SHANK: Use concentration, 7 percent was negative in the HRIPT.

DR. MARKS: Yup. So that's --

DR. SHANK: And that was on honey, no, honey extract.

DR. MARKS: No, honey extract. I had 7 percent was okay.

DR. SLAGA: Most of the data was on honey extract.

DR. SHANK: Yeah.

DR. MARKS: Yeah. And then, for me, the question is can you take the honey extract and read across to everything else here? And I'll throw a ringer in in a second. But let me see, HRIPT, this is page 16, 112 subjects, 7 percent honey extract, no irritation or sensitization.

So, I thought it was okay from a sensitization -- and no reported cases of allergic contact dermatitis. So clinically, there was not an alert. There's a rare type one reaction reported, but that's with ingestion. So, I felt from a sensitization, if we could read across, that that would be okay.

The format, Bart, you asked in your annotated notes the Wave 2 format. Probably the biggest thing for me is it was this way. So, either I print it out, or I've got to take my computer and turn this way to get the summary. Otherwise, it was fine.

I guess it depends. Priya, how much effort was it? Because otherwise, you would just take the raw data from the sensitization and just print the vendors' report.

MS. CHERIAN: Oh, you mean pertaining to summary table?

DR. MARKS: Yeah. The summarization. Bart asked about how did we like the formatting, and it was basically the sensitization data, the HRIPT that you had summarized.

DR. HELDRETH: Oh, I think the question -- sorry. Maybe my question wasn't phrased very well. My question was more, was the fact that this was really summary data as opposed to a full HRIPT study, was that -- were you okay with that? Was that sufficient?

Because I know before we've had issues where we'll see a result where, you know, it'll be a summary. And it'll say, you know, certain patients had arrythmia or something like that, but then there's no explanation of which patients.

DR. MARKS: Yeah. The one in all of these, I think there was one where 28 subjects had a mild reaction. So, going back in and seeing the source data would be helpful for that when there's an alert. Otherwise, I don't know that it's necessary to have all that. We'll see what Don feels. What did you feel, Ron?

DR. SHANK: It was fine for me. I don't think we needed all of the, quote, "boilerplate" on how you select your panel, et cetera.

DR. MARKS: Yeah.

DR. SHANK: We didn't need the demographic data, age, sex, and then the whole pages and pages of zeros. So, the summary was fine for me, but maybe not for dermatologists. I don't know.

DR. MARKS: I thought it was fine, unless there was an alert. So, Tom, what was your comments about honey?

DR. SLAGA: Just to reiterate what it stated, it's probably one of the most common foods in the world. Everybody eats it, every country. It's one of the most complex, because of all the -- what plants they go at or what flower they go at, on and on. It's very -- changes everything, but there's no alerts.

I asked my wife about it, and she said, "Well, it's a little sticky to the skin, but other than that, I don't know any problem with it."

DR. SHANK: Well, it is important to point out the source, the bees.

DR. SLAGA: Yeah, very. We have to really discuss that.

DR. SHANK: Because we use oleander, the honey is toxic. But Priya's covered that very nicely. So it's in there.

DR. SLAGA: Yeah.

DR. MARKS: Lisa?

DR. PETERSON: Yeah. I don't really have anything to add. I had the fact that bees do their thing in nature, you would have a lot that you don't have control over.

DR. SLAGA: That's right.

DR. PETERSON: My only concern had to do with worrying about how the contaminates change depending on what the sources were and, you know, the involvement of pesticides and stuff like that. But I do think that things get pretty dilute when they're used in --

DR. MARKS: Well, we actually have a pesticide -- how are we referring to them now as boilerplates or resource documents? At any rate, we have one in which we -- pardon? Guidance. Yeah.

At any rate, we do have, Lisa, a boilerplate on pesticides. So, I think that's a good point, and we include that in the discussion where there potentially could be contamination with pesticides. We have a similar one for heavy metals. So yeah. So Priya will get that in the discussion in the next rendition.

I felt sensitization was fine. It'll be interesting; I don't know whether I'll mention this tomorrow, but propolis is bee glue. Have you heard of propolis?

DR. SHANK: No.

DR. MARKS: So, propolis is what actually glue these combs together and the hive together. And there has been reports -- it's rare, but there have been reports of allergic contact dermatitis to propolis.

And manufacturing the honey came up in my mind, could it be contaminated with propolis? Propolis is a resinous tree sap plus wax. Honey is the liquid bee food from the flower nectar stored in the wax honeycomb.

So any rate, if honey were contaminated with a large amount of propolis potentially, could cause allergic contact dermatitis. But I think that's a moot subject, particularly, since we have HRIPT that is okay.

DR. SHANK: People chew honeycombs, though.

DR. SLAGA: Yeah. They do.

DR. MARKS: Oh, absolutely.

DR. SHANK: And if there was a sensitizer, wouldn't you get an effect in the buccal cavity?

DR. MARKS: Oh, yes. And that could occur.

DR. PETERSON: I think there are people that are sensitive.

DR. SHANK: There are.

DR. MARKS: Yes, absolutely. It used to be actually one of the North American Contact Dermatitis Group's standard allergens. And we had a fair amount of reactions to them.

DR. ANSELL: Beeswax or --?

DR. MARKS: No, propolis.

DR. ANSELL: Propolis as an isolate, not --

DR. MARKS: Yes. Propolis, which of course is another botanical mixture. And it's defined as the resinous tree sap plus the wax. And that's spelled p-r-o-p-o-l-i-s, also known as bee glue. At any rate, move a tentative report with safe? Does that sound good?

DR. SHANK: Yes.

DR. PETERSON: Yeah.

DR. MARKS: Are you okay with the sensitization, Ron?

DR. SHANK: I am, yes.

DR. MARKS: So tentative.

DR. HELDRETH: Yeah. Our original thought was to throw in the boilerplates for pesticides and heavy metals, but then realized, well, that's something that we always do for botanicals. And these aren't really quite botanicals.

DR. PETERSON: But they're derived from botanicals.

DR. HELDRETH: Right. They're derived from botanicals, but there's an animal involvement in this process. But we can modify those.

DR. ANSELL: Not the heavy metal. The pesticide, potentially; but heavy metal botanical has to do with growing in the ground.

DR. MARKS: Yeah. I would agree with that probably. I don't know, Lisa, what do you think? Could there be enough arsenic in the --?

DR. PETERSON: I mean, once you start thinking -- yeah. I think. But these -- I mean, don't they have to measure? Isn't there some --?

DR. MARKS: Well, that's what we recommend in the boilerplate. We just acknowledge the possibility there could be contamination with either a pesticide or heavy metal. So Jay, you think it's highly unlikely there'd be enough heavy metals in the flower?

DR. ANSELL: I think if you look at the guidance, the pesticide one is probably relevant because it is derived from the plant part. But the heavy metals is not derived from the bee part. It's derived from growing in the ground.

DR. PETERSON: So, one supplier actually measured the levels of different metals and they didn't detect anything. So, I think that's evidence that you're probably right.

DR. SHANK: For cosmetic use, does the formulator specify the source of the honey, orange blossom, clover? Like in food, usually its label, the source.

DR. SLAGA: Yeah.

DR. SLAGA: Orange blossom honey, clover honey, whatever.

DR. ANSELL: Sort of like at the farmers' market.

DR. SHANK: Okay. How about for cosmetics? Is it possible somebody could make honey from where the bee used a toxic source, a toxic plant? Because there are several toxic plants, and there have been human poisonings with honey. Not in this country, but elsewhere.

DR. ANSELL: I do not know.

DR. SHANK: Okay.

DR. MARKS: How clearly -- well, that should be made, I think, again, in the discussion.

DR. SLAGA: Right.

DR. MARKS: I would handle it in the discussion and make it very clear that we're concerned that the honey source is not from toxic plants. Would that satisfy you, Ron, do you think?

DR. SHANK: Well, it's in the report.

DR. ANSELL: I would not go farther than that. This is not being ingested. It's being used topically. In much, much lower concentrations that it would as a food. So, I think mentioning it, making people aware of the potential for pesticides, aware of the --

DR. SHANK: That's probably enough.

DR. ANSELL: Yeah.

DR. SLAGA: If you have too many alerts, then it scares people.

DR. MARKS: Yeah. Absolutely. Okay. And I don't think -- this is different than the botanical, so we don't need formulate to be non-sensitizing because we --

DR. SHANK: Please.

DR. MARKS: Yeah. I know. I agree with you, Ron. So, tomorrow I'll move that a tentative report be issued that these ingredients are safe. And when it comes to comments, I'll mention the pesticide boilerplate -- thanks, Lisa -- and avoiding toxic plants as a source in the discussion. Anything else?

DR. PETERSON: I just have a technical point. I've marked typos and things that I found, and they're commented on, just a few. But you'll get these documents that we've made comments on?

DR. MARKS: Yeah. The flash stick is collected at the end of tomorrow morning's meeting. So typos and those things -- and if it's just editorial, as you can see it's dynamic. Sometimes I or Don, or somebody else, will mention it tomorrow at the meeting. Other times, we expect they'll be captured from today's minutes and what's on the flash stick.

DR. PETERSON: Cool.

DR. HELDRETH: Yeah. The way that we look at it when we get back to -- when the CIR staff gets back to our office, if there's editorial comments, spelling, those sorts of things, in what we call the panel returns, the versions of the documents we get back from each of the panel members, then we move forward to make those changes.

But if it's something substantive, you know, where somebody thought there wasn't enough sensitization data here or there, something like that; something like that, we won't necessarily make the change within the document if it's only from one panel member. That's something that needs to be a consensus on day two.

December 10, 2019

DR. MARKS: So this is the first review of these seven honey-derived ingredients. We were provided a number of data and our team felt we could read across. So, our team moves that we issue a tentative report with safe, and I'll have discussion points after that motion.

DR. BERGFELD: Okay. Don?

DR. BELSITO: No, we're fine with that, safe as used.

DR. BERGFELD: Discussion points?

DR. MARKS: Just that we include the pesticide boilerplate since some of the sources might have pesticide on them, the flowers. And then the other is avoiding toxic plants as a source in the discussion.

Because, Ron, you brought that point. If you had honey derived from oleander, it is toxic. So in the discussion we should mention -- alert that.

DR. BERGFELD: Any other?

DR. SHANK: It's in the report.

DR. MARKS: Yeah.

DR. SLAGA: Yeah, it's in the report.

DR. BERGFELD: Any other?

DR. BELSITO: We also needed to mention that the fillers that are used in the honey powder are not a concern; we don't have data on those. And that good manufacturing practices should be used to limit endotoxins, given the reports of clostridium botulinum.

DR. SNYDER: The fillers we're going to add them to the discussion from a previous report, yeah.

DR. BELSITO: Right. Right.

DR. SNYDER: Yes.

DR. BERGFELD: Any other discussion -- comment or needs to go into the discussion.

DR. MARKS: I'd be interested in -- I brought this up yesterday as a point of interest, really not to change the conclusion; propolis, which is bee glue from tree buds is used to make the hives. And we actually do patch testing that and have found allergic contact dermatitis of propolis.

I guess one could consider if you're dealing with raw honey that might be contaminated with propolis. But I didn't think it was enough of an issue to change the conclusion. And I'm not even sure it really belongs in the discussion, because it potentially could open up a whole other avenue.

But, Don, had you thought about propolis at all?

DR. BELSITO: Yeah, I raised it as well. But you know, propolis is bee's glue.

DR. MARKS: Yes.

DR. BELSITO: It's very thick; I don't think it would be, you know, a manufacturer would not want to incorporate this into honey. You know, I think the greater danger with propolis would be in bee's wax contaminating it.

DR. MARKS: I guess I was thinking in terms when you get -- processed honey is very liquid, like what I used this morning.

DR. BELSITO: Right.

DR. MARKS: But raw honey actually has parts of the cone and stuff and is actually kind of thick.

DR. BERGFELD: Having just gone through my husband filtering his honey. It is quite filtered. And there's a lot of residue left in the cones of honey. And so you aren't taking it down to the wax or the propolis.

DR. MARKS: Yeah. Okay, good.

DR. BERGFELD: All right, any other questions or things to go in the discussion?

MS. CHERIAN: Do we need to add the heavy metals boilerplate?

DR. BELSITO: Yes, and pesticides.

DR. MARKS: Certainly pesticides. We had the discussion about heavy metals, and we didn't think there'd be much in the heavy metals other than what the bees were harvesting. So we didn't think that heavy metals were really that necessary. But obviously again, if we're going to be on the safe side. Do you think heavy metals, Paul, need to be in?

DR. SNYDER: No, I don't think they would be that much of an issue.

DR. BELSITO: Okay.

DR. MARKS: Okay, so we don't need that. Good, thanks, Paul.

DR. BERGFELD: All right, I'll call the question then, all those in favor of a safe conclusion for honey, please indicate. Thank you. And we'll include the discussion in Marks.

Then moving on to the last ingredient in this list of reports advancing, is Vanilla, Dr. Belsito.

Safety Assessment of Honey-Derived Ingredients as Used in Cosmetics

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 7 honey-derived ingredients. All of these ingredients are reported to function in cosmetics as skin-conditioning agents. The Panel considered the available data relating to the safety of these ingredients in cosmetic formulations. Because impurities, particularly pesticides and endotoxins, may be present in these ingredients, formulators should continue to use good manufacturing practices to monitor and limit these possible impurities. The Panel concluded the honey-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This is a safety assessment of the following 7 honey-derived ingredients as used in cosmetic formulations:

Honey	Honey Extract	Hydrolyzed Honey Protein
Honey Cocoates	Hydrogenated Honey	
Honey Powder	Hydrolyzed Honey	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook (*wINCI; *Dictionary*), all of these ingredients function as skin-conditioning agents.[1] Other functions include, but are not limited to, use as a flavoring agent, anti-acne agent, abrasive, binder, depilating agent, exfoliant, hair-conditioning agent, and nail-conditioning agent (Table 1). Use as an anti-acne agent is not considered a cosmetic function in the United States (US) and, therefore, does not fall under the purview of the Panel.

The *Dictionary* defines Honey Cocoates as a complex mixture of esters produced by the reaction of honey with coconut acid.[1] In 2017, the Panel published a safety assessment with the conclusion that coconut acid is safe in cosmetics in the present practices of use and concentration [as described in that safety assessment].[2] In addition, the main components of Honey (i.e., fructose, glucose, maltose, and sucrose)[3] were reviewed by the Panel; in 2019, a safety assessment was published with the conclusion that these component ingredients are safe in the present practices of use and concentration [as described in that safety assessment].[4]

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

It should be noted that there are multiple species of bees that produce honey; however, Honey, used as a cosmetic ingredient, has been reported to be produced by the honeybee species *Apis mellifera*, *Tetragonisca angustula*, *Scaptotrigona pectoralis*, and *Melipona Becheii.*[1] In several studies, the honey used for testing was not produced by these species, but produced by a different honeybee species (e.g., *Apis dorsata*). Data from these studies have been included in the report as these may be helpful in drawing a conclusion of safety for this ingredient group. In most cases, information regarding the type of honey being tested (i.e., method of manufacture, floral source, species of producing bee) was not specified. However, if this information was available, it has been included in the report.

It is often not known how the substance being tested in a study compares to the cosmetic ingredient. In the report text, if it is known that the material being tested is a cosmetic ingredient, the INCI naming convention will be used (i.e., the names of cosmetic ingredients are capitalized (e.g., Honey Extract)). If it is not known that the test substance is the same as the cosmetic ingredient, the generic terminology, in all lowercase (e.g., honey extract), will be used.

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

CHEMISTRY

Definition

According to the *Dictionary*, Honey (CAS No. 8028-66-8) is a saccharic secretion gathered and stored by honey bees of the species, *Apis mellifera*, *Tetragonisca angustula*, *Scaptotrigona pectoralis*, or *Melipona becheii*.[1] All ingredients reviewed in this report are derived from honey. The definitions of the ingredients included in this report are provided in Table 1.

Physical and Chemical Properties

Honey (CAS No. 8028-66-8) may be fluid, viscous, or solid, and ranges in color from clear to dark amber or black.[5] Honey is acidic by nature; however, the pH and acidity levels vary depending upon botanical origin and geographic origin of the honey.[6] The usual pH of honey ranges from 2 - 6. According to a manufacturer, a typical product with Honey Extract,

prepared in water, is light to medium yellow in color, has a pH level of approximately 2.5 - 6.5 at 25°C, and is soluble in any proportion of water.[7]

Natural Occurrence

Honey is commercialized in most countries of the world.[8] In the US alone, there are more than 300 types of honey, each with a unique flavor and color depending on the nectar source. Although there are many varieties of honey, the most common types of commercialized honey include those from botanical sources such as acacia, alfalfa, avocado, blueberry, buckwheat, clover, eucalyptus, fireweed, manuka, orange blossom, sage, tupelo, and wildflower.

Honeybee Species

Apis mellifera, also known as the Western honey bee, is the most common honeybee species worldwide.[9] This species was historically present across sub-Saharan Africa, Europe, parts of Western Asia, and the Middle East, and has now migrated westward to many countries, including the US. Honeybees of the *Tetragonisca angustula* species are stingless honeybees that are widely distributed in the neotropics, from Mexico to Northern Argentina.[10] The *Scaptotrigona pectoralis* and *Melipona becheii* species are both stingless honeybee species found in South America.[11,12]

Honey Production and Extraction

To produce honey, forager bees collect sugar-rich nectar from plant sources.[13,14] Once brought back to the hive, the nectar is distributed, ingested, and regurgitated multiple times. This process involves the physiochemical transformations of nectar, during which sucrose is inversed into dextrose and fructose by enzymes originating from the hypopharyngeal glands of the bees. The regurgitation process also aids in the process of dehydration of the solution. The altered nectar solution is then spread over an empty comb. Further dehydration occurs by the draft created by the flapping of bee wings in the hive. Once approximately 80% of the water content is evaporated, the honeycomb cells are capped with wax for preservation.

Traditionally, honey is collected by first introducing smoke into the beehive to sedate or remove bees.[14] The combs are then removed and squeezed to drain honey. Honey can also be extracted by placing combs in a metallic bowl containing a drainage hole. Burning embers are placed on top of the comb, and melted honey is drained and collected. In order to mechanically extract honey, caps are removed from combs, and placed in an extractor where centrifugation is performed. The honey is then sieved and collected.

Method of Manufacture

Information on the manufacture of Honey Extract and of a tradename mixture containing Honey Extract was provided by suppliers. The methods below regarding Honey Powder and honey protein are general to the processing of these ingredients, and it is unknown if they apply to cosmetic ingredient manufacture.

Honey Extract

According to one supplier, to produce Honey Extract, the honey is first extracted with a specified eluent under appropriate temperature conditions to yield a concentrate.[7] Typical eluents include water, butylene glycol, glycerin, and propylene glycol. The concentrate containing the phytochemical constituents is then blended with the desired diluent and preservation system to produce the final ingredient.

The manufacturing process of a tradename mixture containing 10.6% Honey Extract, 82.9% water, 4.4% propylene glycol dicaprylate/dicaprate, 1.5% phenoxyethanol, 0.3% xanthan gum, and 0.3% potassium sorbate was reported.[15] A mixture of demineralized water, propylene glycol dicaprylate/dicaprate, and honey is combined with xanthan gum to create the final product. The manufacturing process of a different tradename mixture containing 16.5% Honey, 27.6% water, and 55.9% propylene glycol was also reported. Honey is extracted by a mixture of propylene glycol and water.[16] The resulting product is then filtrated.

Honey Powder

A honey powder, for food use, is produced by the combination of honey, an emulsifier, an anti-caking agent, and filler materials of high molecular weight that increase the glass transition temperature.[17] Filler materials include starch, carboxymethyl cellulose, gum Arabic, maltodextrin, and gelatin. The mixture is then powdered by using a either a spray or vacuum drying method with a filler to honey ratio of 50:50.

Honey protein

Honey proteins can be extracted via physical and chemical methods.[18] When physically extracting proteins, honey undergoes ultrafiltration and ultracentrifugation to isolate amylase before purification by ion exchange chromatography. A dialysis method can also be used to remove low molecular weight and interfering compounds by passive diffusion through a semipermeable membrane. Another physical extraction method involves the absorption of honey proteins by beads with specific properties. Combinatorial hexapeptide ligand library and C18 beads are used to capture honey peptidome from honey samples of chestnut, sunflower, eucalyptus, orange, and acacia. The honey peptidome is then filtered and eluted from the beads using a solvent system. Microwave-assisted hydrolysis is another method used to extract proteins from honey.

Chemical methods to extract honey involve co-precipitation using compatible precipitants, such as a sodium tungstate solution, trichloroacetic acid, sulfosalicylic acid, or ammonium sulfate.

Composition

Honey

Honey is a mixture of carbohydrates, proteins, enzymes, amino acids, vitamins, minerals, antioxidants, and other compounds.[14] Enzymes in honey include invertase, glucose oxidase, catalase, and acid phosphorylase. The sugar composition of honey is dependent upon the content of saccharides in the nectar used to produce the honey.[5] Generally, fructose and glucose are found in honey in similar amounts, with D-fructose as the prevalent sugar. Non-saccharide honey components include proteins, free amino acids (including proline), carboxylic acids (gluconic, citric, lactic, malic, succinic, butyric, propionic), essential oils, dyes, and vitamins. An overview of a chemical composition of honey can be found in Table 2.

Twenty-six amino acids have been reported in honey samples.[18] Proline is the most predominant amino acid in floral honey, followed by phenylalanine and glutamic acid. Amino acids account for approximately 0.3 – 1% of total honey by weight.

Phenolic acids and flavonoids are also present in honey.[3] The most common phenolic acids found in honey are 4-dimethylaminobenzoic acid, caffeic acid, *p*-coumaric acid, gallic acid, vallinic acid, syringic acid, and chlorogenic acid. Common flavonoids in honey include apigenin, genistein, pinocembrin, tricetin, chrysin, luteolin, quercetin, kaemferol, galangin, pinobanksin, and myricetin. The amounts of polyphenols in different honeys were quantified via high-performance liquid chromatography with diode-array detection (HPLC-DAD; Table 3). Generally, the quantity of a given polyphenol in the honey was approximately 0.2 mg/100 g honey, except for chestnut honey, which contained approximately 3 mg *p*-coumaric acid/100 g honey.[19]

Depending on the floral source, plant toxins may be transferred to the honey that is produced from their nectar, including secondary metabolites such as pyrrolizidine alkaloids, grayanotoxins, hyoscyamine, hyoscine, saponin, strychnine, gelsemine, tutin, hyenanchin, oleandrin, and oleandrigenin.[20] Honey collected from plants of the *Ericacea*e family (*Andromeda* sp., *Rhodendron ponticum*, *Kalmia* sp., *Lleucothoe* sp. *Lynoia* sp., *Pieris* sp.) has been shown to contain some of these toxins. Honey collected in areas where opium poppy cultivation is widespread has been reported to have narcotic effects.

Allergens, such as pollen, may also be present in honey.[21] Ten grams of honey contains approximately 20 to 100,000 grains of pollen, which retain their allergenic properties during the honey-making process. Other allergens include secretions of pharyngeal and salivary glands of honeybee heads, and honey bee venom.

Several studies included in this report involve the use of tualang honey, which is a Malaysian multi-floral jungle honey produced by *Apis dorsata*. A comparison of the physiochemical characteristics of tualang and manuka honey (a mono-floral honey formed by *Apis mellifera*; found in New Zealand and Australia) is provided in Table 4.[22]

Honey Extract

The phenolic content of acacia, chestnut, orange tree, and woodland honey extracts were evaluated by HPLC.[23] All honey extract samples had similar, but quantitatively different, phenolic profiles. The woodland honey extract was richer in polyphenols compared to the other three extracts, showing high levels of caffeic acid, coumaric acid, ferulic acid, iso-ferulic acid, pinobanksin, and pinocembrin.

Impurities

Environmental contaminants of honey include heavy metals (e.g., lead, cadmium, and mercury), radioactive isotopes, organic pollutants, polychlorinated biphenyls, pesticides (insecticides, fungicides, herbicides, and bactericides), pathogenic bacteria, and genetically modified organisms.[24] Beekeeping contaminants include acaricides (i.e., lipophilic synthetic compounds and nontoxic substances such as organic acids and components of essential oils), antibiotics (e.g., tetracyclines, streptomycin, sulfonamides, and chloramphenicol), and paradichlorobenzene.

A compound that is not naturally present in honey, 5-hydroxymethylfurfural (HMF), may be formed during the heating (via the Maillard reaction) or preservation (e.g., via acid-catalyzed dehydration of hexoses) of honey.[20,25] HMF is a compound that may be mutagenic, carcinogenic, and cytotoxic. The *Codex Alimentarius* has established that the HMF concentration in honey should be lower than 80 mg/kg; however, the European Union recommends a lower limit of 40 mg/kg.[26]

Honey Extract

According to one supplier, heavy metal testing was conducted on Honey Extract in a glycerin and water base.[7] No antimony, arsenic, cadmium, chromium, iron, lead, mercury, or nickel was detected. In addition, no residual pesticides were detected.

USE

Cosmetic

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

According to 2020 VCRP survey data, Honey is reported to be used in 1059 formulations (671 of which are leave-on formulations), and Honey Extract is reported to be used in 398 formulations (192 of which are leave-on formulations; Table 5).[27] All other in-use ingredients are reported to be used in 6 formulations or less. The results of a 2018 concentration of use survey conducted by the Council indicate Honey also has the highest concentration of use; it is used at up to 22% in paste masks and mud packs (which are considered rinse-off formulations).[28] The highest concentration of use reported for leave-on products was in formulations containing Honey Extract at up to 7% in body and hand products. Use concentration data were reported for Honey Cocoates in response to the Council survey (it is used at up to 2% in skin cleansing formulations), but no uses were reported in the VCRP; it should be presumed there is at least one use in a skin cleansing formulation, for which the concentration is reported. Conversely, VCRP data are available for Honey Powder, but concentration of use data were not reported. The ingredients not in use according to the VCRP and industry survey are Hydrolyzed Honey and Hydrolyzed Honey Protein.

Honey is reported to be used in baby products, products that would be used near the eye, and products that could result in incidental ingestion and mucous membrane exposure. Honey is reported to be used in 13 baby products and at up to 0.01%. It is also reported to be used in 20 lipstick formulations (up to 3%), 1 dentifrice formulation (up to 0.00035%), 5 "other" oral hygiene product formulations (up to 0.1%), and 1 mouthwash and breath freshener formulation (concentration unknown). Honey could also result in mucous membrane exposure as it is used at up to 3% in bath soaps and detergent formulation.

Additionally, Honey and Honey Extract are used in cosmetic sprays and could possibly be inhaled; for example, Honey is reported to be used in colognes and toilet waters and in hair sprays at up to 0.25% and 0.1%, 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.[29,30] 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.[30,31] Honey is reportedly used in face powders at concentrations up to 3%, and could possibly be inhaled. Honey Extract is also reported to be used in powders (dusting and talcum) at up to 0.0001%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the air.[32-34]

The honey-derived ingredients in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[35]

Non-Cosmetic

Food

Raw honey has been consumed worldwide for centuries.[36] Honey is commonly used as a sweetener and flavoring agent in many foods. Honey is listed in the US Environmental Protection Agency (EPA) Inert Finder Database as approved for food and non-food use pesticide products.[37] For food use, it is regulated under 40 CFR 180.950a. In addition, the FDA requires proper labeling of honey and honey products to ensure that these products are not adulterated and misbranded. All honey and honey products must be labeled in accordance with sections 402 and 403 of the Federal Food, Drug, and Cosmetic Act (21 USC 342 and 343). The international FAO/WHO Codex Alimentarius Standard requires that:[38]

> Honey sold as such shall not have added to it any food ingredient, including food additives, nor shall any other additions be made other than honey. Honey shall not have any objectionable matter, flavor, aroma, or taint absorbed from foreign matter during its processing and storage. The honey shall not have begun to ferment or effervesce. No pollen or constituent particular to honey may be removed except where this is

unavoidable in the remove of foreign inorganic or organic matter. Honey shall not be heated or processed to such an extent that its essential composition is changed and/or quality is impaired.

Although rare, infant botulism has been reported after ingestion of honey due to *Clostridium botulinum* spores.[39] Because of this, the FDA, the Centers for Disease Control and Prevention, and the American Academy of Pediatrics, recommend not feeding honey to infants younger than 12 months. Neither *Clostridium botulinum* spores nor the neurotoxins are able to penetrate the skin; however, damaged skin may be affected.[40]

Medicine

Honey can be found as an ingredient in over-the-counter (OTC) cough and cold medications.[41] Currently, there is an FDA-approved dermal dressing containing manuka or *Leptospermum* honey, used for the management of wounds and burns.[42] Examples of wounds that are treated with this dressing are diabetic foot ulcers, leg ulcers, pressure ulcers, partial thickness burns, and surgical wounds.[43]

Traditionally, honey has been used as an antibacterial, antiseptic, anti-inflammatory, and apitherapeutic agent.[36] Honey is commonly used for treatment of cuts, eczema, dermatitis, skin diseases, Fournier's gangrene, burns, ulcers, surgical wounds, fungating wounds, pressure sores, and cancer or broken skin.[44] Traditional, Ayurvedic treatments utilize honey for cardiac pain, palpitations, and eye ailments.[45]

TOXICOKINETIC STUDIES

Toxicokinetic studies were not available regarding these honey derived-ingredients. However, toxicokinetic information on some of the relevant, primary components of honey (fructose, glucose, and maltose) can be found in the Panel's report on monosaccharides and disaccharides.[4]

TOXICOLOGICAL STUDIES

No general toxicological studies were found in the published literature, and unpublished data were not submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

The effect of Palestinian honey on spermatogenesis was studied in male albino rats (12 rats/group) after 20 days of treatment.[46] Group A was given a 5% solution of Palestinian honey in drinking water, group B was treated with 5% sucrose in drinking water, and group C served as the control group and was given untreated drinking water. No significant effects on total body weight or weights of the testis, seminal vesicles, spleen, kidneys, liver, heart, or brain were noted. Rats treated with Palestinian honey displayed a significant increase in epididymal sperm count by 37% ($P \leq 0.05$). The activity of testicular marker enzymes for spermatogenesis such as sorbitol dehydrogenase was increased by 31%, and lactate dehydrogenase was reduced by 48%, indicating an induction of spermatogenesis.

A study was performed in order to examine the effect of honey on the reproductive system of rat male offspring.[47] Dams were divided into 10 rats/group. The control group received no treatment while treated animals were given honey (0.2 g/kg bw), daily, from day 1 of pregnancy to day 10, via gavage. In male offspring, testosterone levels were significantly lower in the treated group compared to the control group. Sperm counts, follicle stimulating hormone levels, and testes/epididymis weights were similar in control and honey-treated groups. The percentage of abnormal sperm was significantly higher in offspring of dams treated with honey compared to the control group.

GENOTOXICITY STUDIES

No genotoxicity studies were found in the published literature, and unpublished data were not submitted.

Anti-Mutagenicity

The potential anti-mutagenic effect of various honeys (fireweed, tupelo, Hawaiian Christmas berry, clover, acacia, buckwheat, and soybean) on 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (Trp-p-1), was studied.[48] Trp-p-1 is a commonly encountered food mutagen, and has been demonstrated to be mutagenic in bacteria and carcinogenic in animals. The anti-mutagenic effects of the honeys were assayed according to an Ames assay, with slight modification. All assays were performed in a in a final volume of 1 mL containing potassium phosphate buffer, Trp-p-1 (5 µL of 20 µg/mL in dimethyl sulfoxide), 4% S9 mix (500 µL), test strain *Salmonella typhimurium* TA98 (2×10^{10} cells/mL), and different honey solutions. Acacia, fireweed, soy, and tupelo honeys demonstrated enhanced anti-mutagenicity above 1 mg/mL, with inhibition between 40.3 and 62.9%; concentrations above 20 mg/mL did not further enhance anti-mutagenic effects. Clover and Hawaiian Christmas berry honey were most effective at 20 mg/mL, with 64.8 and 59.6% inhibition, respectively. The greatest inhibitory effect of buckwheat honey was observed at 1 mg/mL (52.1%).

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

The potential anti-carcinogenic effect of tualang honey on breast cancer was studied in rats.[49] Forty female Sprague-Dawley rats were given 80 mg/kg 7,12-dimethylbenz[a]anthracene (DMBA) via gavage. Rats were then divided into four groups. Animals in group 1 were given only distilled water. Animals in groups 2, 3, and 4 were given 0.2, 1, and 2 g/kg bw/day tualang honey diluted in 0.5 mL water, respectively, via gavage, for 150 days. After treatment, animals were euthanized. Breast cancers in the honey-treated groups had smaller tumor size compared to controls. In addition, the number of cancers developed in honey-treated rats was significantly lower than control groups ($P < 0.05$). The majority of the cancers in the control groups were high grade, while cancers in honey-treated groups were of medium- or low-grade. These effects, however, were not dose-dependent.

Anti-Tumorigenicity

The anti-tumoral therapeutic effects of tualang honey and manuka honey was studied in rats (10/group).[50] Thirty female Sprague-Dawley rats were given an 80 mg/kg injection of the carcinogen 1-methyl-1-nitrosourea (MNU); an additional 10 female rats were left untreated. Treatment with honey started when the first tumor reached 10 - 12 mm in size. Positive (tumor induction and no honey treatment) and negative controls (no tumor induction or honey treatment) were included. Treatment groups were fed either tualang or manuka honey (1 g/kg bw/day) for 120 days. On the 120th day of treatment, rats were euthanized. Rats in the positive control group had the highest median number of tumors compared to groups treated with either honey. Groups treated with honey showed a significant reduction in tumor size and weight compared to the positive control group. The percent reduction in the size of primary tumors was greater with tualang honey, as compared to manuka honey. Tumor masses in the positive control group were solid, large in size, and hard in consistency, exhibiting areas of necrosis and hemorrhage. Both honey-treated groups had tumors which were softer, paler, and smaller in size. Tumors in the positive control group were observed to have increased heterogenous nuclei formation, which were hyperchromatic, vesicular, and highly pleomorphic, with moderate cytoplasm increased mitotic activity compared with the honey-treated groups, which had fatty tissue, small nuclei, and cystic spaces.

OTHER RELEVANT STUDIES

Airway Inflammation Reduction

New Zealand white rabbits (5/group) were dosed twice with an intraperitoneal injection of ovalbumin (OVA) and aluminum hydroxide on days 1 and 14.[51] Tualang honey was then given via a nebulizer from days 23 to 25 at concentrations of either 25 or 50%, diluted in sterile phosphate buffer saline (5 mL for 20 minutes). After treatment with aerosolized honey, animals were either euthanized, or, further exposed to aerosolized OVA for 3 days starting from day 28 and euthanized on day 31. The effects of honey on the inflammatory cell response, airway inflammation, and goblet cell hyperplasia were assessed. Treatment with aerosolized honey reduced the number of airway inflammatory cells present in bronchioalveolar lavage fluid and inhibited goblet cell hyperplasia. In addition, treatment with aerosolized honey led to a significant decrease in the thickening of the epithelial and mucosal regions.

Nasal Respiratory Mucosa

A study was performed in New Zealand white rabbits (2/group) to evaluate the effect of manuka honey on nasal respiratory mucosa.[52] The left nasal cavity of each rabbit was irrigated once daily with 1.5 mL of a 33% mixture of manuka honey with saline; groups were treated for either 3, 7, or 14 consecutive days, and then euthanized. The last group was treated for 14 days followed by a 14-day washout period, and then euthanized the following morning. The right nasal cavity of each rabbits served as a control, and was not treated. The mucosa were examined by light microscopy. No histological evidence of inflammation, mucosal injury, or significant morphological changes were observed.

Allergic Potential Following Ingestion

Twenty subjects were used in a 12-week study to determine the allergic potential of manuka and multi-floral honey.[53] The participants ate a normal diet with the inclusion of the allocated honey. For the first 2 weeks, all honey was excluded from the diet; then, participants consumed 20 g honey per day in two doses of 10 g each. After 4 weeks, there was another 2-week "washout" period, and the groups swapped to the other type of honey for 4 weeks. Fasting blood samples were collected at the beginning of the study, starting with the first sample after the initial 2-week washout, and then weekly during the 4-week interventions with honey. Immunoglobin E (IgE) measurements were carried out on frozen serum collected weekly during each of the honey interventions. IgE levels remained at a level consistent with a non-atopic response during the course of the study. The authors concluded that this level of consumption of manuka and multi-floral honey had no significant effect on allergic status.

Cytotoxicity of Honey-Impregnated Wound Dressing

The potential cytotoxic effect of honey-impregnated wound dressings on human skin keratinocytes and dermal fibroblasts was studied.[54] Five and 21 days after initiating the tissue culture, the honey-impregnated wound dressing was introduced directly onto the cells in the test wells to allow for cell growth. Small blocks of commercial dressings were then

inserted into the wells, adjacent and distal to the tissue explants. The amount of test material used was not stated. Keratinocytes and fibroblasts treated with honey implants displayed a modest uniform increase in early cell proliferation and cell counts per mm. Nuclear and cytocavitary networks appeared normal, and cell proliferation was also evident immediately adjacent to the product. No cell toxicity was observed.

Cytotoxicity in Cancer Cells

Renal cell carcinoma cells (ACHN) were cultured in a medium containing 10% fetal bovine serum and 5, 10, or 15% honey for 3 consecutive days.[55] Cell viability was determined by the 3-(4,5-dimethyliazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, and apoptotic cells were determined using annexin V-fluorescein isothiocyanate (FITC) by flow cytometry. Honey decreased cell viability and induced apoptosis in malignant cells in a concentration- and time-dependent manner ($P < 0.001$). The half maximal inhibitory concentration (IC_{50}) values at 48 and 72 hours were 1.7 ± 0.04 and 2.1 ± 0.03 µg/mL, respectively.

A similar study was performed on human breast cancer (MCF-7, MDA-MB-231), immortalized cervical cancer (HeLa), and normal breast epithelial cells.[56] Cells were plated at a concentration of 1×10^5 cells/well. The cells were allowed to adhere overnight, and the culture medium was replaced with fresh assay medium supplemented with 2% fetal bovine serum. Cells were then treated with different concentrations of tualang honey (1 - 10%), and incubated for up to 72 hours. Tualang honey induced a statistically significant increase in cell death in MDA-MB-231, MCF-7, and HeLa cancer cell lines in a dose- and time-dependent manner. Treatment of the normal breast epithelial cell line did not show a clear cytotoxic effect, even after 72 hours of incubation. Flow cytometric analysis of cells stained with annexin V-FITC and propidium iodide showed that tualang honey significantly increased apoptosis in all cancer cell lines compared to untreated cells.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Human

Honey Extract

A human repeated insult patch test (HRIPT) was performed on 112 subjects using a cosmetic product containing 7% Honey Extract.[57] Approximately 0.2 mL of the test substance was applied to the upper back, under an occlusive patch. Patches were allowed to remain in direct skin contact for a period of 24 hours. Applications were made to the same site, three times a week, for a total number of 9 applications during the induction period. After a 2-week rest period, challenge patches were applied to previously untreated test sites. After 24 hours, patches were removed and test sites were evaluated. The test substance did not demonstrate a potential for eliciting dermal irritation or sensitization.

According to a summary report, an HRIPT was performed on 116 subjects using a product containing 0.01% Honey Extract according to the same procedure as above.[58] The product was tested at a 1% dilution in water (effective test concentration, 0.0001% Honey Extract). Seven individuals displayed low-level reactions (mild erythema) during the induction phase, and one individual displayed a high-level reaction in the induction phase. Eight individuals displayed low-level reactions during the challenge phase. (Individual subject scores were not provided.) The test substance was considered by the researchers to be non-sensitizing.

OCULAR IRRITATION STUDIES

Human

Use Study

A prospective, randomized, paired-eye, investigator-masked trial was performed on 25 subjects to determine the clinical safety of manuka honey eye cream on patients with blepharitis.[59] The cream (approximately $0.034 \text{ g} \pm 0.001 \text{ g}$) was placed on the periocular surface of the closed upper and lower eyelids of the affected eye. Applications occurred once a day, at night, for 2 weeks. The untreated eye served as a control. A questionnaire was given to grade the severity of dry eye symptomatology at baseline, and a telephone interview was conducted following the first day of cream application to check for immediate tolerability issues or adverse events. Clinical assessments were performed at baseline, day 7, and day 14 of the treatment period. There were no statistically significant differences in baseline clinical or impression cytology measurements between treated and control eyes. Twenty-three of 25 participants did not report any tolerability issues or adverse effects following the first day of product application. In two individuals, application too close to the eyelash margin and the use of excessive cream was presumed to result in a transient stinging sensation. Irrigation with water and reapplication of a modest quantity of cream resolved the issue in both cases. No other adverse effects were reported throughout the study.

CLINCAL STUDIES

Effect on Damaged Pediatric Skin

Eight pediatric patients ranging from 8 months to 13 years of age were evaluated in this study.[60] Five of the children had second-degree burns, and three had necrotic ulcers, circular skin lesions, and deep cervical trauma. Each child was treated with povidone iodine (10% solution), fusidic acid, and systemic antibiotics, followed by a honey-based ointment. After this initial treatment, patients were instructed to apply honey-containing ointment as well as a dressing impregnated with a polymer containing 20% medical grade honey, daily. The duration and amount of product used in this study were not stated. No adverse effects or allergic reactions were observed.

Case Studies

Anaphylaxis

A 40-year old woman was referred to a clinic after suspected allergy to honey.[61] At the age of 36, she had two episodes of generalized urticaria 20 minutes after ingestion of foods with honey. At the age of 37, five minutes after an inadvertent contact with a teaspoon with traces of honey, the patient reported swollen lips, urticaria, and angioedema. After treatment with oral corticosteroids and antihistamines, symptoms were resolved. Skin prick tests with standard panel of extracts from aeroallergens and common allergenic foods yielded negative results. Prick-to-prick tests (PPT) were performed with the previously consumed honey, and eight other kinds of honey (eucalyptus, sunflower, orange-tree, Arbutus-tree, French lavender, heather, flower incense, and rosemary). Results were positive for all honey types. Thirty minutes after the administration of the PPT, the patients suffered from anaphylaxis, generalized urticaria, swollen lips, tongue, and uvula, and hypotension. The same PPT was performed with these honeys in 6 control volunteers (3 healthy individuals, and 3 atopic with pollen sensitization and rhinitis). None of the volunteers displayed a positive skin reaction.

Epicutaneous Sensitization

A 48-year-old woman had been washing her body and hair with products blended with edible honey, and she applied honey to the face as a face pack.[62] After 8 years of use, the woman developed itching and redness on facial skin as well as conjunctival hyperemia following the use of the face pack containing honey. After washing her body with honey-containing soap, the subject reported urticarial symptoms on her extremities and un-exposed face. One year later, the subject developed abdominal pain and distention after eating yogurt with honey. The patient had positive results for honey-antigen specific IgE antibodies in serum (UA), equivalent to 1.44 UA/mL, but not for honey bee venoms or Api m 10 (*Apis mellifera* venom component). Results for specific IgE against three cross-reactive carbohydrate determinant marker allergens were negative. Prick tests with honey gave positive results. Fifteen minutes after oral challenge with 30 mL of honey, the patient developed eyelid swelling, abdominal pain, and oral tingling.

SUMMARY

The 7 honey-derived ingredients in this report all are reported to function in cosmetics as skin-conditioning agents. Other reported cosmetic functions include flavoring agent, abrasive, binder, depilating agent, exfoliant, hair-conditioning agent, and nail-conditioning agent. Honey derived for cosmetic purposes is reported to be produced by the honeybee species *Apis mellifera*, *Tetragonisca angustula*, *Scaptotrigona pectoralis*, and *Melipona becheii.*

Of the ingredients included in this report, Honey has the most reported uses, with a total of 1059; 671 of these are leave-on products. Honey Extract has the second greatest number of overall uses, with a total of 398 (192 are in leave-on formulations). Honey has the highest concentration of use, and is used at up to 22% in paste and mud packs. The highest concentration of use reported for leave-on products was in body and hand products containing Honey Extract at up to 7%. The ingredients not in use according to VCRP data and the industry survey are Hydrolyzed Honey and Hydrolyzed Honey Protein.

Honey is common in food and food products worldwide. Honey can be found in OTC cough and cold medications. Traditional medicine suggests the use of honey for various ailments and skin issues. Currently, there is an FDA-approved dermal dressing containing honey used for the management of wounds and burns.

The effect of Palestinian honey on spermatogenesis was studied in male albino rats. Rats treated with Palestinian honey displayed a significant increase in epididymal sperm count. The activity of testicular marker enzymes for spermatogenesis, such as sorbitol dehydrogenase, was increased, and lactate dehydrogenase was reduced, indicating an induction of spermatogenesis. The effect of honey on the reproductive system of rat male offspring was studied. Testosterone levels were significantly lower in treated animals compared to control animals. The percentage of abnormal sperms were significantly higher in the offspring of dams treated with honey versus the control group. All other parameters were similar between treated and control group.

The potential anti-mutagenic effect of various honeys on Trp-p-1 was studied. Acacia, fireweed, soy, and tupelo honeys demonstrated enhanced antimutagenicity above 1 mg/mL, with inhibition between 40.3 and 62.9%. Concentrations above 20 mg/mL demonstrated no enhancement of the antimutagenic effects. Clover and Hawaiian Christmas berry honey were most

effective at 20 mg/mL, with 64.8 and 59.6% inhibition, respectively. The greatest inhibitory effect of buckwheat honey was observed at 1 mg/mL (52.1%).

In an anti-tumorigenicity study, Sprague-Dawley rats were given an injection of the carcinogen MNU and either given no treatment or treatment with manuka or tualang honey (1 g/kg bw/day) via diet. Groups treated with honey showed a significant reduction in tumor size and weight compared to the nontreated positive control. In addition, tumors in the positive control were large and hard, while tumors in honey-treated groups were small and soft.

In New Zealand white rabbits, treatment with aerosolized honey reduced the number of airway inflammatory cells present in bronchioalveolar lavage fluid and inhibited goblet cell hyperplasia. In addition, treatment with aerosolized honey led to a significant decrease in the thickening of the epithelial and mucosal regions. The nasal cavities of New Zealand white rabbits were irrigated with a honey and saline solution. No histological evidence of inflammation, epithelial injury, or significant morphological changes were observed.

Twenty subjects were used in a study to determine the allergic potential of manuka and multi-floral honey following ingestion. IgE levels remained at a level consistent with a non-atopic response during the course of the study.

The potential cytotoxic effect of honey-impregnated wound dressings on human skin keratinocytes and dermal fibroblasts was studied. Keratinocytes and fibroblasts treated with honey implants displayed a modest uniform increase in early cell proliferation and cell counts per mm. No cytotoxic effects were observed.

The anti-carcinogenic potential of honey (up to 15%) was studied using renal cell carcinoma cell lines. Honey decreased cell viability and induced apoptosis in malignant cells in a concentration- and time-dependent manner. A similar study was performed using tualang honey (1 - 10%) on human breast cancer, cervical cancer, and normal breast epithelial cell lines. Treatment with honey induced cell death in all cancer cell lines, but no clear cytotoxic effect was observed in the normal breast epithelial cells. In a different study, the effect of tualang honey (0.2 – 2 g/kg) on breast cancer-induced rats was observed. Smaller tumors were observed in honey-treated rats compared to control animals. In addition, the number of cancers developed in honey-treated rats was significantly lower than control groups.

An HRIPT that was performed on 112 subjects using a cosmetic product containing 7% Honey Extract applied using occlusive conditions yielded negative results. In an HRIPT performed on 116 subjects using a test substance containing 0.01% Honey Extract, tested as a 1% dilution, the test substance was considered to be non-sensitizing.

Twenty-five subjects were used in a 2-week prospective study to determine the safety of manuka honey eye cream on blepharitis patients. Twenty-three of 25 participants did not report any tolerability issues or adverse effects following the first day of product application. In two individuals, application too close to the eyelash margin and the use of excessive cream was presumed to result in a transient stinging sensation.

Honey-based ointment was used as part of a treatment of damaged skin in 8 children. No adverse effects or allergic reactions were reported after treatment.

Generalized urticaria was reported in a patient 20 minutes after ingesting foods with honey. After inadvertent contact with traces of honey, the same patient reported other allergic symptoms. Skin prick tests on common allergenic foods yielded negative results, however, prick-to-prick testing using different honey types yielded positive results.

After using cosmetics blended with edible honey and using honey as a face pack for 8 years, a woman reported allergic reactions after using a face pack containing honey and body soap containing honey. A year after these symptoms occurred, the patient experienced abdominal pain after ingestion of honey. Prick tests with honey yielded positive results.

DISCUSSION

The Panel reviewed the available, relevant data to assess the safety of these honey-derived ingredients as used in cosmetics in the present practices of use and concentration. The Panel noted the lack of sensitization data for six of the seven ingredients, but determined that the available sensitization data on Honey Extract could be used to support the safety of the remaining ingredients. The safety of these ingredients is further supported by historical food use and use in wound dressings.

As Honey Powder has been reported to be 50% filler material, the Panel also discussed the safety of the possible filler ingredients (starch, carboxymethyl cellulose, gum Arabic, maltodextrin, and gelatin), and determined that these ingredients are not of concern. All of the named fillers have been previously reviewed by the Panel, and were considered safe as used in cosmetics.

The Expert Panel expressed concern regarding pesticide residues and endotoxins that may be present in these ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit these impurities. In addition, the Panel noted the importance of avoiding the use of honey derived from toxic plant sources for use in cosmetic formulations.

The Panel discussed the issue of incidental inhalation exposure from formulations that may be aerosolized (e.g., colognes and toilet waters at up to 0.25% Honey). The Panel noted that in aerosol products, 95% – 99% of droplets/particles

would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

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

Honey	Honey Extract	Hydrolyzed Honey Protein*
Honey Cocoates	Hydrogenated Honey	
Honey Powder	Hydrolyzed Honey*	

**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. INCI names, definitions, and functions of the honey ingredients in this safety assessment[1,2]

Ingredient	Definition	Function
Honey 8028-66-8	Honey is a saccharic secretion gathered and stored by honey bees of the species, *Apis mellifera*, *Tetragonisca angustula*, *Scaptotrigona pectoralis*, or *Melipona becheii*	flavoring agent; humectant; skin-conditioning agent-humectant; solvent
Honey Cocoates	Honey Cocoates is a complex mixture of esters produced by the reaction of honey with coconut acid [*The fatty acid composition of coconut oil (from which coconut acid* (CAS: 61788-47-4) *is derived) is 0-1% caproic, 5-9% caprylic, 6-10% capric, 44-52% lauric, 13-19% myristic, 8-11% palmitic, 0-1% palmitoleic, 1-3% stearic, 5-8% oleic, 0-2.5% linoleic*]	antiacne agent; film former; skin-conditioning agent – miscellaneous
Honey Extract 91052-95-5	Honey Extract is the extract of Honey	skin-conditioning agents-humectant; skin-conditioning agents-miscellaneous; solvents
Honey Powder	Honey Powder is the powder obtained from dehydrated, ground honey	abrasives; binders; bulking agents; depilating agents; epilating agent; exfoliant; flavoring agent; hair conditioning agent; nail conditioning agent; skin-conditioning agent-miscellaneous
Hydrogenated Honey	Hydrogenated Honey is the end product of controlled hydrogenation of honey	humectants; skin-conditioning agents-humectant; skin-conditioning agents-miscellaneous
Hydrolyzed Honey	Hydrolyzed Honey is the hydrolysate of honey derived by acid, enzyme or other method of hydrolysis	skin-conditioning agents-humectant
Hydrolyzed Honey Protein	Hydrolyzed Honey Protein is the hydrolysate of honey protein derived by acid, enzyme or other method of hydrolysis	hair conditioning agents; skin-conditioning agents-miscellaneous

Table 2. Chemical Composition of Honey[3]

Constituent	g per 100 g honey
water	17.1
carbohydrates	82.4
fructose	38.5
glucose	31
maltose	7.2
sucrose	1.5
proteins, amino acids, vitamins, and minerals	0.5
calcium	0.0044 - 0.0092
potassium	0.0132 - 0.0168
copper	0.000003 - 0.0001
iron	0.00006 - 0.0015
magnesium	0.0012 - 0.0035
manganese	0.00002 - 0.0004
phosphorous	0.0019 - 0.0063
sodium	0 - 0.0076
zinc	0.00003 - 0.0004
ascorbic acid	0.002 - 0.0024
thiamin	< 0.000006
riboflavin	< 0.00006
niacin	< 0.00036
pantothenic acid	< 0.00011
pyridoxine (B6)	< 0.00032

Table 3. Honey polyphenols quantified with the HPLC-DAD method[19]

Honey	Polyphenol	Mean amount (mg per 100 g honey)
acacia	*p*-coumaric acid	0.077 ± 0.003
chestnut	*p*-coumaric acid	2.952 ± 0.004
eucalyptus	quercetin	0.164 ± 0.007
sunflower	caffeic acid	0.242 ± 0.001
sunflower	*p*-coumaric acid	0.107 ± 0
sunflower	kaempferol	0.205 ± 0.003
sunflower	chrysin	0.217 ± 0.002
thyme	*p*-coumaric acid	0.070 ± 0
wild carrot	*p*-coumaric acid	0.223 ± 0.001

Table 4. Physicochemical properties and constituents of tualang vs. manuka honey[22]

Property	tualang honey	manuka honey
Appearance	Dark Brown	Light to Dark Brown
pH	3.55 – 4	3.2 – 4.21
Moisture Content	23.3%	18.7%
Total Reducing Sugars	67.5%	76%
fructose	29.6%	40%
glucose	30%	36.2%
sucrose	0.6%	2.8%
maltose	7.9%	1.2%
potassium	0.51%	1%
calcium	0.18%	1%
magnesium	0.11%	1%
sodium	0.26%	0.0008%
carbon	41.58%	-
oxygen	57.67%	-

- = Not Reported
-tualang honey: Malaysian multi-floral jungle honey produced by *Apis dorsata*
-manuka honey: Australian or New Zealand mono-floral honey produced by *Apis mellifera*

Table 5. Frequency (2020) and concentration (2018) of use of honey ingredients[27,28]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Honey		Honey Cocoates		Honey Extract	
Totals*	**1059**	**0.00001 - 22**	**NR**	**2**	**398**	**0.000002 – 7**
Duration of Use						
Leave-On	*671*	*0.0001 – 3*	*NR*	*NR*	*192*	*0.0000034 – 7*
Rinse-Off	*377*	*0.00001 – 22*	*NR*	*2*	*191*	*0.000002 – 0.01*
Diluted for (Bath) Use	*11*	*NR*	*NR*	*NR*	*15*	*NR*
Exposure Type						
Eye Area	23	3	NR	NR	10	NR
Incidental Ingestion	27	0.00035 – 3	NR	NR	17	NR
Incidental Inhalation-Spray	2; 186[a]; 353[b]	0.001 – 0.25; 0.01 – 0.75[b]	NR	NR	2; 70[a]; 73[b]	0.0000034 – 0.001; 0.00001 – 0.0021[b]
Incidental Inhalation-Powder	186[a]; 7[c]	3; 0.0005 – 3[c]	NR	NR	70[a]	0.0001; 0.001 – 7[c]
Dermal Contact	882	0.00001 – 22	NR	NR	291	0.000002 – 7
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	145	0.000039 – 10	NR	NR	62	0.0000034 – 0.005
Hair-Coloring	2	0.01 – 0.8	NR	NR	25	0.0001 – 0.006
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	209	0.00035 – 3	NR	NR	89	0.00028 – 0.01
Baby Products	13	0.01	NR	NR	NR	0.00051

	Honey Powder		Hydrogenated Honey	
Totals*	**6**	**NR**	**6**	**0.25**
Duration of Use				
Leave-On	*3*	*NR*	*1*	*NR*
Rinse Off	*3*	*NR*	*5*	*0.25*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	2[a]	NR	1[a]	NR
Incidental Inhalation-Powder	2[a]	NR	1[a]	NR
Dermal Contact	6	NR	6	0.25
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – no reported use

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2020 VCRP Data for Honey Ingredients

Honey

Baby Shampoos	1
Baby Lotions, Oils, Powders, and Creams	7
Other Baby Products	5
Bath Oils, Tablets, and Salts	3
Bubble Baths	4
Other Bath Preparations	4
Eyeliner	1
Eye Lotion	11
Eye Makeup Remover	1
Mascara	2
Other Eye Makeup Preparations	8
Cologne and Toilet waters	1
Perfumes	1
Hair Conditioner	56
Hair Straighteners	2
Rinses (non-coloring)	2
Shampoos (non-coloring)	43
Tonics, Dressings, and Other Hair Grooming Aids	31
Wave Sets	1
Other Hair Preparations	9
Hair Shampoos (coloring)	1
Other Hair Coloring Preparation	1
Foundations	9
Lipstick	20
Makeup Bases	1
Makeup Fixatives	1
Other Makeup Preparations	18
Nail Creams and Lotions	1
Dentifrices	1
Mouthwashes and Breath Fresheners	1
Other Oral Hygiene Products	5
Bath Soaps and Detergents	128
Deodorants (underarm)	1
Other Personal Cleanliness Products	42
Aftershave Lotion	1
Shaving Cream	1
Other Shaving Preparation Products	2
Cleansing	55
Depilatories	2

Face and Neck (exc shave)	65
Body and Hand (exc shave)	120
Moisturizing	296
Night	17
Paste Masks (mud packs)	32
Skin Fresheners	6
Other Skin Care Preps	37
Suntan Gels, Creams, and Liquids	1
Indoor Tanning Preparations	1

Total = 1059

Honey Powder

Cleansing	2
Face and Neck (exc shave)	2
Paste Masks (mud packs)	1
Other Skin Care Preps	1

Total = 6

Honey Extract

Bath Oils, Tablets, and Salts	6
Bubble Baths	7
Other Bath Preparations	2
Eye Shadow	2
Eye Lotion	1
Eye Makeup Remover	1
Mascara	3
Other Eye Makeup Preparations	3
Other Fragrance Preparation	2
Hair Conditioner	22
Rinses (non-coloring)	1
Shampoos (non-coloring)	28
Tonics, Dressings, and Other Hair Grooming Aids	10
Other Hair Preparations	1
Hair Dyes and Colors (all types requiring caution statements and patch tests)	1
Hair Tints	22
Hair Shampoos (coloring)	1
Hair Bleaches	1
Blushers (all types)	2
Foundations	1

Lipstick	16
Makeup Bases	1
Other Makeup Preparations	2
Mouthwashes and Breath Fresheners	1
Bath Soaps and Detergents	45
Other Personal Cleanliness Products	12
Cleansing	33
Face and Neck (exc shave)	51
Body and Hand (exc shave)	19
Moisturizing	52
Night	9
Paste Masks (mud packs)	23
Skin Fresheners	1
Other Skin Care Preps	16

Total = 398

Hydrogenated Honey

Cleansing	2
Face and Neck (exc shave)	1
Paste Masks (mud packs)	3

Total - 6

No reported use for: Honey Cocoates, Hydrolyzed Honey, or Hydrolyzed Honey Protein

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: December 3, 2019

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

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

Introduction - It should be made clear that Coconut Acid was reviewed by CIR in reports published (rather than "finalized") in 2011 and 2017. The CIR report published in 2019 (reference 45) on monosaccharides and disaccharides (includes Fructose, Glucose, Maltose and Sucrose), the main components of Honey, should also be mentioned in the Introduction.

Impurities - Please include a reference for the European limit of 40 mg/kg for HMF in honey.

DART - The description of reference 47 states: "When male offspring reached 10 weeks old, these rats were mated with regular estrous cycle females and evaluated." The results of this mating are not described in the CIR report. This information should also be mentioned in the Summary.

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Personal Care Products Council
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Memorandum

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

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

DATE: January 14, 2020

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

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

Key Issues

Either the data on tualang honey included in the report needs to be deleted, or the following statement in the Introduction should be deleted: "however, the relevance of these data have yet to be determined."

Further information on the source of manuka honey should be included in the report. In addition to being made by *Apis mellifera*, this honey is a New Zealand and/or Australian monofloral (manuka bush) honey.

Additional Considerations

Impurities - The HMF limits from the *Codex Alimentarius* should be cited to the *Codex Alimentarius*.

Cosmetic Use - Please state the product category in which Honey Cocoates was reported to be used at a concentration of 2%. For product categories for which use concentrations were reported in the PCPC survey, but no uses were reported in the VCRP, it currently states: "number of formulations unknown". This implies that the number of formulations for other product categories is known. As the VCRP is a voluntary program, the number is just the number that was reported. Please state: "no uses reported to the VCRP".

Non-Cosmetic Use - As reference 41 is a WHO monograph that cites another book chapter for the information on the dermal penetration of *Clostridium botulinum* spores, it is not appropriate to call this "a study".

DART; Summary - Since the dams were treated with honey and the male offspring studied (reference 48), please revise: "significantly higher in animals treated with honey" to "significantly higher in offspring of dams treated with honey".

Dermal Irritation and Sensitization - Rather than stating "test substance" it would clearer if it said

"cosmetic product" (reference 58).

Discussion - It should be noted that the honey powder with fillers is used in food.

Table 1 - Please correct the definition of Hydrogenated Honey ("Hydrogenation" should be "Hydrogenated")

Table 4 - As a footnote to this Table, it would be helpful to define both tualang and manuka honeys.