Safety Assessment of *Rosa canina*-derived Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: March 17, 2017
Panel Date: April 10-11, 2017

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: March 17, 2017
Subject: Draft Final Report on *Rosa canina*-derived Ingredients

At the September 26-27, 2016 Panel meeting, the CIR Expert Panel issued a Tentative Report with a conclusion stating that the 12 *Rosa canina*-derived ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating and non-sensitizing. Comments that were received from the Council (*rosaca042017pcpc)* have been addressed. Additionally, the report has been revised to include 2017 FDA VCRP data (*rosaca042017FDA*) relating to ingredient use frequencies. The following revisions relating to ingredient uses in various product categories include: Rosa Canina Fruit Extract (not used in hair straighteners; new use in lipstick), Rosa Canina Flower Extract (not used in tonics, dressings, and other hair grooming aids), Rosa Canina Fruit (new use in eye lotions and in other hair preparations), Rosa Canina Leaf Extract (not used in hair conditioners or in tonics, dressings, and other hair grooming aids), and Rosa Canina Seed Extract (not used in baby shampoos).

Included in this package for your review is the Draft Final Report (*rosaca042017rep*), , the CIR report history (*rosaca042017hist*), literature search strategy (*rosaca042017strat*), ingredient data profile (*rosaca042017prof*), minutes from the March 26-27, 2016 and September 26-27, 2016 Panel meetings (*rosaca042017min*), 2017FDA VCRP data (*rosaca042017FDA*), and comments that were received from the Council (*rosaca092016pcpc).*

After considering the data included in this safety assessment, the Panel will need to determine whether or not a Final Report with the conclusion that is stated in the first paragraph should be issued at this meeting.

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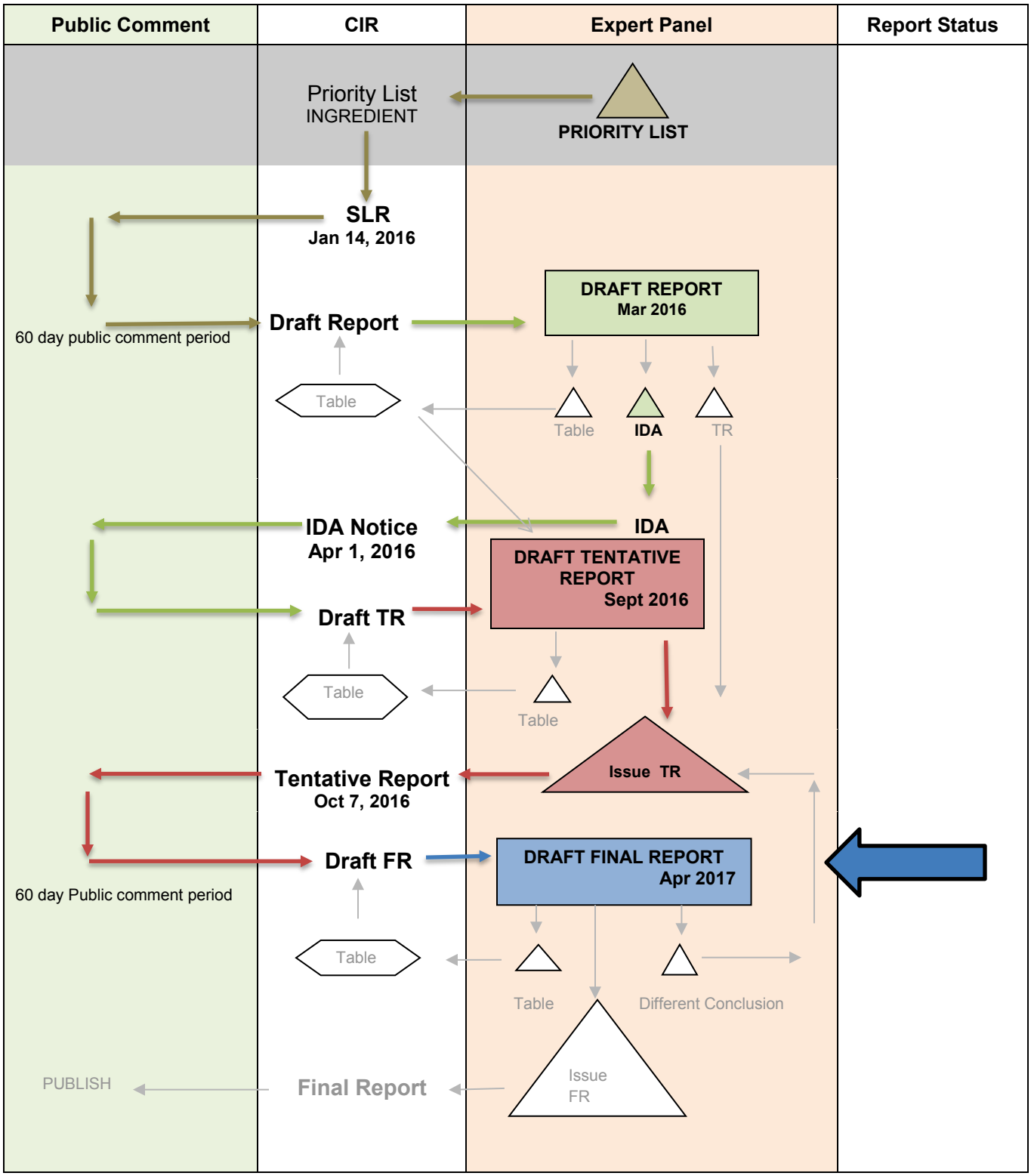
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Rosa canina*-derived Ingredients

MEETING April 2017



CIR History of:

Rosa canina-derived Ingredients

A scientific literature review (SLR) on *Rosa canina*-derived ingredients was issued on January 14, 2016. Unpublished data were received during the 60-day comment period.

Draft Report, Belsito and Marks Teams/Panel: March 31-April 1, 2016

Unpublished data and comments received from the Council during the 60-day comment period have been added/addressed.

The Panel was made aware of publications relating to the composition of Rosa Canina Flower Extract and Rosa Canina Leaf Extract, and agreed that pertinent information should be added to the safety assessment. The Panel also determined that data from the published CIR Final Report on Butylene Glycol should be added, because Butylene Glycol is a major component of Rosa Canina Fruit Extract. The inhibitory effect of Rosa Canina Fruit Extract on skin pigmentation both *in vivo* and *in vitro* was discussed.

It was agreed that Rosa Canina Flower Oil, listed in the *International Cosmetic Ingredient Dictionary and Handbook*, should be added to the safety assessment.

The Panel issued an Insufficient Data Announcement (IDA) with the following data requests:

(1) Method of manufacture
(2) Composition and impurities
(3) Use concentration data on Rosa Canina Bud Extract, Rosa Canina Flower Oil, Rosa Canina Flower Powder, Rosa Canina Fruit Juice, Rosa Canina Leaf Extract, Rosa Canina Seed, and Rosa Canina Seed Powder
(4) 28-day dermal toxicity data
(5) Skin irritation and sensitization data

Draft Tentative Report, Belsito and Marks Teams/Panel: September 26-27, 2016

The safety assessment has been revised to include the ingredient Rosa Canina Flower Oil, a summary of data from the published CIR Final Report on Butylene Glycol, and data (from published literature) relating to the composition of Rosa Canina Flower Extract and Rosa Canina Leaf Extract. Additionally, HRIPT/In-use data on product formulations containing Rosa Canina Flower Extract and updated ingredient use concentration data (received from the Council in response to the IDA) have been incorporated. The updated use concentration data do not include use concentrations for any of the 7 ingredients mentioned in the IDA.

The Expert Panel issued a Tentative Report with a conclusion stating that the 12 *Rosa canina*-derived ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be non-irritating and non-sensitizing.

Rosa Canina Fruit Extract
Rosa Canina Bud Extract*
Rosa Canina Flower
Rosa Canina Flower Extract
Rosa Canina Flower Powder*
Rosa Canina Flower Oil*
Rosa Canina Fruit
Rosa Canina Fruit Juice*
Rosa Canina Leaf Extract
Rosa Canina Seed*
Rosa Canina Seed Extract
Rosa Canina Seed Powder

*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.

Draft Final Report, Belsito and Marks Teams/Panel: April 10-11, 2017

The Draft Final Report has been revised to include the Council's comments (received during 60-day comment period on Tentative Report) and 2017 FDA VCRP data relating to ingredient use frequencies.

***Rosa canina*-derived Ingredients Check List for April, 2017. Analyst – Wilbur Johnson**																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Rosa Canina Fruit Extract								**X**						**X**		**X**		**X**		
Rosa Canina Bud Extract																				
Rosa Canina Flower																				
Rosa Canina Flower Extract														**X**		**X**				
Rosa Canina Flower Powder																				
Rosa Canina Fruit								**X**												
Rosa Canina Fruit Juice																		**X**		
Rosa Canina Leaf Extract					**X**															
Rosa Canina Seed																		**X**		
Rosa Canina Seed Extract																				
Rosa Canina Seed Powder																				

[Rosa canina-derived Ingredients – 12-17-2015 & 8-9-2016 (Updated on 3-5-2017)]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Rosa Canina Fruit Extract		1/1	4/6	4/4	1/2	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Bud Extract		1/1	0/4	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Flower		1/1	1/3	4/7	1/2		0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Flower Extract		1/1	6/251	0/0	1/2	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Flower Oil		1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0
Rosa Canina Flower Powder		1/1	0/3	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Fruit		1/1	22/154	4/5	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Fruit Juice		1/1	5/11	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Leaf Extract		1/1	6/144	1/2	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Seed		1/1	3/10	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Seed Extract		1/1	3/14	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes
Rosa Canina Seed Powder		1/1	0/4	2/2	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	Yes

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
Rosa Canina Fruit Extract		No	No	No	Yes	No	No
Rosa Canina Bud Extract		No	No	No	Yes	No	No
Rosa Canina Flower		Yes	No	No	Yes	No	No
Rosa Canina Flower Extract		No	No	No	No	No	No
Rosa Canina Flower Oil		No	No	No	No	No	No
Rosa Canina Flower Powder		No	No	No	No	No	No
Rosa Canina Fruit		Yes	No	No	No	No	Yes
Rosa Canina Fruit Juice		No	No	No	No	No	No
Rosa Canina Leaf Extract		No	No	No	Yes	No	No
Rosa Canina Seed		Yes	No	No	Yes	No	No
Rosa Canina Seed Extract		No	No	No	No	No	No
Rosa Canina Seed Powder		No	No	No	Yes	No	No

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

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

LINKS

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

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

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

Day 1 of the March 31-April 1, 2016 CIR Expert Panel Meeting – Dr. Belsito's Team

Rosa canina-derived Ingredients

DR. BELSITO: Rosa in here also. So this is the first time we're seeing the report on 11 ingredients that function as skin conditioning agents, fragrances we're not going to deal with, cosmetic astringents, anti acne agents, abrasives and exfoliates. They are reported to be used in 336 formulations must of them leave on, maximum use 7 percent leave on for face and neck product. There is little information other then for the fruit extract for the ingredients extract, flower powder, and seed have no reported uses. So let's take a look at the document and what do we need?

DR. JOHNSON: We didn't have a weighed to submission.

DR. BELSITO: Yeah so it seems that the fruit derived ingredients are all in butylene glycol so shouldn't we have a little discussion from our butylene glycol report? Are the ingredients of the seeds sufficient to clear it or do we want you UV from the composition I don't think we need it in the other data. So basically on the seed all we have is the composition and I thought that we could clear the fruit, add in butylene glycol, clear all the fruit derived and clear the seed but the others were insufficient for composition impurities, concentration of use and other end point sensitization and irritation and in the discussion we had the keratin which we've dealt with before. The effects on pigmentation and the other biologic effects would be below the TTC. That's what I got after I looked at this but I'll open it up for discussion.

DR. LIEBLER: So I'm roughly in the same place as you Don. The only question I had was whether the seed Table 5 composition suffices to cover method of manufacture and I don't know if Rosa Canina seed listed at Table 5 is representative of the cosmetic ingredient. Maybe I'm being a little to persnickety about that but we definitely need flower bud and leaf and we don't have those. We'll get something back like the seeds were obtained, the seeds were dried, the seeds were crushed.

DR. BELSITO: But I do think since the fruits are all in such very high concentrations of butylene glycol that to clear those we need to bring in some from butylene glycol report. So we're going to go all the fruit derives are safe as used everything else is insufficient and what we want is composition impurities, method of manufacture and concentration of use for those where it is missing and sensitization and irritation and concentration of use.

DR. JOHNSON: Does seed go to the insufficient side?

DR. BELSITO: Yes.

DR. LIEBLER: I had one other comment on PDF 11 at the very bottom there's a section entitled cytotoxicity which is basically about these ascities sarcoma cells with an LD 50 for the seed extract of 10 megs per ml which is a bucket load and the authors noted these results indicated possible anti carcinogenic effect. I don't that can be extraculated from this study. In fact I don't think this study is necessarily relevant. I don't think we would conclude for example in our summary of discussion that these are anti carcinogenic based on that.

DR. BELSITO: What page again Dan?

DR. LIEBLER: PDF 11 at the bottom.

DR. BELSITO: So you're suggesting we eliminate that?

DR. LIEBLER: Yes we either eliminate it or our discussion we don't bring this in. We haven't gotten to the discussion yet but when we get to that point I don't agree with the interpretation that the authors put on this.

DR. BELSITO: That is was anti carcinogenic?

DR. LIEBLER: Right I just wanted to flag that so that if we consider this later as part of our discussion I don't think this in and of itself provide any significant evidence of anti carcinogenicity.

DR. JOHNSON: So we just delete the entire statement?

DR. LIEBLER: Well I've had things like this before we've had these odd ball in vitro studies where you dump a bunch of the ingredient and the cells turn purple or something and I've always wanted to exclude those but we've kind of gone back and forth on that.

DR. BELSITO: We can ask the other group.

DR. LIEBLER: Yeah I'm not saying we need to exclude but I don't agree with the author's interpretation.

DR. KLAASEN: I think they put a nice fudge word in it that indicated a possible. They at least say it was anti.

DR. LIEBLER: That's true.

DR. JOHNSON: Dr. Belsito in this it referred us to two publications that relate to the composition relating to the flower and leaf.

DR. BELSITO: But this wasn't in any of the information we have.

DR. JOHNSON: No.

DR. BELSITO: This is all new.

DR. SNYDER: We'll look at it next time.

DR. BELSITO: Yeah.

DR. JOHNSON: Because you had mentioned insufficient data.

DR. BELSITO: Right but we're not really prepared to take a good look at this now. This would be wave three at the last moment so we're going insufficient and this can be brought in any other thing.

DR. JOHNSON: Well actually with respect to the leaf you have the oil and those components.

DR. BELSITO: So the oil from leaves are there.

DR. JOHNSON: And then the leaf extract general classes and compounds.

DR. BELSITO: And then the anti oxidants activities of the whole plant extract it doesn't say.

DR. JOHNSON: It is leaf.

DR. BELSITO: It says total anti oxidant activities of R. Canina extracts it doesn't say leaf.

DR. JOHNSON: Well in the method of manufacture section it indicates that the leaf was the source.

DR. BELSITO: But again we need to look at these more carefully so these can be brought in with whatever information as this is the first time we're looking at it. And this is also volatile oils and this is flower.

DR. JOHNSON: It also has the composition of the flower water in there also.

DR. BELSITO: Okay. Wilbur on PDF Page 8 method of manufacture it says that the part of the rosa canina plant that is used to manufacture rose canina fruit extract is the fruit without achene but when I looked what achene meant it is defined as dried fruit so that sentence makes no sense.

DR. JOHNSON: I included it as (inaudible).

DR. BELSITO: I understand but look up the definition of achene is dried fruit so how can you make a fruit extract if you don't have a fruit or do they just not dry it first? I don't understand that sentence. So right now we're adding butylene glycol, we're clearing the fruit derived and for all others the flower bud leaf and seed insufficient composition, impurities, concentration of use where we don't have it depending upon these we may need other toxicologic end points, carcinogenicity, we need sensitization, irritation and right now I think the keratin and pigmentation the other bio effects that are in here are all below the TTC and can be discussed in the discussion.

DR. LIEBLER: Agree.

DR. BOYER: Before we leave this one can we take a look at Page 10 I just want to point something out very quickly. PDF Page 10 just above the title non cosmetic that section you see the last line in that paragraph considered of estimates of inhalation exposures to spiral particles during the use of lose powder cosmetic products are no more than about 1 micrograms per kilogram per day. We're going to be discussion the respiratory probably beginning with the cyclosiloxanes but I did want to point out that as this report stands now one of our posed sentences for addition to address powders has been incorporated.

Day 1 of the March 31-April 1, 2016 CIR Expert Panel Meeting – Dr. Marks' Team

***Rosa canina*-derived Ingredients**

DR. MARKS: So tomorrow I'll move that these 31 ingredients are safe when formulated to be non irritating and then we'll have the discussion point about renal cancer. And, Tom, you can clarify that.

Okay. Any other comments about phosphoric acid? Next is rosa canina, dog rose. And this is also the first review of these ingredients. There are 11 of them. Is there any concern about the ingredients in this group, meaning the actual ingredients themselves. I think we have to include all of them, all 11.

Tom, Ron, Tom?

DR. SLAGA: I think all ingredients are appropriate.

DR. MARKS: Okay. And what are the needs we have for the safety assessment?

DR. SLAGA: Well, most of the data is related to food extract, which is non genotoxic and non irritating and non sensitizing, but very little data related to anything else.

DR. EISENMANN: One question. There is a flower essential oil in the dictionary that at one point was supposed to be in the report, but it's not actually in the report. I was told it was going to be put in the report, but it hasn't been put in the report. There's no uses, but you've got a flower extract. I don't know if you want the essential oil in it also.

MR. JOHNSON: That particular ingredient was reviewed in the CIR file report on fatty acid oil.

DR. EISENMANN: No, the fruit oil was reviewed in the fatty acid oil report, the flower, which is an essential oil, was not reviewed in that report. It was included in the concentration of use survey. I got no responses. And I don't think it has any uses reported to the VCRP.

DR. MARKS: Any concerns about adding the flower oil? Appropriate here versus the other report. The other would be -- doing it's a no brainer in the other report.

DR. HILL: Can we determine if that's a perfume ingredient? I guess it would have showed up in the concentration or use survey (inaudible).

DR. HELDRETH: It's listed as fragrance ingredients, skin condition agent, emollient.

DR. HILL: I guess what I was fishing for is has it been reviewed by RIFM and used primarily for fragrance. And that's not what you just said, so.

DR. HELDRETH: It's not exclusively listed. It's just listed as one of the function.

DR. HILL: Okay.

DR. MARKS: Do you want to add the flower oil at this point?

DR. SLAGA: I think at this point we can.

DR. MARKS: Sure.

DR. SLAGA: In some cases we delete them, in some cases we add them.

DR. MARKS: Okay.

MR. JOHNSON: Dr. Marks, just one --

DR. MARKS: Oh, yes, I'm sorry.

MR. JOHNSON: Rose hips extract is in RIMFs database and they have limited data on that particular ingredient, which would be the same thing as rosa canina fruit -- extract.

MS. FIUME: So, fruit or flower?

MR. JOHNSON: Fruit. They have limited data, just some occupational exposure data on that ingredient.

DR. HILL: So are you wondering can we roll this in for purposes of reading across --

MR. JOHNSON: Well, RIPM was mentioned, so I just thought I'd juts, you know, add that.

DR. HILL: Yes, okay.

DR. MARKS: The fruit extract, we have it in wave two, in a guinea pig max

test at 20 percent and it was a non sensitizer. And in this report the highest concentration of seven percent. So I thought the fruit extract was fine. That's the only one I felt we could say with definity it's a non sensitizer. The bud, the flower, the leaf, the seed ingredients, I wanted to see HRIPTs.

And then I want to also discuss the inhibition of skin pigmentation with oral exposure on page 13. That was interesting.

So let's go back. Team, were there any other needs? At this point we could send out an insufficient data notice and ask for the HIRPTs or say a guinea pig max sensitization data for the other plant parts, the bud, the flower, the leaf, seed ingredients, at use concentration for the leave-ons. Does that sound reasonable to you all?

DR. SHANK: Yes.

DR. MARKS: Okay. And then page 13, let me go to that. Did that raise concerns to -- oral administration -- this is in that paragraph under animal effects on skin pigmentation. The oral administration of the fruit to brown guinea pigs caused inhibition of skin pigmentation. Proanthocyanidins was found to be the active principle. And then in vitro they mentioned quercetin in here, which we've had problems with in the past. In an inhibitory effect on melanogenesis in melanoma cells in vitro. So I didn't exactly know how to translate that to topical application.

DR. SLAGA: Well, in the third extract would the proanthocyanidins ever reach that level? That's given in -- they say it's the active principle that brings about the pigmentation in guinea pigs.

DR. MARKS: So they administer, what, five milligrams per kilo body weight per day as an aqueous extract diluted to 10 percent. So does that mean they gave 50 milligrams per kilo body weight? It seems like milligrams per kilo, it seems like a lot, but I didn't calculate that out.

DR. SHANK: Where are you?

DR. MARKS: This is in page 13, responding to Tom's question, if it is the proanthocyanidins what's the amount of that chemical in the actual fruit extract that would have been -- is what's exposed by skin much lower than what would have been fed to these animals.

Under the composition can we answer that question? Do we know what percent? Methods, composition?

MR. JOHNSON: I don't see any data, composition of data.

DR. MARKS: The other thing, Tom, to me is would that be relevant to the skin even if -- you know, that's an oral administration, what about topically? Could you use a lower concentration and have an effect on skin pigmentation? You would think it would take a much higher oral does to effect skin pigmentation than say a topical does.

When we send out the insufficient data notice do we want to get more -- how do we want to put it? More information about the inhibitory effect on pigmentation? I don't think we want to ultimately end up with a formulated when not de-pigmenting the skin. (Laughter) I knew, Ron, you would like that one. That would wake you up.

SPEAKER: Yes.

DR. BERGFELD: That's a biological activity though; wouldn't that be a drug activity?

DR. MARKS: But we have dealt with pigmentation issues in the past, yes.

DR. SHANK: It would be a toxic response.

DR. HILL: So I'm pretty sure that we have information from previous reports, from previous papers, about the concentration dependence of those effects. And there were two components that you said, quercetin -- and what was the other one?

MR. JOHNSON: Proanthocyanidins.

DR. HILL: Yes, the proanthocyanidins. Yes, we've got information about those.

SPEAKER: That's in a lot of plants.

DR. HILL: Yes, that's out there. So I mean in the context of do we have concentrations of components in each of these ingredients, I was going to ask for method of manufacture, and I'm not sure we have full characterization in some of these cases.

DR. MARKS: So you would want more method of manufacture? If we got the

composition and got the, say, percentage of these two chemicals in the ingredient. We have an oral study, we have in vitro study, will that still reassure us if it's applied topically? Do you think you can extrapolate that?

DR. HILL: I think so because the use concentrations are so low, although we have some apparent aberrations in the table. Like I'm looking at a seven percent for a fruit extract. But what I'm saying is with method of manufacture it may turn out that, okay, seven percent of the fruit extract, but we really only have.003 percent of stuff in there, and of that.0 percent is those components of concern. And then all the concerns disappear because you're way below anything we have to worry about. And there is sketchy information, but I feel like I'm missing some of the things needed to connect the dots on that.

DR. SLAGA: We could ask for more information on the proanthocyanidins.

MR. JOHNSON: We had in the wave to submission correct use concentration data and --

DR. HILL: Okay. I just pulled up wave two and I didn't put it back there. So --

MR. JOHNSON: And it's the rosa canina flower extract that it has the highest reported use concentration at three percent.

DR. HILL: Three percent? So where is that seven percent coming from?

MR. JOHNSON: That old data.

DR. HILL: Old data?

MR. JOHNSON: Mm-hmm.

DR. HILL: Okay. And that's --

DR. SLAGA: So even if the proanthocyanidins were 10 percent it wouldn't be very much.

DR. HILL: Well, we should be able to do that math if we have the information. That's what I'm driving at. And I think we'll find it's not a concern, but absent submitting the information --

DR. SLAGA: They get 500 milligrams per kilo of the fruit extract in that pigmentation study?

DR. MARKS: Yes.

DR. SLAGA: And they get ultraviolet light to induce it?

DR. MARKS: 500 milligrams per kilo. That's exactly right. But then it was diluted to 10 percent. So it's actually not 500, that would be 50, right? One tenth of that. Now why they just didn't say -- that's on page 13.

DR. SLAGA: Yes, I got it.

MR. BEST: I had a question about -- and so may be this is deep in old data issues, this is not applicable anymore, but in the -- not wave 2, the regular report, the five percent, the indoor tanning preparation, I just had a question about how that related to the pigmentation issue. I wasn't sure what that was, if that was an issue, but that sort of caught my eye, what kind of product that was or -- and if that's -- or is that not in the new data?

DR. MARKS: Which page are you on?

MR. BEST: Sorry. It's page 30 of the report. Not the wave two, it's a five percent indoor tanning preparation. I just -- it just sort of caught me because I know you were talking about the pigmentation and that issue and how it might relate to that. I just don't know.

SPEAKER: Page 32?

MR. BEST: I'm sorry, page 30.

DR. MARKS: Yes, 30. I would agree with you. I don't know either because it seems contradictory that you would add it.

MR. BEST: Right.

SPEAKER: Yes, it seems like the opposite.

DR. MARKS: Okay. So --

SPEAKER: I didn't catch that. It's weird right?

DR. HILL: Yes. And it's so much higher than any other concentrations there. You kind of wonder if that's accurate or it's an error.

DR. MARKS: So we'd like to get the percent composition, more information on Proanthocyanidins. Am I characterizing that correctly at this point, to try and get a handle on the inhibiting skin pigmentation?

DR. SHANK: Yes. We need more than that.

DR. MARKS: Yes.

DR. HILL: Quercetin, glucoside or -- I think it's glucoside. Quercetin or however you say it.

DR. MARKS: Okay. And then you mentioned method of manufacturing; you wanted more information on that, Ron Hill?

DR. HILL: I think, you know, we're doing read across here, even though the concentrations are low and we only -- I'm only finding that for one ingredient. Is there -- did I miss something in wave two?

MR. JOHNSON: There was manufacturing data in wave two.

DR. HILL: So I'm trying to remember what all did we get.

MR. JOHNSON: On Rosa canina, fruit extract, that's the ethanol extract.

DR. HILL: Okay.

MR. JOHNSON: And the butylene glycol extract as well.

DR. HILL: Okay. And that duplicates partly what we -- because the one thing that we did have in method of manufacture already was something about fruit extracts. So these are more fruit extract. So the point is we have all these other ingredients and nothing about how they're prepared at all, yes?

DR. MARKS: So specifically, Ron Hill, you'd like to -- what in the method of manufacture, just again?

DR. HILL: Just an idea with what these substances are that we're really dealing with. I mean if it's flower water we pretty well know what that is, but how are they extracted?

DR. MARKS: Okay.

DR. HILL: Supercritical fluid, ethanol, aqueous, elevated temperature, not steam distill -- what's the story?

DR. MARKS: Okay. Okay. So presumably any other comments?

DR. SHANK: Do we need a lock? It's stuck.

DR. MARKS: We're going to keep on going.

DR. SHANK: Okay.

DR. MARKS: Yes, that's what I -- that's why I asked, you've been quiet there, Ron.

DR. BERGFELD: You can use the new algorithm that was developed for ginko. (Laughter)

DR. MARKS: There you go.

SPEAKER: These are botanicals.

DR. MARKS: That's an interesting proposal, actually, going forward with this. We want to see how it fits.

DR. HILL: Why would we not?

DR. MARKS: Exactly. So, Wilbur, maybe you can, between now and when we see this again, comment on the decision tree as it affects -- I'm going to put that in -- use proposed -- thank you, Wilma -- decision tree, botanical decision tree. Is that how we're going to refer to this, botanical decision tree? I like that. Okay.

DR. SLAGA: Wilbur, could we -- is it possible to get reference 30 by tomorrow morning?

MR. JOHNSON: Sure.

DR. SLAGA: That's the study of -- one of the composition data shows any proanthocyanidins and they obviously -- if they said it's the active principle that paper must have a percentage of the food extract.

SPEAKER: That's ringing a bell. I know I've seen this paper somewhere along the line.

DR. MARKS: Okay. According to Ron Shank there's lots needed.

DR. SHANK: Yes.

DR. MARKS: So let me see here. So I have three things now, method of manufacture, more information on that, more information on the inhibition of skin pigmentation, particularly what the composition of these are, and more information about the two ingredients -- or two chemicals that proanthocyanidins and quercetin. What else do we need, Ron?

DR. SHANK: Skin irritation and sensitization on all of them.
DR. MARKS: Yes, other than the fruit extract.
DR. SHANK: Well, the fruit extract, the sensitization data don't give the concentration.
DR. MARKS: I have --
DR. SHANK: I don't have -- on this completed, I have two.
DR. MARKS: Yes, I have 20 percent in a guinea pig maximization, no irritation, no sensitization. Is that correct?
MR. JOHNSON: That's in the --
DR. MARKS: And that was wave two.
MR. JOHNSON: That was wave two.
DR. MARKS: Yes.
DR. SHANK: Unfortunately I didn't put it on this.
DR. MARKS: But that's the only part of wave two that was reassuring. I agree with you.
DR. SHANK: Okay.
DR. MARKS: That's why I said.
DR. SHANK: It needs sensitization on all of the others?
DR. MARKS: Yes.
DR. SHANK: Irritation --
DR. MARKS: And I put HRIPT. That would be the gold standard in my mind, but if it's --
DR. SHANK: Sensitization, yes.
DR. MARKS: Yes, sensitization, irritation, for the bud, the flower, the leaf, and the seed ingredients. They've used concentration for leave-ons. Good.
DR. SHANK: Twenty-eight day dermal, toxicity for all of them. We have no toxicity in agent.
DR. EISENMANN: Even on the fruit?
DR. BERGFELD: Why not?
DR. EISENMANN: I just thought rose hips are -- this is where the botanical framework might help because I think they would be considered food.
DR. SHANK: Food. But this is not a systemic toxicity -- well, actually this is --
DR. EISENMANN: I mean I'm not questioning the need for the skin data, it's just the systemic toxicity for the fruit, not the flowers or anything else.
DR. SHANK: Okay. You can skip that one.
DR. MARKS: Well, not, is it -- do we know -- I would say leave it in and since it's an insufficient data notice we can come back and say the fruit is okay because it is a food and we know it's safe, but is it GRAS?
DR. EISENMANN: I don't know.
DR. SHANK: I don't think it's GRAS.
DR. MARKS: So why don't we leave it in for all ingredients and see what comes out?
DR. SHANK: I would. Unless you know it's GRAS I don't think --
DR. HILL: Well, and I think we've already been through the limitations of when something is said to be GRAS. So at least we start with asking for something. If it turns out it's something we don't need to be asking for --
DR. EISENMANN: There's a 35 day study in here.
DR. HELDRETH: And it is in CFR. Rose hips -- under substances generally recognized as safe, specifically essential oils, oleo resins, and natural extractives, including rose hips. Meaning the fruit.
DR. MARKS: Are rose hips the same as rosa canina?
MR. JOHNSON: It's the same thing. There's rosa canina fruit.
DR. MARKS: Okay.
DR. SHANK: It's the same plant, same species. Rose hips is from rosa canina.
SPEAKER: Okay. But then for the rest of them we need 28 --
DR. MARKS: So for all the ingredients other than the fruit at this point, Ron

Shank?

DR. SHANK: Well, it -- if rosa canina fruit extract is represented scientifically by rose hips, okay.

DR. MARKS: I think what I'm going to do is put in here 28 dermal tox on all ingredients. Clarify what rose hips are. Does that sound reasonable? Then that way we know -- we don't just pass over the fruit at this point.

DR. SHANK: Right.

DR. MARKS: If rose hips is the fruit. Okay. And then other needs? You seem like you had lots there, Ron Shank, so was there more?

DR. SHANK: Well, it would depend -- the results of the 28 day dermal, what else we'd look at. Mutagenicity data we need.

DR. MARKS: Tom.

DR. SLAGA: We do have the fruit extract. Seed and fruit juice I guess. Let me see what those look like. We have one Ames Assay on fruit extract and one end Ames Assay on boiled fruit juice, or whatever it is. Fruit that was boiled, stewed, and then evaluated. What that has to do with the cosmetic ingredient I'm not sure. That's pretty minimum geno (inaudible).

DR. MARKS: So, Tom, need more data? So mutagenicity data for all of them?

DR. SLAGA: Right now I would say for all of them because one Ames Assay is not good measure of potential mutagenicity.

DR. MARKS: Okay. And anything else, Ron Shank?

DR. SHANK: No.

DR. MARKS: Okay. So tomorrow I presumably will be seconding a motion that an insufficient data notice be issued for these 12 ingredients. We're going to add flower oil to this first review. Wilbur is going to be the first writer to use the proposed botanical decision tree and see how that works. And we need the method of manufacture for these -- more information there, more information on the inhibition of skin pigmentation, HRIPT a/k/a irritation and sensitization on everything other than the fruit extract, 28 dermal tox on all the ingredients, clarifying if rose hips is the fruit, and then mutagenicity data for all.

Okay. Any -- let me see, I think that's the last ingredient. Do you want to take a break? (Laughter)

SPEAKER: A long break.

DR. MARKS: A long break. Okay. Any other comments that anybody has?

Day 2 of the March 31-April 1, 2016 CIR Expert Panel Meeting – Full Panel

***Rosa canina*-derived Ingredients**

DR. BELSITO: Rosa canina so this is the first time we are looking at these 11 ingredients which function as skin conditioning agents, fragrances which of course, we won't look at -- anti-acne agents which I assume is OTC and we won't look at abrasives, (inaudible) and exfoliates. Having looked at this, we felt the first glaring thing was that it turns out that the fruit extract is contained butylene glycol and percentages from 76 to 93. 5 percent so we felt that butylene glycol, in order to clear the safety at least had to be brought in here; we've previously reviewed that. With that in mind, adding butylene glycol, we felt that we could clear all of the fruit derived ingredients as safe as used when formulated to be non-sensitizing, however, for all of the others, the flower, the bud, the leaf and the seed, they were insufficient for composition impurities, concentration of use and depending upon the above sensitization and irritation, there were -- in the discussion there is the quercetin, there is the effect on pigmentation and other biological effects that we felt would be below the TTC for these materials but right now, sufficient for the fruit, insufficient for the other components.

DR. BERGFELD: Dr. Marks' comment? Dr. Marks?

DR. MARKS: We had, I think, similar -- first I think it depends on whether you want to issue an insufficient data notice since this is the first time we have seen this.

DR. BELSITO: Yeah, it's insufficient.

DR. MARKS: That notice versus issuing a tentative report.

DR. BELSITO: Whatever the usual steps are. It's the first time you looked at it and it's insufficient.

DR. MARKS: And we also propose and we will discuss a bit later the botanical decision tree and we thought this would be an opportune time to use that decision tree in handling this group of botanicals so that was our first comment on that. We would add the flower oil. I don't know, Don, if you mentioned that.

DR. BELSITO: Yeah I said flower insufficient.

DR. MARKS: Flower oil as an ingredient.

DR. BELSITO: A component of the flower however looking at the botanical decision tree, since this is not used in any form as a ingested product; I am not sure that helps us. It moves us down to the usual approach to --

DR. MARKS: It may well, Don. I thought that was -- the botanical decision tree was what was going to be the first pass.

DR. BELSITO: It completely fails it at the first step so it's not even worth discussing.

DR. SLAGA: Yeah, that's right.

DR. MARKS: Anyway, Ron Hill, you wanted to see more in the method of manufacture?

DR. HILL: Didn't you list that as one of your --

DR. BELSITO: Yes.

DR. HILL: Okay, yes.

DR. MARKS: Okay good and then we will -- you felt - - we didn't know what percentage of the composition of these ingredients contained the proathrocyanates or the quercetin, which was implicated in the inhibition of skin pigmentation. Apparently, you must have found somewhere where you can get a concentration because we want to know what that was so that we could get a threshold of safety on it so that was another one of our requests and then I think you -- I saw specifically -- pardon?

DR. SLAGA: Wilbur sent a couple of papers related to this and --

DR. BELSITO: Wilbur has that paper right now but by the time you dilute it down and --

DR. SLAGA: After reading them, I have no concerns. It's a really large quantity that they use and as a matter of fact, if you look at a lot of natural botanical with the many polyphemalic acids, there is a tremendous number that bring about the effect of high dosage. In a guinea pig model, they were exposed to ultraviolet light to bring about pigmentation but in culture,

as I said, large amounts are needed and it's interesting when they use human cells to study the (inaudible) activity and has no effect so it's somehow related to animals.

DR. HILL: It's a brown guinea pig specifically, isn't it?

DR. SLAGA: I have no concerns.

DR. MARKS: Good, somehow I missed that yesterday. Did you look at the paper while we were discussing it? It doesn't matter, right? That needs to be made clear, obviously in that discussion.

DR. BELSITO: Well we can incorporate that data, which is new and was not in --

DR. MARKS: And then you had mentioned the sensitivity, the 28 dermal tox on all ingredients was another one of our needs. I don't know if you mentioned that, Don, and then that was one of Ron Shank's concerns and to clarify if rose hips is the fruit, we weren't sure what rose hips were.

DR. BELSITO: Okay.

DR. KLASSEN: We had talks.

DR. MARKS: Yes.

DR. BELSITO: Data for all of them also. Assuming the composition -- depending upon method of manufacturing composition, we may want all of those additional studies or do you want them regardless?

DR. KLASSEN: I would ask for the opportunity --

DR. BERGFELD: Ron Hill? Oh, excuse me Wilbur, go ahead?

DR. JOHNSON: Yes, we do have a chromosomal aberrations essay on the extract of the rosa canina fruit in addition to the test, yes.

DR. BELSITO: Yeah, I said if you added in abuteline glycol, the free derived ingredients would clear. It's the others that are insufficient.

DR. BERGFELD: Ron Hill, did you have a comment?

DR. HILL: Yeah, I just had a comment, which was and I am just bringing people's attention to it more than anything else again, from yesterday is most of the usages in the table are at very low concentrations and then we have this anamolous 7 percent for the fruit extract but then if you look at the definition of "fruit extract," it says the food extract contains a few percent of the fruit extract so that's when the method of manufacture and I am really asking to sort of bring the industry's attention to that 7 percent, what does that really mean and make sure that we clarify that in the next round because if it's. 0000 whatever percent, which most of these are and then you look at constituents of concern, those are very very low levels and that, of course, matters.

DR. BELSITO: The fruit extract was defined as a very small percentage of the fruit in a large amount of butelyine glycol --

DR. HILL: You're right.

DR. BELSITO: So I am assuming it's seven percent of whatever that concentration is in the fruit extract so it's seven --. 07 times the point whatever so it's very low.

DR. HILL: That's my assumption too but it wasn't made fully clear.

DR. BELSITO: You would like Carol to go out and try to clarify that?

DR. HILL: I think so or she already knows it looks like.

DR. EISENMANN: Actually the seven percent went away when I asked for data on it so that's in the way too, I believe so the concentration has gone down with that.

DR. BELSITO: Yeah.

DR. BERGFELD: Well there is a consensus around the table for an insufficient data request.

DR. BELSITO: Right.

DR. BERGFELD: We don't have to vote on that but I would like to see a straw vote of all those that agree that it will go out as insufficient except for -- all right, thank you. Now the question is do we have the list of what is needed?

DR. BELSITO: Yeah.

DR. BERGFELD: Do you think you have the note? I just asked Lillian.

MS. BECKER: I think we have it.

DR. BERGFELD: We have the list so it was between the two of you and Jim; I

want to make sure we have all of that list and you were (inaudible) 28 day toxin, some of the other special toxicology studies. Okay, then we are going to move on to -- I am sorry, Paul?

DR. SNYDER: This is the rosa -- the last sentence of the cosmetic use section. Has the alternative language for the powders, which we preferred the cyclotetrasilocine as opposed to this one.

DR. BELSITO: Right, for the inhalation.

DR. BERGFELD: For the inhalation, yes and I believe that we need to keep addressing that with all of these different documents, to make sure that we have the right inhalation documents and citation in there.

DR. BELSITO: Okay. Anything else? Okay. So rosa canina-derived ingredients. So at the March meeting again an insufficient for these 12 rosa canina-derived ingredients. We wanted method of manufacture; composition and impurities; use concentration on the canina bud extract, canina flower oil, canina flower powder, canina fruit juice, canina leaf extract, canina seed, canina seed powder; 28-day dermal tox; skin irritation and sensitization. The only thing we got was an HRIPT on the flower extract and updated use and concentration.

MR. JOHNSON: And, Dr. Belsito, you also received an end-use test.

DR. BELSITO: So I guess the first thing that I just want to mention, having come back from the European Society of Contact Dermatitis meetings and they had a mini symposium on botanicals and plant-derived ingredients, is that one gentleman stood up and said that what we don't get is a certificate of analysis for the starting plant material. And he was concerned with -- certainly not for nuts and citrus that are picked off of trees, but for things that are harvested from the ground -- the potential for contamination with other weeds that might be growing in that soil. And then if you don't have a certificate of analysis for the starting material, what does that mean when you start extracting it, particularly if we're simply looking at composition of what we know to be the material we're looking at, unaware of the fact that there could be poison ivy thrown in with this material the way it was harvested. And in looking at this report and the other reports for hops and that, we don't have any certificate of analysis for the starting materials that industry begins with. And that's going to be true for all of these ground-growing materials that we've reviewed. So I'm just pointing that out as something that was mentioned. How do we deal with this? Do we want to deal with this or whatever because it's going to come up with other ingredients we're going to look at like hops and ingredients that we've already looked at before.

DR. LIEBLER: Well, we could craft a small boilerplate and it could be a sentence or two at the most that simply says the Panel -- a discussion boilerplate that the Panel is --

DR. SNYDER: In the absence of a certificate of analysis for the starting ingredient that we assume that there are no --

DR. LIEBLER: Right, that there is no significant contamination by other plant species that are not reviewed in this report.

DR. ANSELL: But I wouldn't tie that to the COA.

DR. LIEBLER: No. This term, certificate of analysis, is outside of our purview. But I mean whether the industry decides that's a good idea or not is up to them. But for us, we could say that the Panel assumes that the materials or that the ingredients -- I forget what meeting I'm at -- that the ingredients are those reviewed here rather than -- and then efforts should be made to minimize contamination by other plant species.

DR. ANSELL: Yeah, I would tie that in with saying pesticides.

DR. LIEBLER: It's just like a botanical boilerplate or the heavy metal boilerplate. It's all about minimizing contamination with things not reviewed in this report.

DR. GILL: So the concern was the minimization of the contamination and not so much that the manufacturer, what we may not know what the content is in the certificate of analysis.

DR. LIEBLER: Right. We almost never see those anyway. And while we're reviewing an ingredient, we review the ingredient with the assumption that -- well, if the composition is defined and with chemical species they're usually defined as X percent pure. With plants, it's X percent that plant and we almost never see anything like that. So we simply have to state that one of our assumptions is that that -- or one of our expectations is that contamination by other plant species will be minimized. In fact, we could simply add that to the botanical boilerplate.

DR. BELSITO: I have to tell you that a lot of people in the audience there were in agreement with this individual about that. So I mean I think it's probably important that we craft some language for botanical boilerplates where things that are harvested from the ground could be contaminated.

DR. SNYDER: Not all botanicals that's in it. There's a certain class --

DR. BELSITO: Right, yeah. Not things that grow from trees that aren't going to be contaminated by other things, but things that are harvested from things that are grown on the ground.

DR. ANSELL: I think somewhere in the botanical boilerplate, but it's not a unique concern that other materials manufactured in the facility not be cross- contaminated. There's nut issues of cross-contamination that if they're making drugs in one reactor that it not end up -- so I think it should be crafted and we'll work on crafting an appropriate sentence or two.

DR. LIEBLER: I think it could be added to the existing botanicals boilerplate because we worry about contamination with heavy metals and pesticides. This could simply be added to the same list of clauses in that botanicals boilerplate. And that the ingredients should be limited contamination by heavy metals, pesticides, and other plant species.

MR. JOHNSON: When you use the terminology of "other plant species," I guess it is understood that that includes weeds?

DR. BELSITO: Just any plants, other unrelated plant species.

DR. LIEBLER: So "unrelated" is problematic because then you have to make a determination of what's related and unrelated. So I think you just leave it "other" because we want to make it -- I mean I think that's actually clear; whereas if you start adding -- if you try and make it too clever -- keep it simple.

DR. ANSELL: I'd also like to talk to some of the botanical people because I'm confident that they have controls in place that they're talking about to their suppliers. I think we can craft a sentence or two.

DR. LIEBLER: Sure, I think so. I mean it's a good point. It's one we've sort of overlooked and it's a worthwhile point. We don't want poison ivy.

DR. GILL: We'll bring that language back.

DR. BELSITO: Okay, so that was just a general comment. I thought we could go safe as used with the usual botanical boilerplate when formulated to be nonsensitizing and nonirritating for these based upon the information we got.

DR. LIEBLER: Right. I thought we were still missing composition and impurities on the bud extract, unless we assume that bud is substantially similar to flower.

DR. BELSITO: Since bud is flower. That's what I sort of assumed.

DR. LIEBLER: It's sort of pre-flower.

DR. BELSITO: But if we're going to count downstream from flower, it's upstream from flower, so I don't know. Now we're going upstream.

DR. LIEBLER: That's right.

DR. BELSITO: I was okay with it, but I mean if you want to go insufficient for composition of the bud.

DR. LIEBLER: Okay, Don, this bud's for you. All right. I'm fine with it. Let's go with that. If we have a discussion tomorrow, we'll have a discussion.

DR. BELSITO: Okay. Paul? Curt?

DR. SNYDER: So I had a couple of notes here. Up to 93.5 percent butylene glycol?

DR. BELSITO: Yes. But butylene glycol -- so I went back and looked at the butylene glycol report and it was -- I mean if you do the analysis here, it ends up like being -- in terms of how much of these materials are used, it's like.2 and butylene glycol was approved in underarm deodorants up to 39 percent and in some other products up to

percent. So I mean we really covered the concentration of butylene glycol that would be present.

MS. LORETZ: We have the comment that we weren't sure why there would be specific information on butylene glycol in the report.

DR. BELSITO: Well, I think it was because like one of the extracts was 70 percent butylene glycol, and we wanted to make sure that was covered in terms of is that amount of butylene glycol going to be safe in a product and the answer is yes because these are used in such low concentrations. If you go back to the glycol report, we have concentrations of use for butylene glycol that I think went up to 89 percent.

MS. LORETZ: So then a reference to that report would seem to be the way to --

DR. ANSELL: As opposed to a standalone butylene glycol paragraph under

each of the tox sections.

DR. BELSITO: I don't have a problem with that.

DR. SNYDER: You have that statement in the intro. You just need to reference the butylene glycol report and just make a statement that the levels approved in that report far exceed the levels that would be in this ingredient class -- as an impurity?

DR. BELSITO: Well, it's not an impurity. It's a solvent.

MR. JOHNSON: Because in the report it says that rosa canina fruit extract can contain up to 93.5 percent, but the range is like 77 to 93.5.

DR. BELSITO: But it's used --- I mean if you do the math, it's used at.2 percent I think was the highest level for that extract. And so you get.2 percent butylene glycol. If you look at the butylene glycol report, it's used up to 39 percent underarm deodorants and 89 percent in other leave-ons. So it far exceeds. So I would agree. You don't need to keep repeating it. You simply say at the level of use -- or the level at which butylene glycol would be present in products containing rosa canina, it's significantly -- orders of magnitude lower -- than safe levels of butylene glycol.

DR. SNYDER: As approved in the referenced report.

DR. ANSELL: Rather than carrying butylene glycol in case studies of butylene glycol in ocular irritation.

DR. LIEBLER: So you can strip out all the butylene glycol sections of the report under the different data sections and tox studies, et cetera.

MR. JOHNSON: Okay.

DR. SNYDER: Then the last thing was about the depigmentation of the fruit extract.

DR. BELSITO: Yeah, that was handled in the discussion. It's much higher levels. It was in animals only.

DR. SNYDER: And the other thing, all of the Clark studies are -- oh, we didn't put in any, okay. I had a note that you put butylene glycol in everything except the Clark studies. There's plenty of Clark studies on butylene glycol, but you didn't reference any. But it doesn't matter now because we're not going to include any of that information.

MR. JOHNSON: Now, that statement on butylene glycol should only appear in the introduction, or should it appear in the discussion as well?

DR. SNYDER: I think in both. I think the discussion needs to come back around.

DR. LIEBLER: I agree, both.

MR. JOHNSON: I know the Panel had also requested day dermal toxicity data.

DR. LIEBLER: I don't think we did.

DR. SNYDER: I think that was in lieu of if we didn't get adequate method of manufacture and composition and use data, then we might want to include dermal. But I think that the method of manufacture and composition and use data then make that less.

DR. LIEBLER: And, Wilbur, in the last paragraph of the draft discussion on PDF 33 you have a sentence, "The Panel also noted that it should be made clear they do not agree with the interpretation of results of the positive cytotox assay as an anti-carcinogenic effect." This is a point I raised in the last meeting, but I don't think it deserves to be in the discussion. I don't think it's necessary. So I would delete that sentence.

DR. BELSITO: And then your first sentence under the toxicokinetics studies you say that "toxicokinetic data on rosa canina-derived ingredients were neither found in the published literature nor would finding these in the literature be expected." Why wouldn't it be expected? Why would you not expect to find them?

MR. JOHNSON: That's a boilerplate statement.

DR. GILL: And that was based on comments from the Council that you wouldn't expect toxicokinetic data.

DR. LIEBLER: Well that may be true, but it doesn't need to be there. So I would just suggest "published literature."

DR. BELSITO: I mean it almost sounds like we're saying okay, we wouldn't expect it, so we didn't look for it, rather than saying they weren't found.

DR. SNYDER: Right, none identified or provided. So I want to go back to that

--

DR. KLAASSEN: You wouldn't know what to look for. These are mixtures.

DR. BELSITO: Right.

DR. KLAASSEN: If you were going to do the toxicokinetics on these mixtures --

DR. BELSITO: Yeah, I think there's one report where they say something a little bit more that makes sense, but I still have an issue of just saying it wouldn't be expected.

DR. KLAASSEN: I agree.

DR. LIEBLER: If you're making Curt's point, I agree. That makes sense. This isn't really Curt's point. This is sort of I don't expect it, but what do I know.

DR. GILL: Well, let me ask the Panel since we have that in a number of reports and probably it's been standard by now. Should we include Curt's rationale for why we didn't find any or just leave it that we didn't find it?

DR. BELSITO: I think in one report there seemed to be some rationale. I don't know if was in Christina's --

DR. LIEBLER: So if I understand Curt correctly, he's referring to the fact that these are complex mixtures and toxicokinetics would have to encompass all of the toxicokinetics for all of the chemicals in the mixtures. And we're not going to be able to -- that's not realistic to find. But this is simply saying it would not be expected, meaning that why would you not expect it? It doesn't get into Curt's point. So any language that addresses the complexity and that toxicokinetics are not necessarily unapproachable for this complex mixture, that's okay. This doesn't really hint at that problem. It just simply says it's not expected and the reader is left to wonder what you're thinking.

DR. ANSELL: We would use that language more where there was no expectation of an endpoint, not that the study was unexpected. I mean it's not -- there's no carcinogenicity, but there's no structures of concern.

DR. LIEBLER: Like skin sensitization for the hydrofluorocarbon.

DR. ANSELL: Right.

DR. BELSITO: In the report on helianthus annuus it says, "Data on the toxicokinetics of helianthus annuus- derived ingredients would not be practical because these ingredients are complex mixtures." That explains why you wouldn't expect to find it. But just saying "would not be expected to be found" leaves you -- I just don't like the way that sounds. I mean I think the reading on the sunflower-derived ingredients is that we're going to put that in the way it should go. And then it goes on to say, "However, exposure to the components of these ingredients in cosmetics is expected to be lower than exposure resulting from dietary," so that was for GRAS substances.

DR. SNYDER: I want to go back to the pigmentation issue again. So right above the draft discussion, the second paragraph above the draft discussion --

DR. BELSITO: Let me get back to --

DR. KLAASSEN: What page?

DR. SNYDER: I'm on a Word document so it's irrelevant to your PDF, but it's right above the draft discussion. "The fruit extract caused a reduction in UVB- induced skin pigmentation in guinea pigs."

DR. LIEBLER: This is PDF 33, top.

DR. SNYDER: Thank you. And then in the draft discussion we say, "The Panel was concerned about the presence of quercetin and proanthocyanidins in cosmetics, which could result in skin depigmentation." Well, a reduction in pigmentation and depigmentation is different.

DR. BELSITO: Well, there was -- so what they're doing is they're giving ultraviolet B and they're inducing skin pigmentation. Then the fruit extract reduced the amount of pigmentation that UB induced.

DR. SNYDER: Correct.

DR. BELSITO: But there was another -- wasn't there another -- there were in vitro studies that showed that it was depigmenting, no?

DR. SNYDER: "Quercetin, isolated from a methanolic extract of rosa canina fruit, reduced the melanin content of mouse melanoma cells."

DR. BELSITO: Right. That was in vitro data. And basically what Tom Slaga said at the last meeting is that these levels were extraordinarily higher than the levels that you would expect in product. So it was below the threshold of toxicologic concern essentially.

DR. SNYDER: So I would rather say we were not concerned about the presence of quercetin because we're not concerned about it in the discussion because we say we're concerned.

DR. BELSITO: Where?

DR. SNYDER: In the second paragraph of the draft discussion, next to the last line, "For rosa canina-derived ingredients, the Panel was concerned about the presence of quercetin and proanthocyanidins in cosmetics."

DR. BELSITO: We should say "noted the potential presence" rather than "concerned," and then why we weren't concerned.

DR. SNYDER: Okay, that's better.

DR. LIEBLER: You need to add a sentence about why we're not concerned?

DR. BELSITO: Well, it says, "however, because" -- in the draft discussion "final product formulations" -- well, wait a minute.

DR. LIEBLER: You know, what you could do is that second to last sentence of that paragraph before "for rosa canina-derived ingredients, the Panel was concerned," to "the Panel noted." But you move that sentence up to be the new second sentence in that paragraph.

DR. BELSITO: And keep the word "concerned?" I would still get rid of "concerned."

DR. LIEBLER: No, no. It'd be "noted." But you change that and then you move it up to the beginning.

DR. SNYDER: I would just say "although for rosa- derived ingredients the presence of quercetin and proanthocyanidins were at levels that would not produce skin depigmentation" or something like that.

DR. LIEBLER: So the first sentence in that paragraph introduces the potential problem. And then the second sentence says why we don't think it's a problem. And then you get down to the second to last sentence and you reintroduce another version of the problem. So move the problems up together.

DR. ANSELL: Those two sentences are -- I mean the opening sentence is a concern about the inhibition of pigmentation. The last sentence is talking about depigmentation.

DR. SNYDER: That's what I'm saying, it's two different things.

DR. ANSELL: So they're not even --

DR. LIEBLER: Right, but they both go away for the same reason, so move them up together.

DR. KLAASSEN: It's almost an over --

DR. ANSELL: Well, "could result in skin depigmentation" probably should be "is aware of these studies."

DR. BELSITO: Well, do we even need to repeat that because we go on to say, "in vitro and in vivo studies," which are both the depigmenting and the inhibition of UB- induced pigmentation, "quercetin components were identified as the active principles for this effect. However, the Panel noted the use concentration of this ingredient and, thus, the levels of these components was considered below the threshold of toxicologic concern." So we don't even need to repeat quercetin. We can just eliminate that entire sentence, can't we? We've already dismissed it.

DR. LIEBLER: Sure.

DR. ANSELL: It's a lot of verbiage for something we can dismiss.

DR. BELSITO: Because we say in vitro and in vivo studies, which are the depigmenting and inhibition of depigmentation.

DR. SNYDER: So in the first sentence instead of saying "inhibition of skin pigmentation," just say "skin pigmentation modulation by rosa canina" because in one it was depigmentation and related UB and the other one it was inhibition of the cell line. Two different things, right? It's not just inhibition.

DR. LIEBLER: How about "effects on skin pigmentation?"

DR. SNYDER: There you go.

DR. LIEBLER: So begin that paragraph with the words "effects on skin pigmentation" instead of the "inhibition of."

DR. ANSELL: So the Panel noted the reports on --

MR. JOHNSON: But we're still moving the statement that begins with "For rosa canina-derived?"

DR. SNYDER: No, deleting that.

MR. JOHNSON: Deleting that altogether, okay.

DR. GILL: Are you keeping the "modulation" -- the suggested insertion of "modulation" Paul made? "Effects on skin pigmentation?"

DR. SNYDER: No, I think you --

DR. GILL: And just take out the "modulation?"

DR. SNYDER: "Effects on skin pigmentation by rosa."

DR. BELSITO: "Were reported."

DR. SNYDER: "Were reported."

DR. ANSELL: Then the botanical boilerplate about constituents, that sentence and the caution about formulating, need to be put together again.

MR. JOHNSON: And there's a statement beginning with "Furthermore," is that going to be deleted also?

DR. BELSITO: I'm not sure what you're --

DR. LIEBLER: It's the fourth sentence, third sentence. "Furthermore, it was noted that this inhibitory effect has not been observed in human cell cultures." I would delete it.

DR. SNYDER: Delete it. And I would delete the last two sentences and that third sentence and then just change the wording of the first sentence because the last sentence was also a repeat of the third to last sentence.

DR. BELSITO: Where are you now?

DR. SNYDER: The last sentence, "Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause adverse effects."

DR. ANSELL: That's the boilerplate associated with the statement that final formulations may contain multiple botanicals. So I think those two sentences are our boilerplate that somehow got separated.

DR. SNYDER: By the intervening sentence on --

DR. BELSITO: So we need the last sentence. So let me just go through this. So in the second paragraph under draft discussion, we're saying "The effects on skin pigmentation by rosa canina extract were reported in in vitro and in vivo studies" duh, duh, duh. All of that is fine up until we get to "for rosa canina-derived ingredients." We're deleting that sentence. So we're just changing "inhibition" to "the effects on," changing "was" to "were," and deleting the sentence on "rosa canina-derived ingredients." Is that correct?

DR. LIEBLER: Correct.

DR. BELSITO: Okay.

DR. SNYDER: Are we taking out the "Furthermore" sentence?

DR. LIEBLER: Oh, the "Furthermore" sentence.

DR. SNYDER: That comes out, too.

DR. BELSITO: Where?

DR. SNYDER: "Furthermore," the third sentence. That comes out.

MR. JOHNSON: And when you said "was" to "were," what sentence were you on?

DR. BELSITO: The fourth line down in the sentence that begins with "Furthermore." That's being deleted.

MR. JOHNSON: Right.

DR. LIEBLER: But, Wilbur, the first sentence, first line, is now "effects on skin pigmentation by rosa canina fruit extract were reported" instead of "was" because it's effects now. It's plural.

DR. SNYDER: And that last sentence from Tom about not agreeing with their interpretation of the positive cytotoxicity study?

MR. JOHNSON: That was from Dr. Liebler and he said to delete that.

DR. SNYDER: Oh, I'm sorry.

DR. BELSITO: Where's this?

DR. SNYDER: The last sentence there. "The Panel also noted --

DR. LIEBLER: The last little paragraph, one- sentence paragraph, in the draft discussion. "The Panel also noted that it should be made --

DR. BELSITO: Oh, yeah. I said it was not phrased very well. We also had some data with pesticides we're not going to say anything about that. So we're just deleting everything?

DR. LIEBLER: Just deleting that sentence.

DR. BELSITO: That whole sentence. I'm fine with that. He's one of my colleagues. So we have aerosol uses. Do we have the aerosol boilerplate in the discussion? I can't remember. No. So we need the aerosol boilerplate there?

MR. JOHNSON: Yes, that should be included in the discussion, aerosol.

DR. BELSITO: Right. Now typically in other botanical reports, we've mentioned some of the constituents of concern. Here for depigmentation we mention quercetin and proanthocyanidins. But we didn't mention sensitizers, of which there are a number that I highlighted in the tables. Should we mention anything about those like the eugenol, the linalool? In the past in other reports we're talking about limitations on the hydroperoxides of linalool and limonene. And the composition that we're getting here, certainly we know that eugenol is a sensitizer. There are a number of others, sesquiterpene hydrocarbon. Should we mention any of those or is it just --

DR. LIEBLER: I think if we're going to end up with a conclusion safe when formulated to be nonsensitizing, we pretty much are obligated to mention sensitizers in the discussion, constituents of concern. So we can simply say, "The Panel noted these ingredients contained several constituents of concern for sensitization, including -- "

DR. BELSITO: "Such as eugenol." Let me see what other ones I highlighted. Basically it's on Table 5. So linalool. So you need to mention the hydroperoxides are a very low percentage, eugenol, phenethyl alcohol, benzyl alcohol, the pinenes, sesquiterpene hydrocarbons. You could pick any of those five and I think just mention that IFRA has limits. I can't remember. I know we have limits on eugenol. I don't know if we -- you should check, Wilbur, to see if there's a limit on eugenol. But the limits for the hydroperoxides of linalool have been well described in other reports that we're reviewing today. Eugenol. Dan, do you remember? Does IFRA have a standard for eugenol?

DR. LIEBLER: I don't know.

DR. BELSITO: But you could check with them.

MR. JOHNSON: Now in the discussion you're going to mention those constituents of concern and just indicate the products should be formulated?

DR. BELSITO: Well, I don't think we need -- we've never mentioned all of them. We've always just mentioned "for example." So I think if you're looking at constituents of concern here, the ones that would pop out would be eugenol and linalool for the potential for hydroperoxide formation. So I would say "such as eugenol." Find out if there is -- I mean I'll see if I can get that answer for you before tomorrow from the IFRA database whether there's a standard for eugenol, but it certainly is a sensitizer. And then there is a standard that's been referenced in multiple botanical reports for the hydroperoxide levels for linalool. You can just pick that up from any of the other reports. So I would just say, "For example, eugenol and -- "

DR. SNYDER: And phenethyl alcohol?

DR. BELSITO: Phenethyl alcohol is a labeled one, but I don't know that there's an IFRA standard. I'll check for eugenol and phenethyl alcohol.

DR. ANSELL: Yeah, there is for eugenol.

DR. BELSITO: I thought so.

DR. ANSELL: Between 2/10 and 5/10, depending on the category.

MR. JOHNSON: Is there an IFRA Website, Jay?

DR. ANSELL: Yes.

MR. JOHNSON: Okay.

DR. BELSITO: So you can just mention -- again, I wouldn't even mention phenethyl alcohol. I would simply say, "for example, eugenol where there is an IFRA standard, and linalool where there is an IFRA standard."

DR. SNYDER: Yeah, I would just say it contains a number of potential allergens, recognized allergens.

DR. BELSITO: Both sensitizers, and then in parentheses "(for example, eugenol where there's an IFRA standard, and linalool where there's an IFRA standard for hydroperoxides)." We don't have to list all of the potential sensitizers.

MR. JOHNSON: And don't even mention sesquiterpene hydrocarbons in there, okay.

DR. BELSITO: And that's a broad category of chemical groups. I would just mention those two.

MR. JOHNSON: Okay.

DR. BELSITO: Now on page 41, PDF 41, under current frequency and concentration of use, under incidental inhalation powders you still have the 7 percent. I thought at the last meeting Carol said there wasn't a 7 percent, so I'm presuming that that's been corrected because in your total concentration range under the fruit extract you have it only up to.25. So that needs to -- I don't know what it is in inhalation powders, but the 7 percent is not correct.

DR. SNYDER: So under developmental reproductive toxicity studies, the last sentence of the last paragraph, "Results relating to dominant lethal and cytogenetic effects are summarized in the following section." And if you go into the following section --

MR. JOHNSON: Where are you? I'm at the beginning of the section.

DR. SNYDER: The last sentence.

DR. BELSITO: I don't have that. Where are you?

DR. SNYDER: That last sentence.

DR. BELSITO: Under developmental and repro?

DR. SNYDER: Yeah.

MR. JOHNSON: Okay, that should be deleted because that was in the butylene glycol report.

DR. BELSITO: Data on --

MR. JOHNSON: No, that last sentence.

DR. BELSITO: That's butylene glycol.

MR. JOHNSON: Right.

DR. SNYDER: Oh, okay. All right.

DR. BELSITO: That's all going to go away.

DR. LIEBLER: I noticed that, too. It was just cut and paste.

DR. SNYDER: All right, that's it.

DR. BELSITO: That's it.

MR. JOHNSON: Just one more concern. The Panel had requested use concentration data on several ingredients, and the updated surveys did not indicate any use concentrations for those ingredients for which information was requested.

DR. BELSITO: I mean typically we've dealt with that. When we don't have use concentrations, we assume they're being used in concentrations similar to the other ingredients. But I think we're just throwing in everything and the kitchen sink with our insufficient data request in the hopes that we might get additional information. So we've made some changes with the discussion, Wilbur, primarily in terms of the depigmenting effect and mention of sensitizers, the botanical boilerplate to include restrictions of other plant species, and PCPC may work with that and do a little editorial wording as I understood from Jay. And then we're getting rid of the butylene glycol throughout and just pointing out in the introduction and again in the discussion that the levels of butylene glycol present in this material as used would be significantly, almost two orders of magnitude, below where it's been approved to be used by itself; and then with all that discussion safe as used when formulated to be nonsensitizing and nonirritating. Does that capture everything?

DR. LIEBLER: Think so.

DR. BELSITO: And deleting that comment on the anticarcinogenicity.

DR. LIEBLER: Right.

MR. JOHNSON: Dr. Belsito, the end of the conclusion is going to talk about restricting it to formulated to be nonirritating and nonsensitizing.

DR. BELSITO: Right, the typical botanical.

MR. JOHNSON: Should any statements related to specific studies be included in the discussion? My concern is about sensitization potential.

DR. BELSITO: Wilbur, that's going to be covered by the multiple botanicals. The issue is multiple botanicals, so in final formulation. And we're going to point out the eugenol and the oxidized hydroperoxides and linalool as an example of IFRA restrictions.

MR. JOHNSON: So that covers concerns about irritation and sensitization?

DR. BELSITO: Yeah, that's the usual botanical boilerplate, and we don't need to go further in the discussion other than point out that there are constituents that these are safe. But if you start adding them to other botanicals that have linalool, eugenol, pinene, you could get at levels that would be unsafe in terms of irritation and sensitization. So it's final formulation. The ingredients themselves are fine.

DR. LIEBLER: Correct.

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DR MARKS: Okay. Any other comments? If not, I'll be moving tomorrow with a safe when formulated to be non- irritating. Okay, next ingredient is rosa canina. So this is a draft tentative report, an insufficient data announcement was concluded at the March/April meeting of this year. Under Wilbur's memo, there's a number of items, method of manufacture, composition impurities, use concentration of several of these ingredients, 28 dermal tox, skin irritation and sensitization. Tom, Ron, Ron, we would be moving onto a tentative report, having a conclusion.

DR. SHANK: Well, I had for the food extract.

DR. MARKS: Fruit.

DR. SHANK: Fruit extract--

DR. MARKS: Safe?

DR. SHANK: Safe.

DR. MARKS: Was it, was it all the fruits or just the fruit extract, because I have fruit safe when formulated to be non-sensitizing.

DR. SHANK: Okay.

DR. MARKS: Does that sound--

DR. SHANK: Yes.

DR. MARKS: Uh--

DR. SHANK: But I didn't include flower extract in that.

DR. MARKS: Right. I have all the rest, but flower, leaf and seed were still insufficient. Do we need this 28 day dermal tox? That was mentioned under point four.

DR. SHANK: I have that as still as a need.

DR. SLAGA: Yeah.

DR. SHANK: For the flower extract.

DR. SLAGA: I do too for that.

DR. MARKS: Okay. For the flower extract?

DR. SHANK: Yes.

DR. MARKS: For flower. And the only method of manufacture we got was the fruit extract.

DR. EISENMANN: I had a maximum concentration of.04 percent.

DR. SHANK: What is?

DR. EISENMANN: Flower extract is used at.04 percent. And you still need (inaudible).04 percent, you did get an HRIPT on that product I believe.

DR. MARKS: Yes, you're right on both of those, the fruit and the flower extract from a sensitization and irritation, they were good. So, Ron, do you still want to see that 28 day dermal tox for the flower extract?

DR. SHANK: Well, that's what I have, so let me see.

DR. MARKS: And while you're looking--

DR. SHANK: What page is use concentration on for flower.

DR. EISENMANN: Table Eight.

DR. SHANK: What page is that, please?

DR. EISENMANN: I don't have the page numbers.

DR. MARKS: Okay. Let me go down and see.

DR. SHANK: Fruit.

MR. JOHNSON: That's on PDF page 41.

DR. MARKS: Thank you.

MR. JOHNSON: You're welcome.

DR. HILL: What are we looking at?

DR. SLAGA: Oh, use data.

DR. SHANK: The flower extract.

DR. MARKS: Whether you need a 28 day dermal tox for the flower extract when it's used at 0.04, 24 uses, 0.04, so.

DR. SHANK: Oh, I guess not.

DR. MARKS: Okay. And then for the, let me get rid of that. And then for the needs, we're still where we were before for the bud, flower, leaf, seed, we need method of manufacture, correct. And we need composition and impurities. Is that correct?

DR. SHANK: Yes.

DR. MARKS: And then, as far as the use concentration, we don't have any for the seed extract and the powder. Okay.

DR. HILL: I wanted clarification as to whether, let's see, my reference page is page 21, clarification whether we are using 1.3 butylene glycol or 14 butylene glycol because we're talking about very high percentages of the ingredient.

MR. JOHNSON: Which page--

DR. HILL: So 21 is the, it occurs first on page 21. The reason I ask is because we've got a structure of 1.4, but reason to think that it might be 1.3. We've got butylenes glycol present in that fruit extract at 76.5 to 93.5 percent. It's, it's the major component. So the question is is it in fact 1.3, which is what I think, based on what had in another ingredient report in terms of commonality of use, or is it in fact 1.4 because the 1.4 is what we have as a structure. And we might not have that information, so we need to get clarification.

DR. MARKS: Okay. Any other comments, so tomorrow presumably, I'm going to, I'll be seconding a motion to issue a tentative report with a conclusion that the fruit ingredients, that's the extract, the fruit itself and juice are safe when formulated to be non-sensitizing. The remaining ingredients from the bud, flower, leaf and seed are insufficient, method of manufacture or composition and impurities and use concentration of the seed extract in powder.

MR. JOHNSON: Dr. Marks, can you just repeat that just once more, please?

DR. MARKS: Sure. The whole?

MR. JOHNSON: Yes, please.

DR. MARKS: Safe for the fruit ingredients, that's the extract, fruit and juice, there are three of them, when formulated to be non-sensitizing. The remaining ingredients, the bud, flower, leaf and seed ingredients, insufficient for method of manufacture, composition and impurities and use concentration for the seed extract in powder. That's from number three.

DR. BERGFELD: What did you do with the flower? Because you have contact patch testing for flower.

DR. MARKS: Yeah, flower was okay from a sensitivity, but we don't have the other data, method of manufacture, or composition and impurities. And this would be a tentative report, yeah. So team, does that sound good?

DR. SLAGA: Sounds good.

DR. SHANK: Yes.

DR. MARKS: Okay.

DR. HILL: Yes.

DR. MARKS: The next ingredient.

DR. SHANK: I have--

DR. MARKS: Oh, editorial.

DR. SHANK: No. Well, maybe. On page 33 in the discussion, the second paragraph, I'd like to delete the last two sentences about quercetin and proanthocyanidin. And it says the manufacture should avoid reaching levels that may cause adverse effects. That's basically saying formulated to be non-toxic, which I object to strongly. The paragraph deals with this very well. I don't think the last two sentences are necessary. Certainly the last sentence isn't. And on page 24, under toxicokinetic studies, it says that the toxicokinetic studies wouldn't be expected in the literature. Why would we say that? Why would -- I don't understand that. So I would just eliminate that sentence.

DR. MARKS: Okay. You have those, Wilbur?

MR. JOHNSON: Yes.

DR. HILL: Well, I think the point is how would you, what would you characterize if you tried to do a toxicokinetic of a group of, of a substance that is numerous components.

DR. SHANK: We have that all the time.

DR. HILL: Yes. We have not seen any toxicokinetic studies of botanicals except as relates to a particular constituent of concern.

DR. SHANK: So what provokes you to put it in this document?
DR. HILL: Oh, okay. No, I didn't say it.
DR. SHANK: And not a hundred others that--
DR. HILL: I think we have had a clause like that in some past documents. In fact, I know that we have.
DR. SHANK: That you wouldn't expect to find it in the literature?
DR. HILL: Yes.
MR. JOHNSON: I know the other team suggested the wording that's in the helianthus report, I've forgotten the complete name of that ingredient, to just say that those data would not be expected because these are--
DR. MARKS: Annulus.
MR. JOHNSON: -- complex mixtures.
DR. MARKS: Sunflower.
DR. SHANK: Mm-hmm.
DR. MARKS: So is that, do we need to bring that up tomorrow as an editorial?
DR. SHANK: Yes, and (inaudible) report.
DR. MARKS: Presumably, the Belsito team, since they will be commenting first on this will bring it up. Do, do we need to bring that up tomorrow, or is that editorial?
DR. SHANK: They're going to change, that's fine.
DR. MARKS: Okay, any other comments. Thank you, Ron. Ron Shank, any other comments?
DR. SHANK: No.
DR. MARKS: Okay.
DR. HILL: I'm not sure I understood the distinction between the two things that you just said, but okay, I mean.
DR. BERGFELD: They are the same.
DR. HILL: Yeah, okay. Thank you.
DR. BERGFELD: Differently stated.
DR. HILL: Oh.
DR. BERGFELD: But same impact.
MR. JOHNSON: I guess the rationale as to why they would not be expected, if that's--
DR. SHANK: Well, to do, you can't do toxicokinetic studies on mixed--
DR. HILL: Right.
DR. SHANK: Okay. That's the point. You wouldn't expect it in the literature, why do you say that? They have it, but they're not going to publish it?
DR. HILL: Yeah.
DR. SHANK: So, it's a--
DR. MARKS: Okay.
DR. BERGFELD: Why don't you say it differently?
DR. SHANK: Well, he just did.
DR. BERGFELD: That's okay?
DR. SHANK: Okay.
DR. MARKS: Do you want to repeat that Wilbur, just so that we're all on the same page?
MR. JOHNSON: I'll read from Christina's report. "No relevant published toxicokinetic studies on citrus flower and leaf (inaudible) ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted. Toxicokinetics data were not expected to be found because each botanical ingredient is a mixture of hundreds of constituents."
DR. MARKS: That's exactly what you said, Ron. Okay. Any other comments about dog-rose?
DR. SHANK: Oh, as long as you're there, at some place in the lit-, at the very beginning, when you say -- I have to go back to the put parenthetically rose-hip, when you say rosa canina fruit.
MR. JOHNSON: Yes.

DR. SHANK: Just the very first time it comes up, just say rose hip parenthetically, because everybody knows about rose hips, but seldom do you call them rose fruit in the vernacular.

MR. JOHNSON: Okay.

DR. MARKS: Thank you.

And the first one is Rosa canina. Dr. Belsito?

DR. BELSITO: Okay, so just, again, as a start, this is another botanical, so that new boilerplate we have for other plant products.

So we looked at this at the March meeting. We felt it was insufficient data announcement for 12 of the ingredients. We requested method of manufacture, composition, and impurities data; use concentration data on the bud extract, flower oil, flower powder, fruit juice, leaf extract, seed, seed powder; 28-day dermal tox; skin irritation and sensitization.

We did get HIRPT on Rosa canina flower extract. We got updated ingredient use concentrations. They were added to the report.

And after looking at all of that, we felt that we could go with a safe as used when formulated to be non- sensitizing and non-irritating for all of these ingredients.

DR. BERGFELD: Jim, any comment?

DR. MARKS: We had a different conclusion. We felt that a tentative report could be issued with fruits, the extract, the fruit itself, and the juice safe when formulated to be non-sensitizing. We felt the rest of these botanical ingredients -- the bud, flower, leaf, seed -- was insufficient because of lack of method of manufacture, composition, and impurities, and we didn't have the use concentration for seed extract and powder.

DR. BERGFELD: Comment from the Belsito team?

DR. BELSITO: We felt that we had enough information on the flower to clear the bud. And in terms of lack of information about concentration of use, we very frequently have no information on concentration of use for chemicals that we sign off on and it's under the assumption that they'll be used in a similar concentration range as the others.

When you look at these, they're used in very low concentrations. In fact, there needs to be a correction to the use table because we were told at the last meeting by Carol that that 7 percent was incorrect, and it still appears in the use table. So if you look at the levels of use of these, they're very low.

DR. LIEBLER: I can add that the flower extract, which I think the flower extract gets us to the flower and, by our reasoning the bud, in the PDF page 23, under Rosa canina flower extract, it says, "Data on the composition of aromatic water obtained by hydrodistillation and dry distillation of Rosa canina flowers." I mean, that's got essentially a very brief description of method of manufacture embedded in that sentence. It's not listed in the method of manufacture section, but that was enough for me. This is a pretty routine way to make these kinds of extracts. And so I was comfortable enough with the flower extract to get us to the flower and the bud.

DR. MARKS: How about the leaf and seed?

DR. LIEBLER: Leaf and seed really didn't have that. We have leaf extract and it doesn't say exactly how -- well, it does say, "obtained by hydrodistillation distillation of Rosa canina leaves." Again, a fairly standard practice for producing these extracts. And then it says, "distillate extracted with hexane, dichloromethane, and methanol."

What's a little bit unclear is whether or not those are ways that the sample was prepared to analyze or whether that's the way the material was prepared or the ingredient was prepared. That might be clarified.

So, you know, we felt we were closer to being an acceptable yet minimal description to have a slightly higher comfort level with these.

DR. BELSITO: And the seed, we have composition on the seed in Table 7.

DR. SNYDER: And the leaves. We also have the leaves in Table 6.

DR. MARKS: Team?

DR. HILL: Hang on, I'm looking for Table 7. My sense is it's not in there.

DR. MARKS: So, Don, again, your motion is safe when formulated to be non-sensitizing for all the ingredients.

DR. BELSITO: And non-irritating.

DR. BERGFELD: And non-irritating.

DR. MARKS: And non-irritating, yes.

SPEAKER: Then that'd be fine.

DR. SHANK: The lack of information is covered by the mode concentration of use?

DR. BELSITO: What lack of information?

DR. SHANK: With several of the ingredients.

DR. BELSITO: Oh, we have --

DR. SHANK: Flower extract, for one.

DR. BELSITO: We have composition of the flower. I'm assuming the extract is not going to significantly differ. You know, I mean, could it have slightly higher amounts of certain of the materials? Yes, but, again, they're used at very low levels. And the materials that we would be concerned about are ingredients, like eugenol and linalool for which we're saying formulated not to be sensitizing or irritating, bringing into the discussion that IFRA has limits on these and that in final product those limits should not be exceeded, mentioning things like the linalool hydroperoxides, the limits that IFRA has on eugenol. So I thought we covered those.

DR. LIEBLER: With respect specifically to the flower, Ron, I was -- in addition to the text that I just read, Table 5 basically lists it looks like about 30 chemicals, including things like linalool and eugenol and ionone and so forth. And the three headings are Component after Hydrodistillation of Flower, Component Percent after Dry Distillation of Flower at 50 Degrees, and Component after Dry Distillation of Flower at 100 Degrees. So I thought that was actually a fairly good look at the kinds of things and the flower that we would be concerned about, particularly with these low-use levels.

DR. BERGFELD: So the Marks team, how are you going?

DR. MARKS: Second.

DR. BERGFELD: Second. Any further discussion regarding this group of ingredients? No? All right, we'll call the question.

Al those in favor of the conclusion that was proposed by Don, raise your hands.

Thank you. Unanimous.

DR. HILL: I'm not.

DR. BERGFELD: You're not?

DR. HILL: I'm abstaining.

DR. BERGFELD: Oh, you're abstaining? Thank you.

DR. HILL: Yes, so I can look further into this component thing.

DR. BERGFELD: Okay, thank you. It is my understanding then the discussion will be expanded to include what was discussed here at the table?

DR. BELSITO: Mm-hmm.

DR. BERGFELD: Okay.

Safety Assessment of *Rosa canina*-derived Ingredients as Used in Cosmetics

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The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 12 *Rosa canina*-derived ingredients, which function as skin conditioning agents, fragrance ingredients, cosmetic astringents, anti-acne agents, abrasives, humectants, and exfoliants in cosmetic products. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. The Panel reviewed relevant data relating to the safety of these ingredients and concluded that these ingredients are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating and non-sensitizing.

INTRODUCTION

The safety of the following 12 *Rosa canina*-derived ingredients as used in cosmetics is reviewed in this safety assessment:

Rosa Canina Fruit Extract
Rosa Canina Bud Extract
Rosa Canina Flower
Rosa Canina Flower Extract
Rosa Canina Flower Powder
Rosa Canina Flower Oil
Rosa Canina Fruit (also known as rose hip)
Rosa Canina Fruit Juice
Rosa Canina Leaf Extract
Rosa Canina Seed
Rosa Canina Seed Extract
Rosa Canina Seed Powder

According to the *International Cosmetic Ingredient Dictionary and Handbook*, Rosa Canina Fruit Extract is reported to function as a skin conditioning agent in cosmetic products.[1] Functions reported for other *Rosa canina*-derived ingredients include: skin conditioning agent, fragrance ingredient, cosmetic astringent, antiacne agent, abrasive, humectant, and exfoliant (Table 1). Rosa Canina Flower Powder is reported to function as an anti-acne agent; however, function as an anti-acne agent is not a cosmetic use and therefore the Panel did not evaluate safety for that use.

The Panel evaluated the safety of Rosa Canina Fruit Oil and other plant-derived fatty acid oils in cosmetics, and issued a final report in 2011 with the conclusion that these oils are safe in the present practices of use and concentration.[2] The Panel has also evaluated the safety of butylene glycol, which can be a major component of Rosa Canina Fruit Extract, in cosmetics and issued a final report in 1985 with the conclusion that butylene glycol, hexylene glycol, ethoxydiglycol, and dipropylene glycol are safe as presently used in cosmetics.[3] This conclusion was reaffirmed by the Panel in a 2006 publication.[4]

CHEMISTRY

Plant Identification

Rosa canina (also known as dog rose) is an herb that belongs to the *Rosaceae* family, and is among the plants growing in Northeastern Portugal and in the Hadim, Taskent, and Ermenek regions of Turkey.[5,6] Rose hip is a common name for the dried fruit of *Rosa canina*. The definitions of *Rosa canina*-derived ingredients are presented in Table 1.[1]

Chemical and Physical Properties

Rosa Canina Fruit Extract

Using ultraviolet spectrophotometry, the λ max for Rosa Canina Fruit Extract (ethanol extract) has been reported at ~ 280 nm.[7]

Method of Manufacture

Rosa Canina Fruit Extract

The part of the *Rosa canina* plant that is used to manufacture Rosa Canina Fruit Extract is the fruit without achene. Key steps in the manufacture of Rosa Canina Fruit Extract include: (1) solubilization of *Rosa canina* powder produced from the fruit without achene in a mixture of water and butylene glycol, (2) separation of soluble and insoluble phases, (3) clarification by filtration, (4) decoloration, and (5) filtrations and sterilizing filtration.[8]

The method of manufacture of Rosa Canina Fruit Extract (ethanol extract) has been described as follows:[7]

Dried raw material → extract with 50 vol% ethanolic solution → concentration → adjustment → sedimentation → filtrate → adjustment → packaging

A description of the method of manufacture of Rosa Canina Fruit Extract (butylene glycol extract) is included below.[7]

Dried raw material → extract with 1,3-butylene glycol → filtrate → sedimentation → filtrate → adjustment → packaging

Further details relating to this method of manufacture were not provided.

Composition

Rosa Canina Fruit Extract

Rosa Canina Fruit Extract consists of 0.65% (maximum percentage) Rosa Canina Fruit Extract.[8] Composition data on Rosa Canina Fruit Extract are as follows: Rosa Canina Fruit Extract (maximum percentages: 0.45% to 0.65%), butylene glycol (maximum percentages: 76.50% to 93.50%), and water (maximum percentages: 5.85% to 23.05%). Additional data relating to the composition of the dried matter of Rosa Canina Fruit Extract are: sugars (90%), mineral ashes (9%), and polyphenols (1%).

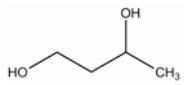

Figure 2. Butylene glycol

Rosa Canina Fruit Extract (ethanol extract or butylene glycol extract) has flavonoid and tannin components, most prominently of which is the glycoside formed from the flavonoid quercetin, namely quercetrin.[7]

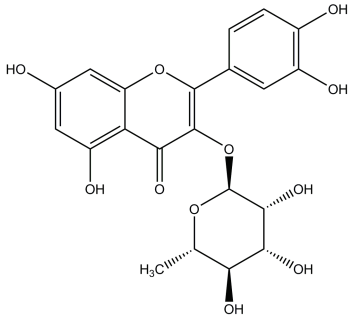

Figure 3. Quercetrin

The highest concentration phenolic acid found in Rosa Canina Fruit Extract is ellagic acid.[9]

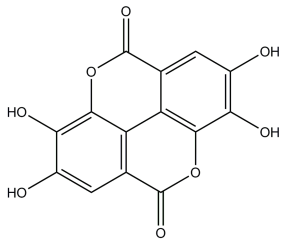

Figure 4. Ellagic Acid

Data relating to the content of some of the phenolic acids and flavonoids in various extracts of Rosa Canina Fruit are presented in Table 2 and Table 3.[10,9]

Rosa Canina Fruit

The fruits of *Rosa canina* contain phenolic acids, proanthocyanidins, tannins, flavonoids, fatty acids, pectins, carotenoids, and fruit acids (ascorbic acid, malic acid, and citric acid).[11] (+)-Catechin, a flavonoid, has been identified as the most abundant flavan-3-ol (3.59 mg/100 g) in Rosa Canina Fruits,[5] and the abundance of ascorbic acid (Vitamin C, 880 mg/100 ml) in Rosa Canina Fruit has also been noted.[12,13]

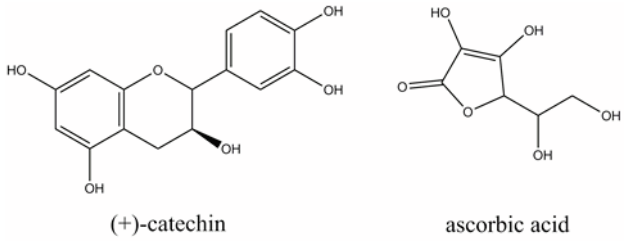

Figure 1. (+)-Catechin and ascorbic acid (vitamin C)

In addition to vitamin C, the following other nutrients in Rosa Canina Fruit have been reported: carotenoids, tocopherol, bioflavonoids, tannins, pectin, sugars, organic acids, amino acids, essential oils, phosphorus (P, 4860 ppm), potassium (K: 5467 ppm), calcium (Ca: 2867 ppm), magnesium (Mg: 1254 ppm), iron (Fe: 27 ppm), copper (Cu: 27 ppm), manganese (Mn: 56 ppm), and zinc (Zn: 30 ppm).[12] According to another source, the following 6 main carotenoids have been identified in Rosa Canina Fruit: epimers of neochrome, lutein, zeaxanthin, rubixanthin, lycopene, and β,β-carotene.[14]

The chemical composition of Rosa Canina Fruit differs, depending on the cultivar, growing region, climate, maturity, cultivation practice, and storage conditions.[15] Significant variations in the following components have been reported: organic acids, sugars, water-soluble vitamins, minerals, and phenolics.[12] The total phenolic content of *Rosa canina* has been found to be 96 mg gallic acid equivalents (GAE)/g dry weight (DW), and the total fat content has been determined to be 1.78%. The results of a fatty acid analysis indicated that *Rosa canina* contains the following 7 major fatty acids: lauric acid (4.8%), palmitic acid (16.4%), linoleic acid (16%), α-linolenic acid (40.5%), nonadecylic acid (4.74%), *cis*-C19:1ω6 (5.79%), and cis-C22:2 ω6 (6.60%).[15] The galactolipid, (2S)-1,2-di-O-[(9Z,12Z,15Z)-octadeca-9,12,15-trienoyl]-3-O-β-D-galactopyranosyl glycerol (GOPO) has been described as another important component of Rosa Canina Fruit.[16] Additional information on the nutritional composition of wild Rosa Canina Fruit is presented in Table 4.[15]

Rosa Canina Bud Extract

Flavonols such as glycosides of quercetin and kaempferol, hydroxycinnamic acids, and ellagitannins were detected in samples of Rosa Canina Bud Extract, with gallotannins being the main components (up to 1.7 g/L).[17]

Rosa Canina Flower Extract

Data on the composition of aromatic water obtained by hydrodistillation and dry distillation of *Rosa canina* flowers (distillate extracted with pentane) from Tunisia are presented in Table 5.[18] This material is more closely related to a flower water ingredient type. The chemical constituents are presented in the order of lowest to highest retention index relative to *n*-alkanes.

Rosa Canina Leaf Extract

Rosa Canina Leaf Extract contains alkaloids, flavonoids, glycosides, saponins, and a volatile oil.[19] Data on the composition of essential oils obtained by hydrodistillation of *Rosa canina* leaves (distillate extracted with hexane, dichloromethane, and methanol) are presented in Table 6.[20] This material is more closely related to a leaf essential oil. The chemical constituents are presented in the order of lowest to highest retention index relative to C_9-C_{21} *n*-alkanes.

Rosa Canina Seed

Composition data on Rosa Canina Seed from 3 growing regions in Turkey are available, and the highest reported mean values for each component are presented in Table 7.[6,21]

Impurities

Rosa Canina Fruit Extract

An impurities analysis of Rosa Canina Fruit Extract for the following components was performed: allergens (26 listed in European Regulation 1223/2009), alkaloids, aflatoxins (B1, B2, G1, and G2), and pesticides. These impurities were not detected, i.e., all concentrations were lower than the threshold sensitivity of the method (not specified).[8] A heavy metals analysis of Rosa Canina Fruit Extract indicated no traces of the following: cadmium, chromium, cobalt, mercury, and vanadium. However, traces of antimony, arsenic, nickel, lead, and selenium were found; less than 2 ppm of heavy metals was reported. According to another soiurce, Rosa Canina Fruit Extract (ethanol extract or butylene glycol extract) contains heavy metals (not more than 20 ppm) and arsenic (not more than 2 ppm).[7]

Rosa Canina Fruit

Three different brands of tea bag containing dried rose hip were mixed and pulverized and 0.5 g was obtained to determine the presence of various elements.[22] The following 14 elements were identified in the powder: Ca (18 ppm), Mg (1909 ppm), Fe (267 ppm), Al (157 ppm), Mn (244 ppm), Zn (22 ppm), Cu (5 ppm), Sr (59 ppm), Ba (47 ppm), Ni (2.9 ppm), Cr (0.9 ppm), Co (0.4 ppm), Pb (0.3 ppm), and Cd (0.1 ppm); these elements were detected in tea (prepared from 0.5 g rose hip in 25 mL water for 30 minutes at 95 °C) in percentages of 6%, 72%, 14%, 4%, 20%, 28%, 60%, 25%, 52%, 25%, 66%, 27% (% = % of mineral originally found in dried rose hips), and not detectable, respectively.

USE

Cosmetic

The safety of the *Rosa canina*-derived ingredients included in this report is evaluated based on data received from the U.S. 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 FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. Collectively, the use frequency and use concentration data indicate that 7 of the 12 ingredients in this safety assessment are currently being used in cosmetic products (See Table 8). Based on these data, the following 5 ingredients are not being used in cosmetics:

Rosa Canina Bud Extract
Rosa Canina Flower Oil
Rosa Canina Flower Powder
Rosa Canina Fruit Juice
Rosa Canina Seed

According to 2017 VCRP data, the greatest reported use frequency is for Rosa Canina Fruit Extract (350 formulations, mostly leave-on products), followed by Rosa Canina Seed Extract (58 formulations, mostly leave-on products) (Table 8).[23] The results of a concentration of use survey conducted in 2016 indicate that Rosa Canina Seed Extract has the highest maximum concentration of use; it is used at concentrations up to 1.5% in leave-on products (lipstick) (Table 8).[24] In

some cases, reported uses appear in the VCRP database, but concentrations of use data were not provided. For example, according to the VCRP, Rosa Canina Leaf Extract and Rosa Canina Seed Powder are being used in 5 and 6 cosmetic products, respectively; however, use concentration data on these ingredients were not provided in the concentration of use survey.

Cosmetic products containing *Rosa canina*-derived ingredients may be applied to the skin and hair or, incidentally, may come in contact with the eyes (e.g., Rosa Canina Fruit Extract at maximum use concentrations up to 0.2% in eye area cosmetics) and mucous membranes (e.g., Rosa Canina Seed Extract at maximum use concentrations up to 1.5% in lipstick). Additionally, some of these ingredients are being used in products that may result in incidental ingestion. For example, Rosa Canina Seed Extract is being used in lipstick at maximum use concentrations up to 1.5%, Rosa Canina Flower Extract is being used in lipstick at maximum use concentrations up to 0.04%, and Rosa Canina Fruit Extract is being used in lipstick at maximum use concentrations up to 0.0015%. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Rosa Canina Fruit Extract is used in aerosol hair sprays at maximum use concentrations up to 0.0002% and in pump hair sprays at concentrations up to 0.25%; Rosa Canina Flower Extract is being used in pump hair sprays at maximum use concentrations up to 0.001% and, in perfumes, at maximum use concentrations up to 0.01%. 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 below 10 µm, compared with pump sprays.[25,26,27,28] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[25,26] Rosa Canina Fruit Extract is also being used in powders (dusting and talcum) at maximum use concentrations up to 0.01%, and in face powders at maximum use concentrations up to 0.002%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[29,30,31]

Noncosmetic

According to FDA, rose fruit (hips) is generally recognized as safe for use in food for human consumption.[32]

In traditional folk medicine, the petals, fruit, and leaves of *Rosa canina* are used in the treatment of various diseases/conditions, such as, nephritis, common cold, flu, coughing, bronchitis, eczema, itching, and biliary diseases.[11] Rosa Canina Fruit contains a wide range of bioactive compounds, including GOPO, vitamin C, phenolics, lycopene, lutein, zeaxanthin, and other carotenoids.[15]

According to another source, a standardized powder of Rosa Canina Fruit is being marketed as an herbal remedy for the treatment of pain in patients with osteoarthritis.[33] Among the components of this powder is a mixture of 3 triterpene acids (oleanolic, ursolic, and betulinic acids).[33,34]

TOXICOKINETIC STUDIES

No relevant published toxicokinetics studies on *Rosa canina*-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted. Toxicokinetics data were not expected to be found because each botanical ingredient is a mixture of many constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Intraperitoneal

Rosa Canina Leaf Extract

The acute intraperitoneal (i.p.) toxicity of Rosa Canina Leaf Extract (methanol extract) was evaluated using groups of 5 albino mice.[19] An estimated acute i.p. LD_{50} of 455.19 ± 23 mg/kg was reported. The animals exhibited tonic signs at doses greater than the LD_{50}.

Short-Term Toxicity Studies

Oral

Animal

Rosa Canina Fruit Extract

Rosa Canina Fruit Extract (aqueous extract diluted to 10% w/v, 500 mg/kg body weight/day) was administered orally to 12 female brownish guinea pigs daily for 35 days.[35] The vehicle control group (12 guinea pigs) received water. The general condition and behavior of all animals were described as normal, and body weight and food consumption in both groups were approximately the same.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Data on the reproductive and developmental toxicity of *Rosa canina*-derived ingredients were not found in the published literature, and unpublished data were not submitted.

GENOTOXICITY STUDIES

In Vitro

Rosa Canina Fruit Extract

The genotoxicity of a product containing a maximum concentration of 0.65% Rosa Canina Fruit Extract was evaluated in the Ames test (Organization for Economic Co-operation and Development [OECD] Protocol #471) using *Salmonella typhimurium* strains (*S. typhimurium* strains not stated).[8] The product was evaluated at doses up to 5,000 µg/plate with and without metabolic activation. It was concluded that the product did not have mutagenic or pro-mutagenic activity in this assay.

Ames test results for Rosa Canina Fruit Extract (butylene glycol extract) were negative.[7] The test concentrations/doses and bacterial strains tested were not stated. Rosa Canina Fruit Extract (butylene glycol extract) also was not genotoxic in the chromosome aberration test using the Chinese hamster lung cell line (CHL/IU). Details relating to the test protocol were not provided.

Rosa Canina Fruit Juice, Rosa Canina Leaf, and Rosa Canina Seed

Rosa Canina Fruit (unclear if *Rosae pseudofructus cum* or *Rosae pseudofructus sine fructibus, Rosa canina* L., Rosaceae) was boiled at 100 °C, stewed for 10 minutes, and then evaluated for genotoxicity in the Ames test.[22,36] Raw, boiled juice, boiled leaves, and dried seeds (concentration of each not stated) were not mutagenic in *S. typhimurium* strain TA 100.

ANTI-GENOTOXICITY STUDIES

In Vitro

Rosa Canina Fruit

In an anti-genotoxicity assay, Rosa Canina Fruit (raw, concentration not stated) decreased the genotoxicity of sodium azide by 44%.[22,36]

Rosa Canina Fruit Extract

The micronucleus test was used to evaluate the genotoxic effects of cypermethrin and fenvalerate (both insecticides); the effect of the water and ethanol extracts of Rosa Canina Fruit on the genotoxicity of these insecticides was also determined in this study.[37]

Using human peripheral lymphocyte cultures *in vitro*, cypermethrin was tested at concentrations of 20, 30, 40, and 50 ppm, and fenvalerate was tested at concentrations of 25, 50, 75, and 100 ppm. Rosa Canina Fruit extracts were tested at a concentration of 100 ppm. The negative control was dimethyl sulfoxide (DMSO, 1%), and ethyl methanesulfonate (1mM) served as the positive control. The Duncan test was used for statistical evaluation. For cypermethrin, the micronucleus frequency was 1.275 at the highest test concentration, and the micronucleus frequency for fenvalerate was 1.6 at the highest test concentration. Micronucleus frequencies were 0.725 and 2.7 for negative and positive controls, respectively. These differences between the experimental and DMSO control groups were statistically significant ($p < 0.05$). In the genotoxicity tests with Rosa Canina Fruit Extracts, the micronucleus frequencies were as follows: 1.0 (cypermethin + water extract), 1.075 (cypermethin + ethanol extract), 1.225 (fenvalerate + water extract), and 1.275 (fenvalerate + ethanol extract). Both extracts (ethanol and water) of Rosa Canina Fruit caused statistically significant reductions ($p < 0.05$) in the micronucleus frequencies that were associated with insecticide exposure. It was concluded that the water and ethanol extracts of Rosa Canina Fruit reduced the genotoxicity of both insecticides.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of *Rosa canina*-derived ingredients were not found in the published literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Cytotoxicity

Rosa Canina Seed Extract

Dried Rosa Canina Seed (100 g) was extracted with petroleum ether, 95% ethanol, or water, with yields of 0.3%, 5.9% and 10%, respectively.[22,38] The aqueous Rosa Canina Seed Extract had little cytotoxic effect on Yoshida ascites sarcoma cells (LC_{50} > 10 mg/mL). However, the ethanol and petroleum ether extracts had a substantial cytotoxic effect on these cells, with LC_{50}s of 3.9 and 1.2 mg/mL, respectively. The authors noted that these results indicated a possible anti-carcinogenic effect. However, this study did not involve testing to determine whether or not Rosa Canina Seed Extract (ethanol and petroleum ether extracts) is cytotoxic to normal cells.

Effect on Skin Pigmentation

Animal

Rosa Canina Fruit Extract

Rosa Canina Fruit Extract (500 mg/kg body weight/day as aqueous extract, diluted to 10% w/v) was administered orally to 12 female brownish guinea pigs daily for 35 days.[35] The vehicle control group (12 guinea pigs) received water. To develop pigmentation, a 4 cm^2 area of shaved skin was irradiated with 0.384 J/cm^2 (0.8 mw/cm^2 x 8 minutes) using a short wave ultraviolet (290 to 320 nm; UVB) lamp on days 8, 10, and 12. The animals were killed on day 36. The skin lightening effect of Rosa Canina Fruit Extract was determined by measuring the "L*"value (lightness) with a reflectance spectrophotometer, and was evaluated quantitatively by determining the change in the L* value during the 35-day oral dosing period. Though the L* value of the irradiated area in the vehicle control group decreased substantially due to UVB-induced pigmentation, the L* value in the experimental group was statistically significantly higher (compared to control) at each time point after irradiation. UVB-induced skin pigmentation was reduced after dosing with Rosa Canina Fruit; thus, the oral administration of Rosa Canina Fruit Extract to brown guinea pigs caused inhibition of skin pigmentation. Proanthocyanidins in Rosa Canina Fruit Extract was found to be the active principle responsible for the inhibitory effect on pigmentation of guinea pig skin. It should be noted that, according to another study (*in vitro*), proanthocyanidins from grape seeds had no effect on the expression of tyrosinase protein in normal human melanocytes.[39]

In Vitro

Rosa Canina Fruit Extract

The effects of compounds isolated from a methanolic extract of Rosa Canina Fruit on melanin biosynthesis in B16 mouse melanoma cells was investigated.[40] Quercetin, one of the components isolated from Rosa Canina Fruit, was added to the culture medium at concentrations of 10 µm, 20 µm, and 40 µm; the melanin content was reduced (compared to untreated control cells) in a dose-dependent manner to 64%, 34.5% , and 1%, respectively. It should be noted that, according to another study, the enhancement of melanogenesis by quercetin has been observed in human melanoma cells (20 µM quercetin) and normal epidermal melanocytes (1 µM quercetin).[41]

Rosa Canina Fruit Extract (aqueous extract) was added to B16 mouse melanoma cell cultures in vitro at concentrations of 250 µg/ml, 500 µg/ml, and 1000 µg/ml to confirm its melanogenesis-inhibitory effect. Untreated cultures served as negative controls. Additionally, arbutin (known inhibitor of melanogenesis) served as the positive control. Rosa Canina Fruit Extract had an inhibitory effect on melanogenesis in mouse melanoma cells, having caused the following concentration-dependent reduction in melanin content when compared to negative control cultures: 65.6% at 250 µg/ml, 37.8% at 500 µg/ml, and 19% at 1000 µg/ml. The reduction in melanin content occurred without any significant cytotoxicity.[35]

Immune System Effects

Animal

Rosa Canina Fruit Extract

A study was performed to investigate the potential for Rosa Canina Fruit Extract (hydro-alcoholic extract) to induce immunomodulatory activity using 45 rats (3 groups of 15).[42] The 3 groups received normal saline (10 mg/kg), Rosa Canina Fruit Extract (250 mg/kg), and Rosa Canina Fruit Extract (500 mg/kg) orally, by gavage, daily for a period of 4 weeks. At Rosa Canina Fruit Extract doses of 250 mg/kg and 500 mg/kg, the gamma globulin level, neutrotrophil and monocyte counts, and phagocyte activity increased statistically significantly, when compared to the normal saline group. Lymphocyte percentages were statistically significantly decreased in treatment groups at weeks 2 and 3. On days 14 and 21, neutrophil levels increased in the 250 mg dose group. The phagocytic activity in both test groups was significantly higher, compared to the control group, during all days of the study. There was no statistically significant difference in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphates (ALP) when compared to the control group. However, Rosa Canina Fruit Extract (both doses) statistically significantly increased thiobarbituric acid reactive substances (TBARS) and also decreased glutathione (GSH) levels when compared to the control group on day 28. It was concluded that Rosa Canina Fruit Extract might have immunomodulatory effects, based on these data.

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation and Sensitization

Animal

Rosa Canina Fruit Extract

In a skin irritation test involving 3 rabbits (strain not stated), results for the butylene glycol extract of Rosa Canina Fruit (0.3% solids – 100% of the butylene glycol extract) were negative.[7] Details relating to the test protocol were not provided.

The skin sensitization potential of Rosa Canina Fruit Extract (butylene glycol extract) was evaluated using 10 guinea pigs (strain not stated).[7] The following concentrations of Rosa Canina Fruit Extract were tested: 4% and 20% of the original solution (0.3% solids) (1st induction), 20% of the original solution (2nd induction), and 4% and 20% of the original solution (challenge). Additional details relating to the test protocol were not presented. Test results were classified as negative.

Human

Rosa Canina Fruit Extract

The skin irritation potential of a cosmetic product diluted to a maximum concentration of 0.0975% Rosa Canina Fruit Extract was evaluated using 10 adult subjects.[8] The product was applied and left in place under an occlusive patch for 48 h. Neither the location of the test site on the bodies of the subjects nor the concentration/dose per cm^2 of the exposed skin was stated. The product was classified as non-irritating.

In another study, the skin sensitization potential of the diluted product tested in the preceding study was evaluated using 110 normal volunteers in accordance with the method of Marzulli and Maibach.[8] The product was applied to the back using an occlusive patch with filter paper. The concentration/dose per cm^2 of the exposed skin was not stated. The 3-week induction phase was followed by a 2-week non-treatment period and then a 1-week challenge phase. The product was classified as non-irritating and non-sensitizing.

Rosa Canina Flower Extract

The skin irritation and sensitization potential of a lip balm containing 0.04% Rosa Canina Flower Extract was evaluated using 106 male and female healthy subjects.[43] Approximately 0.2 g of the test substance was applied to the upper back (between the scapulae) using a 1" x 1" semi-occlusive patch, which remained in place for 24 h. Reactions were scored at the time of patch removal and just prior to application of the next patch. The patches were applied 3 times per week for a total of 9 induction applications. After a 2-week (approximately) non-treatment period, a challenge patch was applied for 24 h to a new test site. Reactions were scored at 24 h and 72 h (or 120 h) post-application. The lip balm did not have skin irritation or sensitization potential in this study.

In another study, the skin sensitization potential of a lip liner containing 0.018% Rosa Canina Flower Extract was studied using 202 healthy male and female subjects.[44] The product (0.2 g) was applied to the infrascapular area of the back using an occlusive patch or a semi-occlusive patch (each 2 cm x 2 cm). The test procedure was similar to that stated in the preceding study, with the exceptions that induction reactions were scored at 48 h (or 72 h) post-application of the 24-h induction patch, and challenge reactions were scored at 48 h and 72 h post-application. No adverse events were reported in this study, and the authors concluded that, under occlusive and semi-occlusive conditions, there was no evidence of sensitization to the lipliner containing 0.018% Rosa Canina Flower Extract.

OCULAR IRRITATON STUDIES

Data on the ocular irritation potential of *Rosa canina*-derived ingredients were not found in the published literature, and unpublished data were not submitted.

CLINICAL STUDIES

Case Reports

Rosa Canina Fruit
and Rosa Canina Fruit Extract

An anaphylactic reaction was observed in a male patient, sensitized to *Rosaceae* (without related pollinosis), after consumption of a tea containing Rosa Canina Fruit.[45] The tea also contained hibiscus, apple, orange peel, and elderberry. The patient had no history of asthma or rhinitis, but had presented with an oral allergy syndrome to peach and almonds and had also experienced an anaphylactic reaction after eating cherries. Prick test results were positive for Rosa Canina Fruit Extract. The presence of specific IgE against the Rosa Canina Fruit in the tea was also demonstrated, using *in vitro* and *in vivo* methods, suggesting that Rosa Canina Fruit caused the anaphylactic reaction. Cutaneous tests involving other ingredients in the tea were negative.

Thirteen workers (asthma [9 subjects]; rhinitis [5 subjects]; urticaria [1 subject]) with respiratory symptoms related to occupational exposure to powdered Rosa Canina Fruit were evaluated.[46] Based on the results of positive skin prick tests, 7 of the workers were found to have evidence of IgE specific to Rosa Canina Fruit (1 mg/ml). Four workers with histories of work-related asthma underwent bronchopulmonary challenges with Rosa Canina Fruit, and 2 of the workers had positive challenges with greater than 20% declines in forced expiratory volume (FEV_1) measurements. It was concluded that Rosa Canina Fruit is an occupational allergen that is capable of producing asthma.

In-Use Test

Rosa Canina Flower Extract

The cutaneous acceptability of a cosmetic investigational product (night cream) containing approximately 0.005% Rosa Canina Flower Extract was studied using 48 female subjects.[47] Approximately 50% of the subjects had "sensitive" skin and 20% to 25% had a history of atopy. During 4 weeks, the product was applied once per day (in the evening) to the face and neck (insisting on the eye contours). The following reactions were observed in 7 subjects: discomfort (4 subjects – prickling in particular), irritation + discomfort and palpebral swelling (2 subjects), and "small pimples" + discomfort (1 subject). Only the reactions observed in 2 subjects (irritation + discomfort and palpebral swelling) were considered pertinent. The authors noted that no abnormal clinical sign was observed by the dermatologist after 4 weeks of product use.

Other Clinical Reports

Rosa Canina Fruit Extract

A double-blind, placebo-controlled clinical trial involving 2 groups of 16 subjects was performed.[48] One group received placebo tablets (1 per subject) and the other group received tablets containing Rosa Canina Fruit Extract (100 mg + excipients, 1 per subject) once per day for 12 weeks. The Rosa Canina Fruit Extract tested was an aqueous ethanol extract of Rosa Canina Fruit containing its seeds, dextrin, cyclodextrin, and not less than 0.1% tiliroside (glycosidic flavonoid). There were no abnormalities, subjective symptoms, or findings suggesting clinical problems during the study.

Rosa Canina Fruit

Rosa Canina Fruit (powder form) was evaluated in a double-blind, placebo-controlled clinical trial involving 44 subjects (active treatment group) and 45 subjects (placebo group).[49] The active treatment group was instructed to take 5 capsules, each containing 0.5 g Rosa Canina Fruit (powder form) daily for 6 months. The other group was treated with placebo of a similar taste according to the same procedure. There were no adverse effects of any kind that were related to dosing with Rosa Canina Fruit (powder form).

SUMMARY

Rosa canina, the plant source of ingredients reviewed in this safety assessment, is an herb that belongs to the *Rosaceae* family. Rosa Canina Fruit Extract is reported to function as a skin conditioning agent in cosmetic products.[1] Functions reported for other *Rosa canina*-derived ingredients include: skin conditioning agent, fragrance ingredient, cosmetic astringent, anti-acne agent, abrasive, humectant, and exfoliant.

Using ultraviolet spectrophotometry, the λ max for Rosa Canina Fruit Extract (ethanol extract) has been reported at ~ 280 nm (the short end of UVB).

Collectively, information supplied to FDA by industry as part of the VCRP and a survey of ingredient use concentrations conducted by the Council indicate that the following *Rosa canina*-derived ingredients are being used in cosmetic products: Rosa Canina Fruit Extract, Rosa Canina Flower, Rosa Canina Flower Extract, Rosa Canina Fruit, Rosa Canina Leaf Extract, Rosa Canina Seed Extract, and Rosa Canina Seed Powder. The highest use frequency is reported for Rosa Canina Fruit Extract (350 uses). The Council survey data also indicate that *Rosa canina*-derived ingredients are being used in cosmetics at maximum ingredient use concentrations up to 1.5% (i.e., Rosa Canina Seed Extract in leave-on products [lipstick]).

In traditional folk medicine, the petals, fruit, and leaves of *Rosa canina* are used in the treatment of various diseases/conditions, such as, nephritis, common cold, flu, coughing, bronchitis, eczema, itching, and biliary diseases.

The fruits of *Rosa canina* contain phenolic acids, proanthocyanidins, tannins, flavonoids, fatty acids, pectins, carotenoids, and fruit acids (ascorbic acid, malic acid, and citric acid). (+)-Catechin, a flavonoid, has been identified as the most abundant flavan-3-ol (3.59 mg/100 g) in Rosa Canina Fruits, and the abundance of ascorbic acid (Vitamin C, 880 mg/100 ml) in Rosa Canina Fruit has also been noted. In addition to vitamin C, the following other nutrients in Rosa Canina Fruit have been reported: carotenoids, tocopherol, bioflavonoids, tannins, pectin, sugars, organic acids, amino acids,

essential oils, phosphorus, potassium, calcium, magnesium, iron, copper, manganese, and zinc. Additionally, the following 6 main carotenoids have been identified in Rosa Canina Fruit: epimers of neochrome, lutein, zeaxanthin, rubixanthin, lycopene, and β-carotene. The chemical composition of Rosa Canina Fruit differs, depending on the cultivar, growing region, climate, maturity, cultivation practice, and storage conditions.

Flavonols such as glycosides of quercetin and kaempferol, hydroxycinnamic acids, and ellagitannins were detected in samples of Rosa Canina Bud Extract, with gallotannins being the main components. Rosa Canina Leaf Extract contains alkaloids, flavonoids, glycosides, saponins, and a volatile oil. Rosa Canina Seed contains fatty acids and various elements, some of which are common to Rosa Canina Fruit.

An acute i.p. LD_{50} of 455.19 ± 23 mg/kg was reported for Rosa Canina Leaf Extract (methanol extract) in a study involving groups of 5 albino mice. Toxic signs were observed at doses greater than the LD_{50}.

Rosa Canina Fruit (500 mg/kg body weight/day, aqueous extract diluted to 10% w/v) was administered orally to 12 female guinea pigs daily for 35 days. The general condition and behavior of all animals were described as normal, and body weights and food consumption were comparable to control values.

Rosa Canina Fruit Extract (aqueous ethanol extract, 100 mg + excipients per tablet) was administered orally to 16 subjects once daily for 12 weeks. The test substance was an aqueous ethanol extract of Rosa Canina Fruit containing its seeds, dextrin, cyclodextrin, and not less than 0.1% tiliroside (glycosidic flavonoid). There were no abnormalities, subjective symptoms, or findings that may have been indicative of clinical effects during the study. In a similar study, 44 subjects were instructed to take 5 capsules, each containing 0.5 g Rosa Canina Fruit (powder form) daily for 6 months. Dosing did not result in any adverse effects.

A product containing a maximum concentration of 0.65% Rosa Canina Fruit Extract did not have mutagenic or pro-mutagenic activity in *Salmonella typhimurium* strains when evaluated in the Ames test (with and without metabolic activation). Ames test results for Rosa Canina Fruit Extract (butylene glycol extract, test concentration not stated) were also negative. Additionally, Rosa Canina Fruit Extract (butylene glycol extract, test concentration not stated) was not genotoxic in the chromosome aberration test using the Chinese hamster lung cell line (CHL/IU).

Rosa Canina Fruit Juice, Rosa Canina Leaf, and Rosa Canina Seed (concentrations not stated), were not mutagenic to *Salmonella typhimurium* strain TA 100 in the Ames test.

In an anti-genotoxicity assay, Rosa Canina Fruit (raw, concentration not stated) decreased the genotoxicity of sodium azide by 44%. Rosa Canina Fruit Extract (at 100 ppm, water and ethanol extracts) reduced the genotoxicity of 2 insecticides, cypermethrin and fenvalerate, in the micronucleus test.

Rosa Canina Seed Extract (5.9% as ethanol extract and 0.3% as petroleum ether extract) had a significant cytotoxic effect on Yoshida ascites sarcoma cells, with LC_{50} values of 3.9 and 1.2 mg/mL, respectively. Rosa Canina Seed Extract (10% as aqueous extract) had a poor cytotoxic effect on these cells ($LC_{50} > 10$ mg/L).

In a skin irritation test involving 3 rabbits, results for the butylene glycol extract of Rosa Canina Fruit (0.3% solids – 100% of the butylene glycol extract) were negative.

The skin sensitization potential of Rosa Canina Fruit Extract (butylene glycol extract) was evaluated using 10 guinea pigs (strain not stated), and the following concentrations were tested: 4% and 20% of the original solution (0.3% solids) (1st induction), 20% of the original solution (2nd induction), and 4% and 20% of the original solution (challenge). Test results were negative.

A lip balm containing 0.04% Rosa Canina Flower Extract was evaluated for skin irritation and sensitization potential using 106 male and female subjects. Study results were negative. In another study, the skin sensitization potential of a lip liner containing 0.018% Rosa Canina Flower Extract was studied using 202 male and female subjects. The lip liner did not induce sensitization in this study.

A cosmetic product diluted to a concentration of 0.0975% maximum Rosa Canina Fruit Extract was evaluated in a 48-h occlusive patch test using 10 adult subjects. Results were negative. The skin sensitization potential of the same product was evaluated in a repeated insult patch test using 110 normal volunteers. The product was classified as non-irritating and non-sensitizing.

In a use test, the cutaneous acceptability of a cosmetic investigational product (night cream) containing approximately 0.005% Rosa Canina Flower Extract was studied using 48 female subjects, some with a history of sensitive skin/atopy. The following reactions were observed in 7 subjects: discomfort (4 subjects - prickling in particular), irritation + discomfort and palpebral swelling (2 subjects), and "small pimples" + discomfort (1 subject). Only the reactions observed in 2 subjects (irritation + discomfort and palpebral swelling) were considered pertinent. No abnormal clinical signs were observed after 4 weeks of product use.

Positive skin prick tests (1 mg/ml Rosa Canina Fruit) were reported for 7 of 9 subjects exposed to powdered Rosa Canina Fruit in the workplace.

An anaphylactic reaction was observed in a male patient after consumption of a tea containing Rosa Canina Fruit. Prick test reactions to the fruit were positive, and the presence of specific IgE against the fruit was demonstrated using *in vitro* and *in vivo* methods.

Neither toxicokinetic data nor data on the carcinogenicity and reproductive and developmental toxicity of *Rosa canina*-derived ingredients were identified in the published literature.

Oral dosing with Rosa Canina Fruit Extract (aqueous extract, 10% w/v) caused a reduction in UVB-induced skin pigmentation in guinea pigs. Rosa Canina Fruit Extract (aqueous extract) also caused a concentration-dependent (250, 500, and 1000 µg/ml) decrease in the melanin content of B16 mouse melanoma cell cultures *in vitro*. Quercetin, isolated from a methanolic extract of Rosa Canina Fruit, reduced the melanin content of B16 mouse melanoma cells in a concentration-dependent manner.

Data suggestive of immunomodulatory activity induced by Rosa Canina Fruit Extract (hydro-alcoholic extract)have been identified in the published literature.

DISCUSSION

The Panel has evaluated the safety of butylene glycol, a major component of Rosa Canina Fruit Extract, in cosmetics and issued a final report in 1985 with the conclusion that butylene glycol, hexylene glycol, ethoxydiglycol, and dipropylene glycol are safe as presently used in cosmetics. This conclusion was reaffirmed by the Panel in a 2006 publication. Rosa Canina Fruit Extract contains 76.5% to 93.50% butylene glycol, but the Panel agreed that safety test data from the final report on butylene glycol should not be included in this safety assessment. The Panel determined that, given the low use concentration of Rosa Canina Fruit Extract in cosmetics (up to 0.25%), the concentration of butylene glycol in this ingredient is orders of magnitude lower than the maximum use concentration of butylene glycol (> 50%; considered a safe use concentration) that is stated in the published final report.

An effect of Rosa Canina Fruit Extract on skin pigmentation was reported in *in vitro* and *in vivo* studies, and the quercetin and proanthocyanidins components of this ingredient were identified as the active principles for this effect. The Panel noted that use concentrations of this ingredient and, thus, the levels of these components in cosmetics, are considered below the threshold of concern for this effect.

The Panel determined that linalool and eugenol, two of the components of *Rosa canina*-derived ingredients, are constituents of concern based on their irritation and sensitization potential, and noted that the International Fragrance Association has established limits relating to eugenol in finished products and the hydroperoxide content of linalool. The Panel noted that because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels in the final formulation of botanical constituents that may cause sensitization or other adverse effects.

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

Rosa Canina Fruit Extract is used in aerosol hair sprays at maximum use concentrations up to 0.0002% and in pump hair sprays at concentrations up to 0.25%; Rosa Canina Flower Extract is being used in pump hair sprays at maximum use concentrations up to 0.001% and, in perfumes, at maximum use concentrations up to 0.01%. Rosa Canina Fruit Extract is also being used in powders (dusting and talcum) at maximum use concentrations up to 0.01%, and in face powders at maximum use concentrations up to 0.002%. The Panel discussed the issue of incidental inhalation exposure during cosmetic use, and agreed that incidental inhalation exposures to these ingredients in such cosmetic products would not cause adverse health effects.

CONCLUSION

The CIR Expert Panel concluded that the following 12 *Rosa canina*-derived ingredients are safe in the present practices of use and concentration in cosmetics as described in this safety assessment, when formulated to be non-irritating and non-sensitizing.

Rosa Canina Fruit Extract
Rosa Canina Bud Extract*
Rosa Canina Flower
Rosa Canina Flower Extract
Rosa Canina Flower Powder*
Rosa Canina Flower Oil*
Rosa Canina Fruit
Rosa Canina Fruit Juice*
Rosa Canina Leaf Extract
Rosa Canina Seed*
Rosa Canina Seed Extract
Rosa Canina Seed Powder

*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.

Table 1. Definitions and functions of the ingredients in this safety assessment.[1]

Ingredient/CAS No.	Definition	Function
Rosa Canina Fruit Extract	Rosa Canina Fruit Extract is the extract of the fruit of *Rosa canina*. It is also defined as a hydroglycolic extract (water/butylene glycol) of 0.65% (maximum percentage) Rosa Canina Fruit Extract.[8]	Skin-Conditioning Agents - Miscellaneous
Rosa Canina Bud Extract	Rosa Canina Bud Extract is the extract of the buds of *Rosa canina*.	Skin-Conditioning Agents - Miscellaneous
Rosa Canina Flower	Rosa Canina Flower is the petals of the flower of *Rosa canina*.	Fragrance Ingredients
Rosa Canina Flower Extract	Rosa Canina Flower Extract is the extract of the flowers of *Rosa canina*.	Cosmetic Astringents
Rosa Canina Flower Oil	Rosa Canina Flower Oil is the volatile oil obtained from the flowers of *Rosa canina*.	Fragrance Ingredients; Skin-Conditioning Agents - Emollient
Rosa Canina Flower Powder	Rosa Canina Flower Powder is the powder obtained from the dried, ground flowers of *Rosa canina*.	Antiacne Agents; Skin-Conditioning Agents - Miscellaneous
Rosa Canina Fruit	Rosa Canina Fruit is the fleshy fruit of *Rosa canina*.	Cosmetic Astringents
Rosa Canina Fruit Juice	Rosa Canina Fruit Juice is the liquid expressed from the hips of *Rosa canina*.	Cosmetic Astringents
Rosa Canina Leaf Extract	Rosa Canina Leaf Extract is the extract of the leaves of *Rosa canina*.	Skin-Conditioning Agents - Miscellaneous
Rosa Canina Seed	Rosa Canina Seed is the seed of *Rosa canina*.	Abrasives; Skin-Conditioning Agents - Miscellaneous
Rosa Canina Seed Extract	Rosa Canina Seed Extract is the extract of the seeds of *Rosa canina*.	Humectants; Skin-Conditioning Agents - Emollient
Rosa Canina Seed Powder	Rosa Canina Seed Powder is the powder obtained from the dried, ground seeds of *Rosa canina*.	Abrasives; Exfoliants

Table 2. Content of Some Phenolic Acids and Flavonoids in Rosa Canina Fruit Extracts.[10]

Components	Water Extract of Fresh Fruit	Water Extract of Air-dried Fruit	Methanol Extract of Fresh Fruit	Methanol Extract of Air-dried Fruit
Phenolic Acids (µg/g of dry weight)				
p-Hydroxybenzoic Acid	< loq*	< loq	< loq	< loq
Vanillic Acid	< loq	< loq	< loq	< loq
Gallic Acid	11.3 ± 0.64	5.11 ± 0.19	1.86 ± 0.09	2.32 ± 0.11
Protocatechuic acid	9.79 ± 0.39	14.2 ± 0.66	8.04 ± 0.32	13.7 ± 6.61
p-Coumaric Acid	< loq	< loq	1.53 ± 0.07	1.48 ± 0.05
Ferulic Acid	< loq	< loq	< loq	< loq
Flavonoids (µg/g of dry weight)				
Amentoflavone	< loq	< loq	< loq	< loq
Kaempferol-3-O-glucoside	< loq	< loq	1.77 ± 0.06	3.04 ± 0.13
Quercitrin	40.4 ± 1.39	27.1 ± 0.10	95.2 ± 3.29	113 ± 6.78
Quercetin-3-O-glucoside	2.54 ± 0.09	< loq	9.40 ± 0.36	12.1 ± 0.64
Hyperoside	2.53 ± 0.09	< loq	7.73 ± 0.33	8.50 ± 0.36
Epicatechin	2.35 ± 0.07	1.72 ± 0.06	2.92 ± 0.10	4.74 ± 0.20
Catechin	7.83 ± 0.41	7.35 ± 0.17	4.23 ± 0.15	2.37 ± 0.08
Quinic Acid	(1.36 ± 0.02) x 10^3	(1.17 ± 0.02) x 10^3	(1.52 ± 0.01) x 10^3	(1.39 ± 0.02) x 10^3

*loq = limit of quantification

Table 3. Composition of Dried Rosa Canina Fruit Extract (Tea, Acetone Extract).[9]

Compound	Amount (µg/kg Rosa Canina Fruit Tea Extract)
Flavonoids	
Catechin	12.59 ± 0.53
Rutin	63.35 ± 2.86
Quercetin	296.5 ± 11.69
Kaempferol	53.38 ± 1.76
Myricetin	25.23 ± 1.12
Phenolic Acids	
Gallic Acid	3.31 ± 0.15
Protocatechuic Acid	6.94 ± 0.25
Caffeic Acid	5.06 ± 0.21
Syringic Acid	11.03 ± 0.46
Coumaric Acid	13.28 ± 0.48
Vanillic Acid	14.39 ± 0.63
Ferulic Acid	6.07 ± 0.24
Ellagic Acid	444.61 ± 17.36
Vitamins	
Vitamin C	39,170 ± 82.5

Table 4. Nutritional Composition of Wild Rosa Canina Fruit.[15]

Nutrient Proximates	Value per 100 g
Water	58.66 g
Energy	162 kcal
Protein	1.6 g
Total lipid (fat)	0.34 g
Ash	1.18 g
Carbohydrate, by difference	38.22 g
Fiber, total dietary	24.1 g
Sugars, total	2.58 g
Minerals	
Calcium (Ca)	169 mg
Iron (Fe)	1.06 mg
Magnesium (Mg)	69 mg
Phosphorus (P)	61 mg
Potassium (K)	429 mg
Sodium (Na)	4 mg
Zinc (Zn)	0.25 mg
Copper (Cu)	0.113 mg
Manganese (Mn)	1.02 mg
Vitamins	
Vitamin C, total ascorbic acid	426 mg
Thiamin	0.016 mg
Riboflavin	0.166 mg
Niacin	1.3 mg
Pantothenic Acid	0.8 mg
Vitamin B-6	0.076 mg
Vitamin A, RAE	217 µg
Carotene, beta	2350 µg
Carotene, alpha	31 µg
Cryptoxanthin, beta	483 µg
Vitamin A	4345 IU
Lycopene	6800 µg
Lutein + zeaxanthin	2001 µg
Vitamin E (alpha-tocopherol	5.84 mg
Tocopherol, beta	0.05 mg
Tocopherol, gamma	1.34 mg
Tocopherol, delta	0.14 mg
Vitamin K (phylloquinone)	25.9 µg

Table 5. Composition of Aromatic Water from Distillation of Rosa Canina Flowers [Plant Source: Tunisia].[18]

Chemicals/**Chemical Classes**	Component (%) after Hydrodistillation of Flower	Component (%) after Dry Distillation of Flower at 50°C	Component (%) after Dry Distillation of Flower at 100°C
2,5-dimethylfuran	NR*	NR	2.1
E-3-hexenol	NR	0.4	NR
1-(2-furanyl)-ethanone	NR	NR	0.3
α-pinene	3.5	0.7	0.5
5-methylfurfural	NR	NR	1.1
β-pinene	0.7	NR	NR
benzyl alcohol	NR	0.2	NR
linalool	0.5	0.3	NR
2-phenethyl alcohol	13.6	58.4	4.5
eugenol	45.1	23.7	22.9
β-caryophyllene	2.6	0.7	3.3
α-guaiene	0.5	NR	0.6
β-ionone	NR	NR	0.3
δ-guaiene	NR	NR	0.4
caryophyllene oxide	0.5	NR	NR
8-heptadecene	NR	NR	6.8
1-heptadecene	6	0.9	NR
heptadecane	0.4	NR	0.4
1-nonadecene	0.4	NR	0.8
nonadecane	6.5	1.1	10.1
n-eicosane	0.6	0.21	3.4
n-heneicosane	4.4	1	10.2
docosane	1	0.9	1.9
tricosane	NR	1.3	4.2
tetracosane	2	NR	NR
pentacosane	2.7	NR	NR
hexacosane	1.3	NR	NR
Monoterpene Hydrocarbons	4.2	0.7	0.5
Sesquiterpenes Hydrocarbons	3.1	0.7	4.3
Oxygenated Sesquiterpenes	0.5	NR	0.3
Alkanes/Alkenes	25.3	5.4	37.8
Alcohols	59.3	83	27.4
Furan Derivatives (O-heterocyclic)	NR	NR	3.2
Norisoprenoids	NR	NR	0.3

*NR = Not Reported

Table 6. Composition of Essential Oils from *Rosa canina* Leaves in Two Areas of Tunisia.[20]

Chemicals	Component (%) [Plant Source: Feija, Tunisia]	Component (%) [Plant Source: Aindraham, Tunisia]
Benzaldehyde	Trace amount	Trace amount
α-Pinene	Trace amount	Trace amount
n-Decane	Trace amount	Trace amount
Benzene Acetaldehyde	0.8	Trace amount
cis-Linalool Oxide	Trace amount	Trace amount
2-Methyl Decane	Trace amount	Trace amount
trans-Linalool Oxide	Trace amount	Trace amount
n-Nonanol	1.9	2.1
Linalool	1.9	2.1
α-Campholenal	Trace amount	Trace amount
n-Undecane		
trans-Pinocarveol	Trace amount	Trace amount
trans-Verbenol	Trace amount	Trace amount
2-*trans*, 6-*cis*-Nonadienal	Trace amount	Trace amount
Pinocarvone	Trace amount	Trace amount
2-*trans*-Nonen-1-al	Trace amount	Trace amount
Borneol	Trace amount	Trace amount
Terpinen-4-ol		
Methyl Salicylate		
α-Terpineol	0.5	Trace amount
Myrtenol	Trace amount	Trace amount
n-Decanal	0.2	Trace amount
trans-Carveol	Trace amount	Trace amount
Citronelol	Trace amount	Trace amount
Geraniol	Trace amount	Trace amount
Vitispirane	9.1	22.5
n-Undecanal	0.2	0.4
Decanoic Acid (= Capric Acid)	Trace amount	Trace amount
trans-β-Damascenone	0.5	0.9
α-Ylangene	0.8	Trace amount
α-Ionone		
α-Gurjunene	Trace amount	Trace amount
trans-β-Caryophyllene	0.4	Trace amount
Geranyl Acetone	Trace amount	Trace amount
α-Himachalene	Trace amount	2.4
trans-β-Ionone	Trace amount	Trace amount
γ-Himachalene	0.4	1
ar-Curcumene	0.4	1
Viridiflorene	0.2	0.9
α-Dehydro-*ar*-himachalene	2.2	1.2
α-*trans,trans*-Farnesene	Trace amount	Trace amount
n-Pentadecane		
γ-Dehydro-*ar*-himachalene	2.6	1

Table 6. Composition of Essential Oils from *Rosa canina* Leaves in Two Areas of Tunisia.[20]

Chemicals	Component (%) [Plant Source: Feija, Tunisia]	Component (%) [Plant Source: Aindraham, Tunisia]
α-Calacorene	0.6	0.4
Hexenyl Benzoate		
Presilphiperfol-1-ene	3.9	3.7
Dodecanoic Acid (= Lauric Acid)	6.4	Trace amount
Spathulenol	3.4	3.4
β-Caryophyllene Oxide	3.4	3.4
Globulol	Trace amount	Trace amount
Humulene Epoxide	2.3	2
n-Hexadecane		
Benzyl Benzoate		
Tetradecanoic Acid (= Myristic Acid)	5.1	3.5
Hexadecanoic Acid (= Palmitic Acid)	23.2	15.5
Phytol Acetate	4.9	6.3
Linoleic Acid	7.9	13.5

Table 7. Composition Data on Rosa Canina Seed.[6,21]

Myristic Acid (14:0)	0.21 ± 0.06%*
Palmitic Acid (16:0)	3.17 ± 0.18%
Palmitoleic Acid (16:1)	1.01 ± 0.11%
Stearic Acid (18:0)	2.47 ± 0.84
Oleic Acid (18:1)	18.42 ± 1.12%
Linoleic Acid (18:2)	54.41 ± 3.24%
Linolenic Acid (18:3)	18.41 ± 1.16%
Arachidic Acid (20:0)	2.61 ± 0.14%
Behenic Acid (22:0)	0.64 ± 0.03%
Moisture	6.61 ± 0.64%
Crude Oil	17.82 ± 1.14%
Ash	4227.46 ± 161.54%
Sodium (Na)	114.71 ± 6.64 ppm; < 0.25 to 24.49 µg/g
Potassium (K)	46.81 ± 6.71 ppm
Iron (Fe)	14.11 ± 2.11 ppm; 0.45 to 27.11 µg/g
Zinc (Zn)	976.14 ± 26.41 ppm
Manganese (Mn)	476.14 ± 12.64 ppm
Calcium (Ca)	3.53 to 76.92 µg/g
Chromium (Cr)	0.188 to 3.60 µg/g
Magnesium (Mg)	0.90 to 26.74 µg/g
Phosphorus (P)	< 1.25 to 266.5 µg/g
Sulfur (S)	8.45 to 648.7 µg/g

*typical fatty acid composition in seed (%)

Table 8. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[23,24]

	Rosa Canina Fruit Extract		Rosa Canina Flower		Rosa Canina Flower Extract	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals*/Conc. Range**	350	0.0000014-0.25	10	0.009-0.5	23	0.0001-0.04
Duration of Use						
Leave-On	299	0.0000014-0.25	7	0.009-0.5	22	0.0001-0.04
Rinse off	51	0.000009-0.1	3	NR	1	0.0001-0.001
Diluted for (bath) Use	NR	0.0075-0.1	NR	NR	NR	NR
Exposure Type						
Eye Area	175	0.0002-0.2	NR	NR	4	NR
Incidental Ingestion	21	0.0015	NR	NR	5	0.04
Incidental Inhalation- Possible Sprays	36*	0.00015-5*	4*	NR	4*	0.0001*
Incidental Inhalation - Sprays	NR	0.0002-0.25	NR	NR	NR	0.001-0.01
Incidental Inhalation- Powders	31	0.001-0.01	1	NR	NR	NR
Dermal Contact	290	0.0000014-0.25	10	0.009-0.5	23	0.001-0.04
Deodorant (underarm)	NR	0.0000014-0.00003	NR	NR	NR	NR
Hair - Non-Coloring	23	0.000009-0.25	NR	NR	NR	0.0001-0.001
Hair-Coloring	9	0.00003-0.0014	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	34	0.0001-0.1	NR	NR	5	0.04
Baby Products	NR	NR	NR	NR	NR	NR
	Rosa Canina Fruit		**Rosa Canina Leaf Extract**		**Rosa Canina Seed Extract**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	14	0.0003	5	NR	58	0.00029-1.5
Duration of Use						
Leave-On	12	NR	4	NR	57	0.0005-1.5
Rinse off	2	0.0003	1	NR	1	0.00029-0.1
Diluted for (bath) Use	1	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	NR	NR	NR	6	0.1
Incidental Ingestion	NR	NR	1	NR	10	1.5
Incidental Inhalation- Sprays	NR	NR	2*	NR	9*	0.029*
Incidental Inhalation- Powders	NR	NR	NR	NR	5**	NR
Dermal Contact	13	0.0003	4	NR	45	0.0005
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	2	0.00029-0.1
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	2	NR	10	1.5
Baby Products	NR	NR	NR	NR	2	NR
	Rosa Canina Seed Powder					
	# of Uses	Conc. (%)				
Totals/Conc. Range	6	NR				
Duration of Use						
Leave-On	2	NR				
Rinse off	3	NR				
Diluted for (bath) Use	1	NR				
Exposure Type						
Eye Area	NR	NR				
Incidental Ingestion	NR	NR				
Incidental Inhalation- Sprays	NR	NR				
Incidental Inhalation- Powders	NR	NR				
Dermal Contact	6	NR				
Deodorant (underarm)	NR	NR				
Hair - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Mucous Membrane	3	NR				
Baby Products	NR	NR				

Table 8. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[23,24]

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Use Product Uses.
*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
**It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
*** Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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2017 FDA VCRP Data

Rosa Canina Fruit Extract

03B - Eyeliner	1
03C - Eye Shadow	165
03D - Eye Lotion	5
03F - Mascara	1
03G - Other Eye Makeup Preparations	3
05A - Hair Conditioner	8
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	3
05H - Wave Sets	1
05I - Other Hair Preparations	4
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	9
07A - Blushers (all types)	14
07B - Face Powders	31
07C - Foundations	8
07E - Lipstick	20
07I - Other Makeup Preparations	1
09B - Mouthwashes and Breath Fresheners	1
10A - Bath Soaps and Detergents	11
10E - Other Personal Cleanliness Products	2
12A - Cleansing	12
12C - Face and Neck (exc shave)	21
12D - Body and Hand (exc shave)	4
12F - Moisturizing	7
12G - Night	4
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	2
12J - Other Skin Care Preps	4
Total	**350**

Rosa Canina Bud Extract (No FDA Data)

Rosa Canina Flower

07B - Face Powders	1
07C - Foundations	2
12F - Moisturizing	1
12G - Night	1
12H - Paste Masks (mud packs)	3
12I - Skin Fresheners	2
Total	**10**

Rosa Canina Flower Extract

03C - Eye Shadow	1
03D - Eye Lotion	2

03E - Eye Makeup Remover	1
07E - Lipstick	5
07F - Makeup Bases	1
11A - Aftershave Lotion	4
12A - Cleansing	2
12C - Face and Neck (exc shave)	3
12F - Moisturizing	4
Total	**23**

Rosa Canina Flower Powder (No FDA Data)

Rosa Canina Fruit

02A - Bath Oils, Tablets, and Salts	1
03D - Eye Lotion	1
05I - Other Hair Preparations	1
07I - Other Makeup Preparations	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	5
12D - Body and Hand (exc shave)	1
12G - Night	1
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	1
Total	**14**

Rosa Canina Fruit Juice (No FDA Data)

Rosa Canina Leaf Extract

07E - Lipstick	1
10E - Other Personal Cleanliness Products	1
12F - Moisturizing	1
12J - Other Skin Care Preps	2
Total	**5**

Rosa Canina Seed (No FDA Data)

Rosa Canina Seed Extract

01B - Baby Lotions, Oils, Powders, and Creams	2
03B - Eyeliner	2
03F - Mascara	3
03G - Other Eye Makeup Preparations	1
07E - Lipstick	10
07I - Other Makeup Preparations	9
12A - Cleansing	1
12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	4
12F - Moisturizing	24

Total	**58**

Rosa Canina Seed Powder

02A - Bath Oils, Tablets, and Salts	1
10E - Other Personal Cleanliness Products	2
12A - Cleansing	1
12J - Other Skin Care Preps	2
Total	**6**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: October 31, 2016

SUBJECT: Tentative Report: Safety Assessment of *Rosa canina*-Derived Ingredients As Used In Cosmetics (release date: October 7, 2016)

Key Issues

Table 1 - The definition of plant extracts in the Dictionary do not include the solvent. Therefore, it is not appropriate to add a definition of Rosa Canina Fruit Extract that includes a solvent. If solvents are added to Table 1, it is not clear why only butylene glycol is mentioned as the method of manufacture also describes an ethanol extract, and the Dictionary has trade names that include other solvents including CO_2 and sunflower seed oil.

Discussion - IFRA does not have a standard for linalool in finished products as implied by the Discussion. The IFRA standard states that the level of peroxides in linalool must be kept to the lowest practical level.

Additional Considerations

Composition/Impurities, Rosa Canina Leaf Extract - Since leaves were distilled, please revise: "This material is more closely related to a flower essential oil" to "This material is more closely related to a leaf essential oil".

Acute, Intraperitoneal - What "toxic signs" were exhibited in mice at doses greater than the LD_{50}?

Summary - As it states that 3 rabbits were used in the skin irritation test, "number not stated" needs to be deleted.

Table 7 - Please indicate what the percentage signs with the fatty acids represent. Is it the percent of total fatty acids, or the percent of total composition? The units for ash need to be corrected as it is impossible for *Rosa canina* seed to contain 4227.46 ± 161.54% ash.

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