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

Status: Draft Tentative Report for Panel Review
Release Date: September 2, 2016
Panel Date: September 26-27, 2016

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

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: September 2, 2016
Subject: Draft Tentative Report on *Rosa canina*-derived Ingredients

An Insufficient Data Announcement with the following data requests was issued at the March 31 – April 1, 2016 CIR Expert Panel Meeting.

(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

In accordance with the Panel's recommendations at the March 31 – April 1 Expert Panel Meeting, the safety assessment (now a Draft Tentative Report) has been revised to include the ingredient Rosa Canina Flower Oil, data summaries from the published CIR Final Report on Butylene Glycol and more recent published literature (italicized in the report text), and data from the published literature relating to the composition of Rosa Canina Flower Extract and Rosa Canina Leaf Extract. The data summaries on butylene glycol are included because this ingredient is a major component of Rosa Canina Fruit Extract. Additionally, HRIPT/In-use data on product formulations containing Rosa Canina Flower Extract and updated ingredient use concentration data (all 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 requested in the IDA. The data on *Rosa canina*-derived ingredients that have been added to the report text are enclosed within borders. It should also be noted that the Draft Tentative Report contains a draft discussion that captures the Panel's concerns/positions that were voiced during deliberations at the March 31 – April 1, 2016 Expert Panel Meeting. Particularly, concerns relating to the potential skin depigmentation effect of Rosa Canina Fruit Extract are included.

Included in this package for your review is the draft safety assessment (*rosaca092016rep*), the published CIR Final Report on Butylene Glycol (rosaca*092016prev*), the CIR report history (*rosaca092016hist*), literature search strategy (*rosaca092016strat*), ingredient data profile (*rosaca092016prof*), minutes from the March 26-27, 2016 Panel meeting (*rosaca092016min*), 2016 FDA VCRP data (*rosaca092016FDA*), and data received from the Council (*rosaca092016data1a, rosaca092016data1b, rosaca032016data 2, and rosaca032016data3*), and comments received from the Council (*rosaca092016pcpc).* Council comments have been addressed.

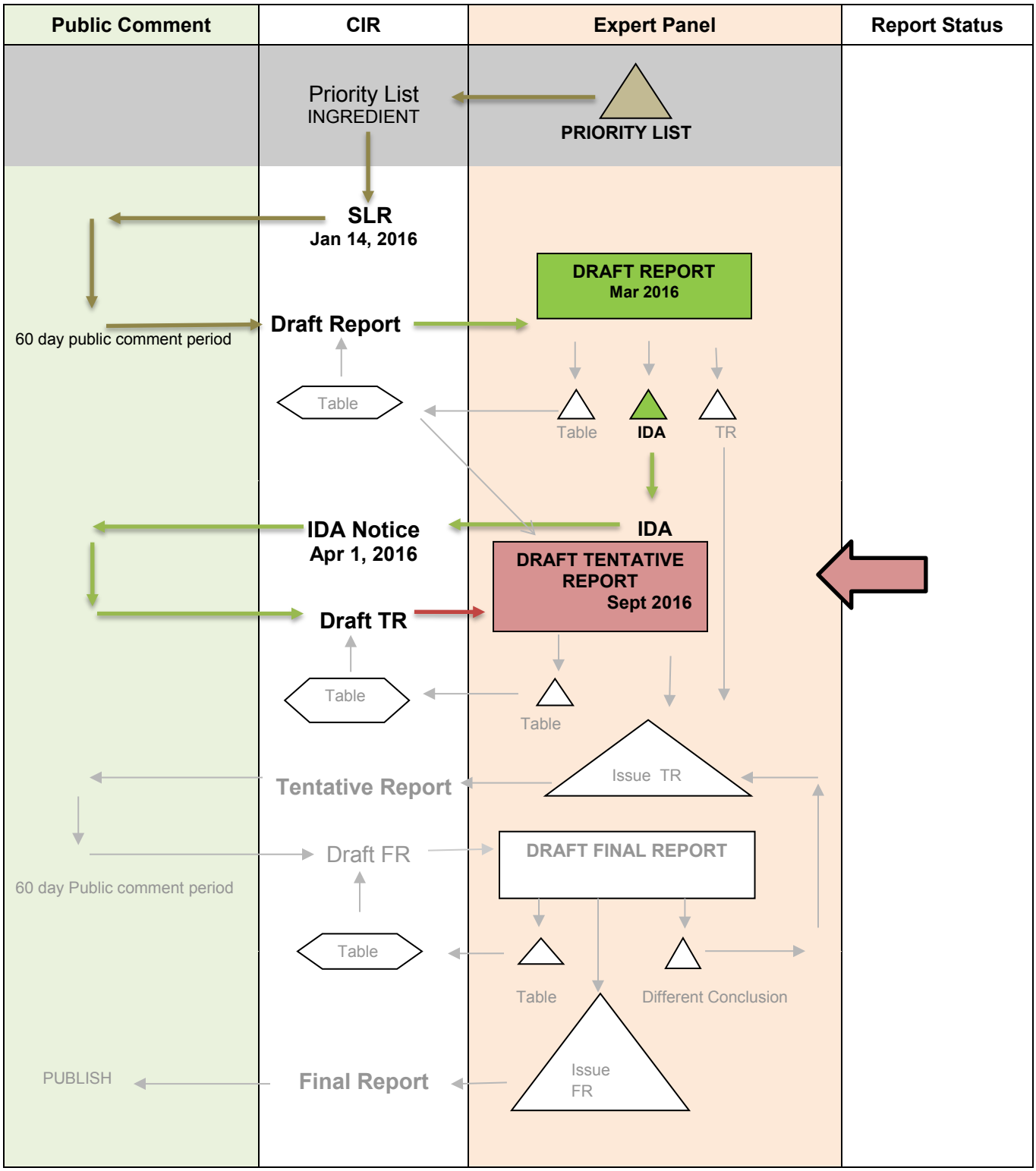
After considering the data included in this safety assessment, the Panel will need to determine whether to issue a Tentative Report with an insufficient data conclusion or a conclusion of safe with qualifications.

1620 L Street, N.W., Suite1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Rosa canina*-derived Ingredients

MEETING Sept 2016



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.

***Rosa canina*-derived Ingredients Check List for September, 2016. 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]

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.

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

Status: Draft Tentative Report for Panel Review
Release Date: September 2, 2016
Panel Date: September 26-27, 2016

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

1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

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, antiacne agents, abrasives, humectants, and exfoliants in cosmetic products. The Panel reviewed relevant data relating to the safety of these ingredients and concluded [to be determined].

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
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*, the functions of these ingredients in cosmetic products include: skin conditioning agent, fragrance ingredient, cosmetic astringent, antiacne agent, abrasive, humectant, and exfoliant (Table 1).[1] Rosa Canina Flower Powder is the only ingredient in this group that is reported to function as an anti-acne agent (anti-acne agent is not regarded as a cosmetic use in the U.S., but is a drug use[2], and the Panel will not evaluate safety for that use).

The Panel has 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.[3] The Panel has also 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.[4] This conclusion was reaffirmed by the Panel in a 2006 publication.[5] Data from the published final report on butylene glycol and more recent data on this ingredient are italicized within the report text. The more recent data relate to genotoxicity, reproductive and developmental toxicity, and case reports indicating butylene glycol-induced contact sensitization.

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.[6,7] 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.[8]

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.[9]

The method of manufacture of Rosa Canina Fruit Extract (ethanol extract) has been described as follows:[8]

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.[8]

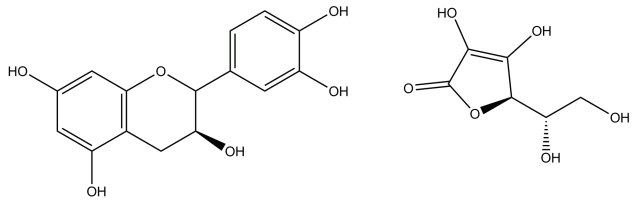
Dried raw material → extract with 1,3-butylene glycol → filtrate → sedimentation → filtrate → adjustment → packaging

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

Composition/Impurities

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).[12] (+)-Catechin, a flavonoid, has been identified as the most abundant flavan-3-ol (3.59 mg/100 g) in Rosa Canina Fruits,[6] and the abundance of ascorbic acid (Vitamin C, 880 mg/100 ml) in Rosa Canina Fruit has also been noted.[13,14]



(+)-catechin ascorbic acid

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).[13] 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.[15]

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.[16] 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.

The chemical composition of Rosa Canina Fruit differs, depending on the cultivar, growing region, climate, maturity, cultivation practice, and storage conditions.[17] Significant variations in the following components have been reported: organic acids, sugars, water-soluble vitamins, minerals, and phenolics.[13] 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%).[17] 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.[18]

Additional information on the nutritional composition of wild Rosa Canina Fruit is presented in Table 4.[17]

Rosa Canina Fruit Extract

Rosa Canina Fruit Extract consists of 0.65% (maximum percentage) Rosa Canina Fruit Extract.[9] Additional information relating to the composition of this ingredient is found in Table 1. 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%).

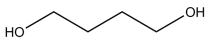


Figure 2. Butylene glycol

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).[9] 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.

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.[8]

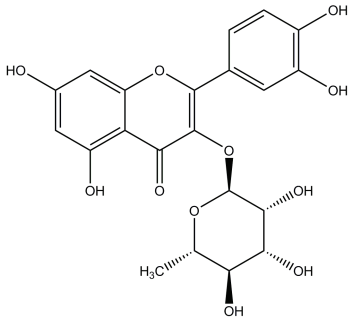


Figure 3. Quercetrin

Additionally, 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).[8]

The highest concentration phenolic acid found in Rosa Canina Fruit Extract is Ellagic Acid.

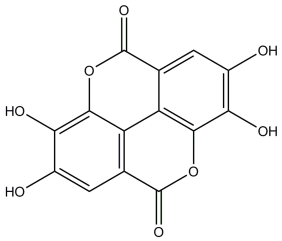


Figure 4. Ellagic Acid

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.[10,11]

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).[19]

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.[20] 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.[21] 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.[22] 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.[7,23]

USE

Cosmetic

The safety of the *Rosa canina*-derived ingredients included in this safety assessment 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 2016 VCRP data, the greatest reported use frequency is for Rosa Canina Fruit Extract (342 formulations, mostly leave-on products), followed by Rosa Canina Seed Extract (36 formulations, mostly leave-on products) (Table 8).[24] 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).[25] 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 7 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.[26,27,28,29] 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.[26,27] 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.[30,31,32]

Noncosmetic

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.[12] The health benefits of Rosa Canina Fruit have been attributed to its wide range of bioactive compounds, including GOPO, vitamin C, phenolics, lycopene, lutein, zeaxanthin, and other carotenoids.[17]

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

Toxicokinetics data on *Rosa canina*-derived ingredients were neither found in the published literature, nor would finding these in the literature be expected.

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

In rats dosed orally, butylene glycol was metabolized to acetoacetate and β-hydroxybutyrate.[4]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

In an acute dermal toxicity study involving rabbits, an LD_{50} of > 2 g/kg was reported for a product formulation containing 5% butylene glycol.[4]

Oral

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

In acute oral toxicity studies involving rats and guinea pigs, LD_{50}s of 23 g/kg and 11 g/kg, respectively, were reported.[4]

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.[21] An estimated acute i.p. LD_{50} of 455.19 ± 23 mg/kg was reported. The animals exhibited toxic signs at doses greater than the LD_{50}.

Short-Term Toxicity Studies

Dermal

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

A product formulation containing 3% butylene glycol was applied to the skin of 8 albino rabbits daily (daily dose of 500 mg/kg) for 4 weeks. No test substance-related systemic effects, based on microscopic examination results, were observed.[4]

Oral

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. 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.

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

In a short-term (5 days) oral toxicity study involving groups of 8 rats, dose-related (up to 7 g/kg) depression of activity was observed.[4]

Human

Rosa Canina Fruit Extract

A double-blind, placebo-controlled clinical trial involving 2 groups of 16 subjects was performed.[36] 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.

Chronic Toxicity Studies

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

No test substance-related toxic effects, including changes in organs examined microscopically , were observed in groups of 60 Sprague-Dawley rats fed diets containing 1% to 10% butylene glycol in the diet for 2 years.[4] *There also were no toxic effects in groups of 8 beagle dogs fed butylene glycol at concentrations of 0.5% to 3% in the diet for 2 years.*

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.

Oral

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

The effect of butylene glycol ingestion on pregnant rats and their offspring was evaluated. Groups of pregnant rats received butylene glycol (9% w/v) in drinking water, and treatment was continued throughout gestation and lactation. Treatment with butylene glycol had no effect on the length of gestation. Rats that ingested butylene glycol throughout gestation bore offspring with a slight increase in the RNA content of neurons obtained from the cerebral cortex at 18 days. In 8- and 18-day-old pups, protein synthesis in the liver was significantly reduced.[4]

A study was performed to evaluate the effect of butylene glycol on reproductive performance and its teratogenic, dominant lethal, and cytogenetic effects[38]. Five generations of Wistar rats were used. Male and female rats were fed either a control diet or a diet supplemented with butylene glycol at a concentration of 5%, 10%, or 24%. For 4 of 5 generations of dams and pups, reproduction and lactation parameters were comparable to controls. However, the pregnancy rate of F_{1A} rats decreased during 5 successive mating cycles; no pups were obtained in the high-dose group of the fifth series of litters (F_{2E} generation). If this finding is excluded, the viability of F_2 generation pups revealed no significant differences between litters or between control and test groups. No definitive dose-related teratologic findings were observed in either soft or skeletal tissue examinations of F_{3B} generation rats. But, there was a frequent occurrence of incomplete ossification of sternebrae in mid- and high-dose fetuses; missing sternebrae were noted especially in high dose fetuses. Both skeletal tissue findings were suggestive of slight delayed fetal growth. Results relating to dominant lethal and cytogenetic effects are summarized in the following section.

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 (OECD Protocol #471) using *Salmonella typhimurium* strains (*S. typhimurium* strains not stated).[9] 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.[8] 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.[16,39] Raw, boiled juice, boiled leaves, and dried seeds (concentration of each not stated) were not mutagenic in *S. typhimurium* strain TA 100.

In Vivo

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

The following results on butylene glycol are reported in a study that is summarized in the preceding section on Developmental and Reproductive Toxicity.[38] In the dominant lethal assay of the F_{1B} generation, the mutagenic index (percentage resorptions per implant sites) did not indicate a dose-related trend. In the 3-generation cytogenetic study, no 1,3-butanediol-related chromosomal aberrations were noted.

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%.[16,39]

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.[40]

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 (at highest insecticide test concentrations) 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.[16,41] The aqueous rosa canina seed extract had little cytotoxic effect on Yoshida ascites sarcoma cells ($LD_{50} > 10$ mg/mL). However, the ethanol and petroleum ether extracts had a substantial cytotoxic effect on these cells, with LD_{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, proanthocyanidins from grape seeds had no effect on the expression of tyrosinase protein in normal human melanocytes.[42]

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.[43] 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 and normal epidermal melanocytes.[44]

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

Non-human

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).[45] 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 statiostically 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 (number and strain not stated), results for the butylene glycol extract of Rosa Canina Fruit (0.3% solids – 100% of the butylene glycol extract) were negative.[8] 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).[8] 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.

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

Minimal skin irritation was observed in rabbits following a 24-h application or daily application (4 days) of undiluted butylene glycol.[4]

Several products containing 5% to 21.4% butylene glycol were applied (under occlusion) to the skin of rabbits for 24 h. Reactions ranging from no irritation to moderate irritation were observed.[4]

A product formulation containing 3% butylene glycol was applied to the skin of 8 albino rabbits daily (daily dose of 500 mg/kg) for 4 weeks. Slight erythema was observed.[4]

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.[9] 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.[9] 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.

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

Undiluted butylene glycol was applied for 24 h to 37 subjects (under occlusion) or 39 subjects (semi-occlusive condition). Mild irritation was observed in 1 subject (semi-occlusive application). Skin irritation was not observed in the remaining subjects tested.[4]

In an HRIPT, 50% aqueous butylene glycol was applied (under occlusion for 24 h) to 200 subjects. Mild skin fatigue was observed in 2 subjects, and there was no evidence of sensitization in any of the 200 subjects tested.[4]

In single-insult occlusive patch tests involving human subjects, products containing 3% to 21.4% butylene glycol produced no more than minimal skin irritation.[4]

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.[46] 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.[47] 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.

Photosensitization/Phototoxicity

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

Four studies included exposure to UV light as a supplement to the prophetic patch tests and HRIPTs on a nail lotion containing 5% butylene glycol. Reactions were not observed after UV exposure in any of the subjects patch tested with the nail lotion.[4]

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.

Animal

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

Undiluted butylene glycol (505 mg) was irritating to the rabbit eye.[4] *Other study results indicated that neither undiluted butylene glycol (0.1 ml) nor 40% aqueous butylene glycol was irritating to the eyes of 6 rabbits.*

Several product formulations containing 5% to 21.35% butylene glycol produced not more than minimal, transient irritation when instilled into the eyes of rabbits.[4]

Human

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

A severe stinging sensation was observed after 1 drop of butylene glycol was instilled into the eyes of human subjects.[4]

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.[48] 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.[49] 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.

Butylene Glycol (a major component of Rosa Canina Fruit Extract)

Recurrent severe pruritic edema of the eyelids, followed by redness and scaling, was observed in a 16-year old girl.[50] *Various cosmetic products, particularly an eyeliner, were considered as possible causes. Patch tests involving the eyeliner and all ingredients of the eyeliner were performed. A papular reaction was observed after 2 days of open application of the eyeliner. This reaction was viewed as confirmation of a high degree of contact sensitization. The patient also had a 3+ reaction to 2% aqueous butylene glycol and 20% shellac in ethanol. Results were negative for the remaining ingredients.*

A case of a 28-year-old woman with an itchy erythematous eruption on her face was reported.[51] *Two days of closed patch testing of her own cosmetics and many of the hypo-irritant skin care products yielded positive results. Butylene glycol was a common ingredient in most of the products that elicited a positive reaction. A second series of patch testing revealed a positive reaction to butylene glycol at test concentrations of 1% and 5%. The authors noted that allergic contact dermatitis due to butylene glycol is rather uncommon.*

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.[52] 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

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).[37] 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*-derived ingredients have the following functions in cosmetic products: skin conditioning agent, fragrance ingredient, cosmetic astringent, antiacne 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 (342 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 LD_{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 ($LD_{50} > 10$ mg/L).

In a skin irritation test involving 3 rabbits (number and strain not stated), 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) (1^{st} induction), 20% of the original solution (2^{nd} 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.

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.

DRAFT DISCUSSION

Because Rosa Canna Fruit Extract contains 76% to 93.5% butylene glycol, the Panel agreed that safety test data summaries from the CIR Final Report on Butylene Glycol should be incorporated for use in evaluating the safety of Rosa Canina Fruit Extract in cosmetics.

The inhibition of skin pigmentation by Rosa Canina Fruit Extract 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. However, 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. Furthermore, it was noted that this inhibitory effect on skin pigmentation has not been observed in human cell cultures treated with quercetin or proanthocyanidins. However, because final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For *Rosa canina*-derived ingredients, the Panel was concerned about the presence of quercetin and proanthocyanidins in cosmetics, which could result in skin depigmentation. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause adverse effects.

The Expert Panel expressed concern about pesticide residues and heavy metals 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.

The Panel also noted that it should be made clear that they do not agree with the interpretation of results of a positive cytotoxicity study involving Rosa Canina Seed Extract and ascites sarcoma cells as an anti-carcinogenic effect.

CONCLUSION

To be determined.

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.[9]	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).[11]

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.[17]

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].[20]

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.[22]

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.[22]

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.[7,23]

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

Table 8. Current Frequency and Concentration of Use According to Duration and Type of Exposure.[24,25]

	Rosa Canina Fruit Extract		Rosa Canina Flower		Rosa Canina Flower Extract	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	342	0.0000014-0.25	8	0.009-0.5	24	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	43	0.000009-0.1	1	NR	2	0.0001-0.001
Diluted for (bath) Use	NR	0.0075-0.1	NR	NR	NR	NR
Exposure Type						
Eye Area	173	0.0002-0.2	NR	NR	4	NR
Incidental Ingestion	1	0.0015	NR	NR	5	0.04
Incidental Inhalation- Sprays	37*	0.00015*-0.25	4*	NR	5*	0.0001*-0.01
Incidental Inhalation- Powders	30	0.01 -7**	1	NR	NR	NR
Dermal Contact	279	0.0000014-0.25	8	0.009-0.5	23	0.001-0.04
Deodorant (underarm)	NR	0.0000014-0.00003	NR	NR	NR	NR
Hair - Non-Coloring	47	0.000009-0.25	NR	NR	1	0.0001-0.001
Hair-Coloring	13	0.00003-0.0014	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	11	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	4	0.0003	7	NR	36	0.00029-1.5
Duration of Use						
Leave-On	3	NR	5	NR	34	0.0005-1.5
Rinse off	NR	0.0003	2	NR	2	0.00029-0.1
Diluted for (bath) Use	1	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	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**	0.0005**
Dermal Contact	4	0.0003	4	NR	21	0.0005
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	2	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	3	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.[24,25]

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

References

1. Nikitakis, J. and Breslawec H. P. International Cosmetic Ingredient Dictionary and Handbook. 14 *ed*. Washington, DC: Personal Care Products Council, 2014.

2. Food and Drug Admnistration (FDA). Rulemaking history for OTC acne drug products. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm069967.htm. Last Updated 2015. Date Accessed 12-18-2015.

3. Burnett, C. Heldreth B. Bergfeld W. F. Belsito D. V. Hill R. A. Klaassen C. D. Liebler D. C. Marks J. G. Jr. Shank R. C. Slaga T. J. and Snyder P. W. Final report. Plant-derived fatty acid oils as used in cosmetics. 2011. pp.1-100. Washington, D.C.: Cosmetic Ingredient Review.

4. Elder, R. L. Final Report on the Safety Assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol. *Journal of the American College of Toxicology*. 1985;4(5):223-248.

5. Andersen, F. A. Annual Review of Cosmetic Ingredeint Safety Assessments - 2004/2005. Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol. *International Journal of Toxicology*. 2006;25(2):10-18.

6. Guimaraes, R. Barros L. Duenas M. Carvalho A. M. Queiroz M. J. R. P. Santos-Buelga C. and Ferreira I. C. F. R. Characterizaton of phenolic compounds in wild fruits from Northeastern Portugal. *Food Chemistry*. 2013;141:3721-3730.

7. Ozcan, M. Nutrient composition of Rose (*Rosa canina* L.) seed and oils. *Journal of Medicinal Food*. 2002;5(3):137-140.

8. Personal Care Products Council. Summary information. Rosa Canina Fruit Extract (ethanol and butylene glycol extracts). Unpublished data submitted by the Personal Care Products Council on 2-29-2016. 2016. pp.1-2.

9. Anonymous. Summary information. Rosa canina fruit extract. Unpublished data submitted by the Personal Care Products Council on 2-10-2016. Last Updated 2016.

10. Nadpal, J. D. Lesjak M. M. SiIbul F. S. Anackov G. T. Cetojevic-Simin D. D. Mimica-Dukic N. M. and Beara I. N. Comparative study of biological activities and phytochemical composition of two rose hips and their preserves: *Rosa canina* L. and *Rosa arvensis* Huds. *Food Chemistry*. 2016;(192):907-914.

11. Tumbas, V. T. Canadanovic-Brunet J. M. Cetojevic-Simin D. D. Cetkovic G. S. Dilas S. M. and Gille L. Effect of rosehip (*Rosa canina* L.) phytochemicals on stable free radicals and human cancer cells. *J.Sci.Food Agric.* 2012;92:1273-1281.

12. Ashtiyani, S. C. Najafi H. Jalalvandi S. and Hosseinei F. Protective effects of *Rosa Canina* L fruit extracts on renal disturbances induced by reperfusion injury in rats. *Iranian Journal of Kidney Diseases*. 2013;7(4):290-298.

13. Ercisli, S. Chemical composition of fruits in some rose (Rosa spp.) species. *Food Chemistry*. 2007;104(4):1379-1384.

14. Gao, X Bjork L. Trajkovski V. and Uggla M. Evaluaiton of antioxidant activities of rose hip ethanol extracts in different test systems. *J.Sci.Food Agric.* 2000;80(14):2021-2027.

15. Horvath, G. Molnar P. Rado-Turcsi E. Deli J. Kawase M. Satoh K. Tanaka T. Tani S. Sakagami H. Gyemant N. and Molnar J. Carotenoid composition and *in vitro* pharmacological activity of hips. *Acta Biochimica Polonica*. 2012;59(1):129-132.

16. Chrubasik, C. Roufogalis B. D. Müller-Ladner U. and Chrubasik S. Review article. A systematic review on the *Rosa canina* effect and efficacy profiles. *Phytotherapy Research*. 2008;22:725-733.

17. Fan, C. Pacier C. and Martirosyan D. M. Rose hip (*Rosa canina* L): A functional food perspective. *Functinal Foods in Health and Disease*. 2014;4(11):493-509.

18. Larsen, E., Kharazmi, A, Christensen, LP, and Christensen, SB. An antiinflammatory galactolipid from rose hip (Rosa canina) that inhibits chemotaxis of human peripheral blood neutrophils in vitro. *J Nat Prod.* 2003;66(7):994-995.

19. Ieria, F. Innocentib M. Possieric L. Gallorib S. and Mulinaccib N. Phenolic composition of "bud extracts" of *Ribes nigrum* L.., *Rosa canina* L., and *Tilia tomentosa*, M. *Journal of Pharmaceutical and Biomedical Analysis*. 2015;115:1-9.

20. Hosni, K. Kerkenni A. Medfei W. Brahim N. B. and Sebel H. Volatile oil constituents of rosa canina L.: Quality as affected by the distillation method. *Organic Chemistry International*. 2010;2010:1-7.

21. Mandade, R. J. Choudhury A. Harsulkar A. and Wakade R. Role of the *Rosa canina* L. leaf extract as an antidiarrheal drug in rodents. *Indian J.Pharmacol.* 2011;43(3):316-319.

22. Ghazghazi, H. Miguel M. G. Hasnaoui B. Sebel H. Ksontini M. Figueiredo A. c. Pedro L. G. and Barroso J. G. Phenols, essential oils and carotenoids of *Rosa canina* from Tunisia and their antioxidant activities. *African Journal of Biotechnology*. 2010;9(18):2709-2716.

23. Szentmihalyi, K. Vinkler P. Lakatos B. Illes V. and Then M. Rose hip (Rosa canina L.) oil obtained from waste hip seeds by different extraction methods. *Bioresource Technology*. 2002;82:195-201.

24. Food and Drug Administration (FDA). Information supplied to FDA by industry as part of the VCRP FDA database. 2016. Washington, D.C.: FDA.

25. Personal Care Products Council. Updated concentration of use by FDA product category - Rosa canina-derived ingredients. Unpublished data submitted by the Personal Care Products Council on 4-25-2016. 2016. pp.1

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

27. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 20200. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

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

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

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

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

32. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 11-3-2015. Cosmetic Powder Exposure.

33. Saaby, L. and Nielsen, CH. Triterpene acids from rose hip powder inhibit self-antigen- and LPS-induced cytokine production and CD4⁺ T-cell proliferation in human mononuclear cell cultures. *Phytother Res.* 2012;26(8):1142-1147.

34. Saaby, L. Jager A. K. Moesby L. Hansen E. W. and Christensen S. B. Isolation of immunomodulatory triterpene acids from a standardized rose hip powder (*Rosa canina* L.). *Phytother.Res.* 2011;25:195-201.

35. Fujii, T., Ikeda, K, and Saito, M. Inhibitory effect of rose hip (Rosa canina L.) on melanogenesis in mouse melanoma cells and on pigmentation in brown guinea pigs. *Biosci.Biotechnol Biochem.* 2011;75(3):489-495.

36. Nagatomo, A. Nishida N. Fukuhara I. Noro A. Kozai Y. Sato H. and Matsuura Y. Daily intake of rosehip extract decreases abdominal visceral fat in preobese subjects: a randomized, double-bliond, placebo-controlled clinical trial. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. 2015;8:147-156.

37. Willich, S. N. Rossnagel K. Roll S. Wagner A. Mune O. Erlendson J. Kharazmi A. Sörensen H. and Winther K. Rose hip herbal remedy in patients with rheumatoid arthritis - a randomized controlled trial. *Phytomedicine*. 2010;17(2):87-93.

38. Hess, F. G. Jr. Cox G. E. Bailey D. E. Parent R. A. and Becci P. J. Reproduction and teratology study of 1,3-butanediol in rats. *Journal of Applied Toxicology*. 1981;1(4):202-209.

39. Karakaya, S. and Kavas A. Antimutagenic activities of some foods. *J.Sci.Food Agric.* 1999;79:237-242.

40. Kasimoglu, C. and Uysal, H. Mutagenic biomonitoring of pirethroid insecticides in human lymphocyte cultures: use of micronuclei as biomarkers and recovery by Rosa canina extracts of mutagenic effects. *Pharm Biol.* 2014;53(5):625-629.

41. Trovato, A., Monforte, MT, Rossitto, A, and Forestieri, AM. In vitro cytotoxic effect of some medicinal plants containing flavonoids. *Boll.Chim.Farm.* 1996;135:263-266.

42. Uehara, S. Mizutani Y. Nakade M. Sakata O. Sasaki I. Arakane K. Suzuki T. Uchida R. and Tokutake S. *J.Jpn.Cosmet.Sci.Soc.* 2003;27:247-256.

43. Fujii, T. and Saito M. Inhibitory effect of quercetin isolated from rose hip (*Rosa canina* L.) against melanogenesis by mouse melanoma cells. *Biosci.Biotechnol.Biochem.* 2009;73(9):1989-1993.

44. Nagata, H. Takekoshi S. Takeyama R. Homma T. and Osamura R. Y. *Pigment Cell Res.* 2004;17:66-73.

45. Sadigh-Eteghad, S. Tayefi-Nasrabadi H. Aghdam Z. Zarredar H. Shanehbandi D. Khayyat L. and Seyyed-Piran S. *Rosa canina* L. fruit hydro-alcoholic extract effects on some imunological and biochemical parameters in rats. *BioImpacts*. 2011;1(4):219-224.

46. Consumer Product Testing Co. Repeated insult patch test of a lip balm containing 0.04% Rosa Canina Flower Extract. Unpublished data submitted by the Personal Care Products Council on 4-20-2016. 2010. pp.1-13.

47. TKL Research. Repeated insult patch test of a lip liner containing 0.018% Rosa Canina Flower Extract. Unpublished data submitted by the Personal Care Products Council on 4-21-2016. 2012. pp.1-10.

48. Lleonart, R. and Corominas, MaLM. Tea infusion, another source of Rosaceae allergy. *Allergy*. 2007;62:89-90.

49. Kwaselow, A. Rowe M. Sears-Ewald D. and Ownby D. Rose hips: a new occupational allergen. *J.Allergy Clin.Immunol.* 1990;85(4):704-708.

50. Magerl, A. Pirker C. and Frosch P. J. Allergic contact eczema from shellac and 1,3-butylene glycol in an eyeliner. *J.Dtsch Dermatol.Ges.* 2003;1(4):300-302.

51. Aizawa, A. Ito A. Masui Y. and Ito M. Case of allergic contact dermatitis due to 1,3-butylene glycol. *J.Dermatol.* 2014;41(9):815-816.

52. Institute d'Expertise Clinique. In-use test under dermatological control: night cream containing 0.005% Rosa Canina Flower Extract. Unpublished data submitted by the Personal Care Products Council on 4-21-2016. 2008. pp.1-40.

JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 4, Number 5, 1985
Mary Ann Liebert, Inc., Publishers

8

Final Report on the Safety Assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol

Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are viscous liquids used in the cosmetic industry as humectants, emulsifiers, plasticizers, and solvents.

The results of acute, subchronic, and chronic oral toxicity studies using a variety of animal species indicate a low order of toxicity for the Glycols. Results of parenteral injection, inhalation, and acute and subchronic cutaneous toxicity studies likewise support a low order of toxicity. Butylene Glycol, Ethoxydiglycol, and Dipropylene Glycol caused minimal to mild irritation of rabbit skin, whereas Hexylene Glycol was moderately irritating. The Glycols produced mild to severe ocular irritation when tested in rabbits, with Hexylene Glycol producing the most severe irritation. Although undiluted Hexylene Glycol produced severe ocular irritation, a 25 percent aqueous solution produced no signs of irritation. Undiluted Butylene Glycol was not an eye irritant to rabbits but was to humans.

Human skin patch tests on undiluted Butylene Glycol and undiluted Hexylene Glycol produced a very low order of primary skin irritation. A repeated insult patch test on Butylene Glycol produced no evidence of skin sensitization.

Based on the available data it is concluded the Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are safe as presently used in cosmetics.

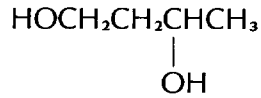
INTRODUCTION

Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are viscous liquids used in the cosmetic industry as humectants, emulsifiers, plasticizers, and solvents.

CHEMICAL AND PHYSICAL PROPERTIES

Structure/Composition

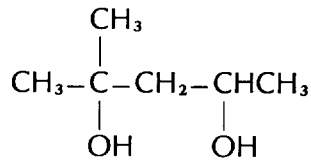
1. Butylene Glycol is an aliphatic diol. It conforms to the formula:



CAS Number: 107-88-0

Other names include 1,3-Butanediol and 1,3-Butylene Glycol.[1]

2. Hexylene Glycol is the aliphatic alcohol that conforms to the formula:



CAS Number: 107-41-5

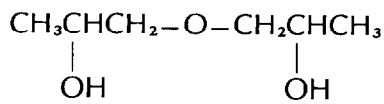
Other names are 2-Methyl-2,4-Pentanediol and 2,4-Pentanediol,2-Methyl-.[1]

3. Ethoxydiglycol is the ether alcohol that conforms to the formula:

CAS Number: 111-90-0

Other names include Diethylene Glycol Monoethyl Ether; Ethanol, 2-(2-Ethoxyethoxy)-; 2-(2-Ethoxyethoxy)Ethanol.[1]

4. Dipropylene Glycol is a mixture of diols that conforms generally to the formula:



The material of commerce is primarily a mixture of 3 isomers, with the majority being disecondary (85 to 90 percent). Primary-secondary and diprimary isomers, along with up to 5 percent unidentified material, make up the remainder.

CAS Number: 110-98-5

Other names are: Di-1,2-Propylene Glycol; 1,1'-Oxybis-2-Propanol; 2-Propanol,1,1'-Oxybis-.[1,2]

Properties

Butylene Glycol is a clear, practically colorless, viscous, hygroscopic liquid. It is odorless and has a slightly sweet, characteristic taste. Butylene Glycol is miscible in all proportions with water, acetone, and alcohol. It is immiscible with fixed oils and insoluble in aliphatic hydrocarbons, benzene, toluene, and carbon tetrachloride. This glycol does dissolve most essential oils and synthetic flavoring substances.[3-7]

Hexylene Glycol is a clear hygroscopic liquid with a mild, sweet odor. It exhibits exceptional solvency for a variety of materials and is miscible with aliphatic and aromatic hydrocarbons as well as with such polar substances as water, fatty acids, and alcohols. It is combustible.[5,6,8]

Ethoxydiglycol is a colorless hygroscopic liquid, soluble in water and most organic solvents.[4,9]

Dipropylene Glycol is a colorless, slightly viscous liquid that is soluble in water, ethanol, and acetone.[5]

Other physical and chemical properties of the glycols are shown in Table 1.

Production

Butylene Glycol is produced by the catalytic hydrogenation of acetaldehyde using as catalysts Raney nickel, copper, or platinum oxide. It is purified by distillation.[6,7,10]

TABLE 1. Properties of Glycols

Property	*Butylene Glycol*	*Hexylene Glycol*	*Ethoxydi-glycol*	*Dipropylene Glycol*	*Reference*
Molecular weight	90.12	188.18	134.18	134.18	4
Boiling point (°C)	208 (0.8 atm)	197(760mm)	195(760mm)	229-32	4
	207.5	197.1(760mm)	–	222-38(760mm)	2, 7, 8
Freezing point (°C)	−50	–	−105	Supercools	2, 6, 7, 9
Specific gravity (g/ml)	1.0053^{20}_{4}	0.9254^{17}_{4}	0.9881^{20}_{4}	1.0224^{20}_{20}	4
	1.0053^{20}_{20}	0.9233^{20}_{20}	0.988^{25}_{25}	$1.020-1.030^{20}_{20}$	2, 7-9
Refractive index n_D^{20}	1.4418	1.4250	1.4300	–	4
	1.4412	1.4276	–	1.439	2, 7, 8
Vapor pressure	0.06 mm	–	0.26 mm	0.01 mm	2, 4, 5, 9
Viscosity (cps)	103.9 (25°C)	41.7 (20°C)	–	–	7,8
Solubility					
Water	Soluble	Soluble	Soluble	Soluble	3, 4
Alcohol	Soluble	Soluble	Soluble	Soluble	3, 4
Ether	Insoluble	Soluble	Soluble	–	4
Acetone	Soluble	–	Soluble	Soluble	2, 4, 7
Benzene	Insoluble	–	Soluble	–	4, 7
Carbon tetrachloride	Insoluble	–	–	–	7
Aliphatic hydrocarbons	Insoluble	Soluble	–	–	7,8
Aromatic hydrocarbons	–	Soluble	–	–	8
Fatty acids	–	Soluble	–	–	8

Hexylene Glycol is manufactured by the condensation of 2 molecules of acetone to produce diacetone alcohol, which is further hydrogenated to produce Hexylene Glycol. This is then purified by distillation.[8]

Ethoxydiglycol is prepared from the reaction of ethylene oxide with ethanol followed by purification by distillation.[9]

Dipropylene Glyol is the reaction product of propylene glycol and propylene oxide.[2,11]

Analytical Methods

Chemical and chromatographic methods may be used for the identification and separation of the glycols. Chemical methods involve oxidation of the glycols with subsequent reaction with a reagent.[12] Gas chromatography may be used for the identification of glycols.[13,14]

Impurities

Butylene Glycol has a minimum gas chromatographic assay of 99.5 percent by weight. It contains a maximum of 0.5 percent water, up to 0.005 percent acetic acid, and trace amounts of branched 1,3-Butylene Glycol.[7]

Hexylene Glycol contains a maximum of 0.1 percent water and 0.005 percent acetic acid.[8]

Ethoxydiglycol has a minimum gas chromatographic assay of 99.0 percent and contains water and acetic acid to maximums of 0.1 and 0.01 percent, respectively. Known impurities include diethylene glycol and triethylene glycol.[9]

The isomer distribution of Dipropylene Glycol is as specified by the commercial buyer. It contains up to 0.1 percent water, up to 0.01 percent acetic acid, and up to 0.001 percent inorganic chlorides. The maximum combustion residue of Dipropylene Glycol should not exceed 0.005 percent.[2]

USE

Noncosmetic Use

Butylene Glycol has been tested as a parenteral drug solvent,[11] in the manufacture of polyester plasticizers, and as a humectant for cellophane and tobacco.[6] It serves as a surfactant, coupling agent, and solvent.[5] Butylene Glycol has both indirect food additive (IFA) and direct food additive (DFA) status with the Food and Drug Administration when used as a solvent for flavors,[15] as an antioxidant and stabilizer, and as a component of packaging (21 Code of Federal Regulations [CFR] 173.220; 177.1200; 175.105; 177.1680; 177.1210; 178.2010).[16]

Hexylene Glycol has IFA status as a defoaming agent (21 CFR 176.210).[16] It is also used in hydraulic brake fluids, printing inks, and textile dye vehicles. Hexylene Glycol serves as a coupling agent, as a fuel and lubricant additive and as an emulsifying agent.[5,11]

Exthoxydiglycol has IFA status for use as a component of paperboard and adhesives (21 CFR 175.105; 176.180).[16]

Dipropylene Glycol is an IFA ingredient for use in adhesives, lubricants, and as a defoaming agent (21 CFR 175.105; 178.3910; 176.200).[16] It is also used as a solvent for nitrocellulose and shellac and as a partial solvent for cellulose acetate. Other applications include solvent mixtures, lacquers, coatings, and printing inks.[5]

Cosmetic Use

The glycols generally are used as cosmetic emulsifiers, solidifiers, plasticizers, cosolvents, and film producers.[17,18] Butylene Glycol is used as a humectant, especially in hair sprays and setting lotions.[18–20] It helps retard the loss of aromas from essential oils, preserves against spoilage by microorganisms, and is used as a solvent for benzoates. Special grades of Dipropylene Glycol (based on odor quality) are used as carriers for perfume oils.[2]

Cosmetic product formulation data on the use and occurrence of the glycols in finished products are made available by the Food and Drug Administration (FDA) and compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations. Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the value reported by the cosmetic formulator may not necessarily reflect the true concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Since data are only submitted within the framework of preset concentration ranges, the opportunity exists for a 2- to 10-fold overestimation of the actual concentration of an ingredient in a particular product (Table 2).[21]

Butylene Glycol is used in 165 products at concentrations from less than 0.1 percent to greater than 50 percent. It is used in hair and bath products, eye and facial makeup, fragrances, personal cleanliness products, and shaving and skin care preparations.[21]

Hexylene Glycol is used in 85 cosmetic formulations at concentrations of use ranging from less than 0.1 percent to 25 percent. The types of products in which Hexylene Glycol is used include bath and hair preparations, eye makeup, soaps, and skin care preparations.[21]

Ethoxydiglycol has been reported as an ingredient in 80 product formulations at concentrations from less than 0.1 percent to 50 percent. The types of products include eye makeup, fragrances, hair and nail preparations, and shaving and skin care preparations.[21]

Dipropylene Glycol is reported as an ingredient in 50 cosmetic formulations in concentrations ranging from less than 0.1 percent to 50 percent. It is used in hair care and bath products, perfumes, facial makeup, doedorants, and shaving and skin care preparations.[21]

The Glycols may contact all parts of the integument to which the products are applied and may remain in contact for several hours daily.[21]

TABLE 2. Product Formulation Data[21]

Product Category*	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)					
		>50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Butylene Glycol							
Bath oils, tablets, and salts	1	–	–	1	–	–	–
Other bath preparations	4	1	–	3	–	–	–
Eyeliner	3	–	–	–	3	–	–
Eye shadow	13	–	12	1	–	–	–
Eye makeup remover	4	–	–	–	4	–	–
Mascara	34	–	–	5	29	–	–
Other eye makeup preparations	1	–	–	–	1	–	–
Colognes and toilet waters	3	–	1	–	–	2	–
Perfumes	2	–	–	–	2	–	–
Other fragrance preparations	1	–	–	1	–	–	–
Hair conditioners	5	–	–	2	1	1	1
Hair shampoos (noncoloring)	1	–	–	–	–	–	1
Tonics, dressings, and other hair grooming aids	1	–	–	–	1	–	–
Blushers (all types)	7	–	1	3	3	–	–
Face powders	1	–	–	–	1	–	–
Makeup foundations	19	–	3	16	–	–	–
Makeup bases	1	–	–	1	–	–	–
Rouges	2	1	–	1	–	–	–
Other makeup preparations (not eye)	2	–	1	1	–	–	–
Cuticle softeners	1	–	–	1	–	–	–
Bath soaps and detergents	1	–	–	1	–	–	–
Deodorants (underarm)	1	–	1	–	–	–	–
Other personal cleanliness products	1	–	–	–	1	–	–
Aftershave lotions	4	–	–	–	2	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	13	–	–	2	10	–	1
Face, body, and hand skin care preparations (excluding shaving preparations)	8	–	1	2	2	1	2
Moisturizing skin care preparations	11	–	3	2	6	–	–
Night skin care preparations	1	–	–	–	–	–	1
Paste masks (mudpacks)	3	–	–	1	1	1	–
Skin fresheners	6	–	–	–	4	1	1
Wrinkle smoothers (removers)	2	–	–	–	1	–	1
Other skin care preparations	7	–	–	2	3	1	1
Suntan gels, creams, and liquids	1	–	–	–	1	–	–
1981 TOTALS	165	2	23	46	76	9	9

TABLE 2. (Continued)

Product Category*	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)				
		>10–25	>5–10	>1–5	>0.1–1	≤0.1
Hexylene Glycol						
Bath oils, tablets, and salts	4	1	3	–	–	–
Bubble baths	3	–	–	2	1	–
Eye makeup remover	1	–	–	–	1	–
Hair conditioners	7	–	1	2	4	–
Permanent waves	1	1	–	–	–	–
Hair rinses (noncoloring)	1	1	–	–	–	–
Hair shampoos (noncoloring)	29	–	10	13	5	1
Hair dyes and colors (all types requiring caution statement and patch test)	20	17	–	3	–	–
Hair bleaches	1	–	–	1	–	–
Bath soaps and detergents	3	–	–	3	–	–
Deodorants (underarm)	2	–	–	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	4	–	–	3	1	–
Face, body, and hand skin care preparations (excluding shaving preparations)	1	–	–	1	–	–
Moisturizing skin care preparations	3	–	–	2	1	–
Paste masks (mudpacks)	1	–	1	–	–	–
Skin fresheners	3	–	–	1	2	–
Other skin care preparations	1	–	–	1	–	–
1981 TOTALS	85	20	15	32	17	1

Product Category*	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)					
		>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Ethoxydiglycol							
Mascara	1	–	–	–	–	1	–
Colognes and toilet waters	3	–	–	2	–	1	–
Hair conditioners	4	–	–	–	2	2	–
Hair shampoos (noncoloring)	1	–	–	–	–	1	–
Wave sets	1	–	–	–	1	–	–
Hair dyes and colors (all types requiring caution statement and patch test)	14	–	–	4	10	–	–
Hair tints	13	–	–	–	13	–	–
Hair bleaches	5	–	–	–	5	–	–
Other hair coloring preparations	1	–	–	–	1	–	–
Nail polish and enamel remover	1	–	–	1	–	–	–
Aftershave lotions	2	–	–	–	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	14	1	–	1	8	3	1

TABLE 2. (Continued)

Product Category*	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)					
		>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Face, body, and hand skin care preparations (excluding shaving preparations)	3	–	–	–	1	1	1
Moisturizing skin care preparations	3	–	–	2	1	–	–
Night skin care preparations	2	–	–	–	1	–	1
Paste masks (mudpacks)	3	–	1	–	1	1	–
Skin lighteners	1	–	–	–	1	–	–
Skin fresheners	3	–	–	–	2	–	1
Other skin care preparations	5	–	–	1	3	1	–
1981 TOTALS	80	1	1	11	50	13	4

Product Category*	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)					
		>50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Dipropylene Glycol							
Bath oils, tablets, and salts	1	1	–	–	–	–	–
Colognes and toilet waters	2	–	–	2	–	–	–
Perfumes	12	6	4	–	1	1	–
Sachets	1	1	–	–	–	–	–
Other fragrance preparations	1	1	–	–	–	–	–
Hair sprays (aerosol fixatives)	1	–	–	–	–	–	1
Hair shampoos (noncoloring)	1	–	–	1	–	–	–
Tonics, dressings, and other hair grooming aids	1	–	1	–	–	–	–
Wave sets	4	–	–	4	–	–	–
Lipstick	4	–	–	1	1	–	2
Makeup bases	1	–	–	–	1	–	–
Deodorants (underarm)	4	–	–	–	4	–	–
Aftershave lotions	2	–	–	–	1	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	4	–	–	–	–	–	4
Face, body, and hand skin care preparations (excluding shaving preparations)	3	–	–	–	3	–	–
Foot powders and sprays	1	–	–	–	–	1	–
Moisturizing skin care preparations	3	–	–	1	2	–	–
Skin fresheners	2	–	1	–	–	1	–
Wrinkle smoothers (removers)	1	–	–	–	1	–	–
Other skin care preparations	1	–	–	1	–	–	–
1981 TOTALS	50	9	6	10	14	4	7

*Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Excretion

Romsos and associates[22] investigated the effects of Butylene Glycol on lipid metabolism in rats, pigs, and chicks. The animals were fed a basal high carbohydrate diet that contained approximately 20 percent protein and 5 percent fat. In the test diets, Butylene Glycol was substituted isocalorically for the carbohydrate. The diets were offered ad lib except for 1 experiment in which pigs were fed to satiety twice daily. Controls received the basal diet. Addition of up to 20 percent Butylene Glycol to the diet did not affect body weight gain of the 3 species. Blood β-hydroxybutyrate content increased in all 3 species. Plasma triglyceride concentrations decreased in the rat, increased in pigs, and remained the same in chicks. Plasma glucose decreased in the rat and remained stable in pigs and chicks. Dietary Butylene Glycol decreased the rate of fatty acid synthesis in the liver of rats, but there was no such effect in pigs or chicks.

Mehlman et al.[23] studied the metabolic fate of Butylene Glycol in the rat. Two groups of 14 rats each were fed for up to 7 weeks either a control diet of 70 percent carbohydrate and 30 percent fat or 45 percent carbohydrate, 30 percent fat, and 25 percent Butylene Glycol. Body weight gain and epididymal fat pad weight decreased in test animals receiving the test diet. Blood acetoacetate and β-hydroxybutyrate concentrations were increased significantly. Blood pyruvate concentration was decreased significantly in animals fed this glycol for 7 weeks. The metabolism of glucose and Butylene Glycol to ketones by hepatic tissue taken from test animals was also studied. The conversion of glucose to lactate and pyruvate was decreased, as was the concentration of ketones. In liver slices, Butylene Glycol was metabolized to acetoacetate and β-hydroxybutyrate. Butylene Glycol, therefore, is metabolized in the cytosol and converted by the liver to ketones; it is then oxidized in the tricarboxylic acid cycle.

Tate et al.[24] also studied the metabolic fate of Butylene Glycol in rats. They found that the conversion of the glycol to β-hydroxybutyrate in the liver was dependent on NAD^+ and inhibited by pyrazole. They found that hepatic alcohol dehydrogenase was the catalyst in the catabolism of the glycol to an intermediate aldol and then to β-hydroxybutyrate.

Mehlman et al.[25] also reported that hepatic alcohol dehydrogenase was the enzyme responsible for the initial oxidation of Butylene Glycol.

The metabolites of Butylene Glycol in the brain of rats were determined by Morris et al.[26] The animals were fed diets containing 1 of the following: 47 percent dietary calories as glucose, 47 percent calories as Butylene Glycol, or 47 percent calories as ethanol for 62 days. The animals were killed and metabolites in the brain were determined. Butylene Glycol significantly decreased glutamate, lactate, and pyruvate concentrations. Glucose concentrations and the NADP/$NADPH_{IDH}$ ratios were also decreased.

Rats and mice excreted up to 40 percent of a 200 mg daily oral dose of Hexylene Glycol in the urine.[27] An oral 1 mmol/kg dose of Hexylene Glycol administered to rabbits was excreted as glucuronate (67 percent of original dose).[28]

When administered orally or by subcutaneous injection to rabbits, Ethoxydiglycol was oxidized in the body or excreted as glucuronate. Such administration was followed by a marked increase in the urinary content of glucuronic acid.[29]

Reproductive Physiology

The effect of the ingestion of Butylene Glycol on pregnant rats and on the metabolism of their offspring was studied.[30] Groups of pregnant rats were given water (control) or Butylene Glycol (9 percent w/v) in drinking water. Treatment was continued throughout the period of gestation and lactation. The length of gestation was not affected by the glycol. The investigators found that rats that ingested Butylene Glycol through gestation bore offspring with a slight increase in RNA content in neurones taken from the cerebral cortex at 18 days. In 8- and 18-day-old pups, protein synthesis in the liver was significantly reduced. In amino acid incorporation studies, neuronal perikarya from 8-day-old pups incorporated 45 percent more amino acids into acid-insoluble polypeptides than did controls. However, protein synthesis in neurons from 18-day-old pups was severely inhibited by maternal ingestion of the glycol. Therefore, maternal treatment with the glycol exerted opposite effects on neuronal protein synthesis at different stages of postnatal development of progeny. Amino acid incorporation by free and membrane-bound ribosomes from liver of 8- and 18-day-old pups was increased by Butylene Glycol.

Neuropharmacology and Behavior

Ayers and Isgrig[31] studied the effect of Butylene Glycol on the behavior of rats in several experiments. To study its effect on voluntary activity (running), the compound was administered intragastrically in a 3.5 g/kg dose, once a week for 3 weeks. Glycerol, water, sucrose, or a sham was administered on 4 other days in the week. Butylene Glycol depressed voluntary running activity; this finding might be due to the glycol's interference with hunger motivation, since intubation of the compound depressed food and water intake. These investigators also studied the dose-effect of Butylene Glycol on food and water intake and urine output in several different experiments. In one study, groups of 8 male Charles River Sprague-Dawley rats were fed Butylene Glycol in doses of 0, 1.75, 3.5, 5.25, or 7.0 g/kg. Corn oil was added to the last 4 dosages to produce a constant caloric value. Distilled water and lecithin (emulsifier) were also added to produce a constant dose volume of 11.4 ml/kg. Each dose was administered to each animal daily over a 5-day period. Ingestion of the glycol produced a dose-related depression of activity and food and water intake. In another experiment, 10 male Charles River Sprague-Dawley rats were trained to balance on a rotating dowel. Butylene Glycol (7.0 g/kg) was administered once a week for 3 weeks. Other animals received glycerol, sucrose, or ethanol. The glycol produced more falls than any of the other test compounds. The glycol-treated rats were barely able to stand, and Butylene Glycol apparently acted as a CNS depressant or a muscle relaxant.

The effects of Butylene Glycol on neuropharmacology, behavior, and CNS function were studied in male and female Sprague-Dawley rats, which were given IP doses of 0.2 g/ml of Butylene Glycol in sterile 0.15 M saline.[32] Control animals were given equal volumes of saline. Another group of rats was fed a liquid diet containing Butylene Glycol in increasing concentrations (0.07 g/ml for 2 days; 0.08 g/ml for 2 days; 0.09 g/ml for 3 days; then 0.1 g/ml for 5 days). The IP administration of the glycol caused a dose-related impairment of motor coordina-

tion 1 hour after treatment as measured by aerial righting reflex. Administration of the compound depressed cGMP content in the cerebellum but did not alter plasma-leuteinizing hormone. "Conflict behavior," as measured by the number of electrical shocks accepted by rats, was attenuated after treatment with glycol, i.e., more shocks were accepted by treated rats than by control rats. Compound treatment also caused a decrease in blood pH and blood pressure. When ethanol-withdrawn rats were acutely treated with Butylene Glycol, a dose-related decrease in tremors was observed. Feeding of rats caused no significant motor coordination impairment, and all rats gained weight. After 12 days, the glycol was removed from the diet. No tremors developed after 1 hour, but 1 of 9 rats developed seizures. After 7.5 hours, tremors increased, and 33 percent of the rats developed seizures; 1 died.

Microbiological Effects

Butylene Glycol can be used as the sole carbon source by some strains of mycobacteria.[33] However, other investigators found it to be toxic to some microorganisms and useful as a cosmetic preservative.[19] Harb and Toama[34] reported that Butylene Glycol is the most efficient polyol as an antimicrobial agent. It inhibits both gram-positive and gram-negative microorganisms, as well as molds and yeast. However, it is not sporicidal. Those microbes against which Butylene Glycol is effective include *Escherichia coli, Pseudomonas aeroginosa, Staphylococcus aureus, Corynebacterium hofmanii, Aspergillus niger, Aspergillus fumigatus, Pityrosporum oxalicum, Fusarium sp.,* and *Candida albicans.*

Animal Toxicology

Oral Toxicity

Acute Studies

The acute oral LD_{50} of Butylene Glycol was 23 g/kg in rats[6,35] and 11 g/kg in guinea pigs.[35] A nail lotion containing 5.0 percent Butylene Glycol had an LD_{50} of >5 g/kg in rats,[36] and a product containing 21.35 percent Butylene Glycol produced no deaths when fed to rats at 15 g/kg.[37]

Windholz[6] reported the acute oral LD_{50} of Hexylene Glycol in rats was 4.70 g/kg. Other sources reported an oral LD_{50} of 4000 mg/kg for rats,[35] 3200 mg/kg for rabbits,[38] 2800 mg/kg for guinea pigs,[38] and 3900 mg/kg for mice.[35] A skin care product formulation containing 1.6 percent Hexylene Glycol was found to be "slightly toxic" or "practically nontoxic" when administered orally to groups of 10 rats in 4 separate assays.[39] An eye makeup remover containing 1.0 percent Hexylene Glycol caused no deaths when administered orally to 10 mice at 15 ml/kg.[40]

The acute oral LD_{50} values for Ethoxydiglycol are: in rats, 5.54 g/kg; in mice, 6.58 g/kg; and in guinea pigs, 3.87 g/kg.[41] A paste mask product formulation containing 2 percent Ethoxydiglycol caused no signs of toxicity when administered orally to 10 rats at 13 ml/kg.[42] A body lotion containing 1.0 percent Ethoxydiglycol caused no deaths when 15 ml/kg oral doses were administered to 10 mice.[43]

The acute oral LD_{50} of Dipropylene Glycol in rats was 15 g/kg.[35] A shaving preparation containing 7.2 percent Dipropylene Glycol had an oral LD_{50} of >5 g/kg.[44]

Subchronic Studies

For subchronic effects of Butylene Glycol, see also the Metabolism section of this report.

Larsen[27] reported that Hexylene Glycol fed to mice daily at 5, 10, or 20 mg Hexylene Glycol for 57 to 81 days produced no effect on growth curves. Also, rats receiving up to 150 mg of this glycol in the diet daily for 4 months had no abnormality in growth, behavior, or fertility; some changes were present in renal tissue of rats of the 200 mg/day group.[27]

No effect was caused by the daily consumption of 0.49 g/kg Ethoxydiglycol by each of 5 rats for 30 days. However, 0.87 g/kg caused reduced feed consumption.[45]

Four groups of Charles River Wistar rats, each consisting of 12 males and 12 females, were fed diets containing 0 (control), 0.25, 1.0, or 5.0 percent Ethoxydiglycol for periods up to 90 days. Observations were made of body weight, food intake, hematological parameters at 6 and 12 weeks, kidney function, blood urea concentration, and urine composition. Organs examined were the liver, kidneys, brain, spleen, heart, adrenals, and gonads. The investigators found that throughout the 90 days, the general conditions remained good. One male rat in the 5 percent group died on Day 23; there was weight loss and degeneration of renal tubules and liver. Growth rates of male and female rats were reduced when fed the 5 percent diet, and this was associated with a decrease in food consumption. No hematological changes were produced by any diet. However, activity of urinary glutamic-oxaloacetic transaminase was increased in both sexes fed the 5 percent diet, which was indicative of impaired renal function. An increase in weight of the kidneys occurred in both sexes fed the 5 percent diet. No other important changes were found.[46]

The effect of subchronic ingestion of Ethoxydiglycol was studied in rats, mice, and pigs. The glycol was fed for 90 days to groups of 15 male and 15 female rats at dietary concentrations of 0 (control), 0.5, or 5 percent and to groups of 20 male and 20 female mice at dietary concentrations of 0 (control), 0.2, 0.6, 1.8, or 5.4 percent. Three groups of 4 male and 4 female pigs were fed daily oral doses of 0 (control), 167, 500, or 1500 mg/kg. There was a reduction of growth in rats and mice at the highest concentrations. All 3 species had reduced hemoglobin concentration at the highest doses administered. Oxaluria occurred in rats and mice at highest concentrations. Three pigs given 1500 mg/kg per day for up to 21 days died with signs of uremia. For the surviving pigs, the dose was then reduced to 1000 mg/kg per day. Six of the 20 male mice fed the 5.4 percent diet died of renal damage. The relative weights of the kidneys was increased in all 3 species fed the highest concentration of glycol and in mice fed the 1.8 percent diet. Microscopic changes were hydropic degeneration of the proximal renal tubules in all 3 species fed the highest dosage and in pigs receiving 500 mg/kg per day. Hydropic degeneration of the hepatocytes was observed in those pigs above a dose of 500 mg/kg. Hepatic cell enlargement was found in those mice fed the 1.8 and 5.4 percent diets. The "no effect" level for Ethoxydiglycol in rats was 0.5 percent of the

diet. In mice it was 0.6 percent of the diet, and in pigs it was 167 mg/kg per day.[47]

Chronic Studies

Butylene Glycol was fed to Sprague-Dawley weanling rats and beagle dogs for 2 years. In the rat study, 60 male and 60 female control rats were fed a basal diet and water ad lib. Three test groups of 30 male and 30 female rats each were fed diets containing 1.0, 3.0, or 10.0 percent Butylene Glycol for 2 years. Observations were made on body weight, food consumption, compound consumption, pharmacological effects, urinalysis, and gross appearance. Erythrocyte and leukocyte counts, packed cell volume, and hemoglobin values were determined. At 1 year, 10 animals from each group were killed, and all survivors were killed at the end of 2 years. Representative organs were weighed and examined microscopically. These tests were negative for deleterious or toxic effects due to the ingestion of Butylene Glycol at any dietary concentration.[48]

In the study using beagle dogs, a control group of 4 males and 4 females were fed a basal diet, and 3 similar groups received diets containing 0.5, 1.0, or 3.0 percent Butylene Glycol. Daily or weekly observations were made of feed intake, elimination, clinical appearance, pharmacological effects, and feed and compound consumption. The blood, urine, and representative organs were examined as with the rat portion of the study described above. Two animals from each group were killed after 1 year and the remainder after 2 years. As with the rats, no toxic effects were produced by the ingestion of Butylene Glycol at any dietary concentration.[48]

Ethoxydiglycol was fed to rats at 1.0 g/kg per day for 2 years. The rats had slight hepatic damage, some interstitial edema in the testes, and in 1 animal, oxalate crystals in the kidney.[26]

Parenteral Toxicity

The subcutaneous LD_{50} of Butylene Glycol in mice and rats was 16.5 ml/kg and 20.1 ml/kg, respectively.[11] No deaths were caused by intraperitoneal injection of 1.0 g/kg Butylene Glycol into 5 mice.[49] Butylene Glycol was evaluated for tissue irritation using chicken pectoral muscle. Injections of 0.5 ml of the glycol, 1.3 cm deep into the right and left pectoral muscle of each of 6 chickens, caused only minimal tissue irritation.[50]

Hexylene Glycol had a subcutaneous LD_{50} of 13 g/kg in rabbits and rodents.[38] The intraperitoneal LD_{50} of Hexylene Glycol in the mouse was 4.5 ml/kg.[51] NIOSH[35] lists the intraperitoneal LD_{50} in mice as 1299 mg/kg.

The subcutaneous LD_{50} of Ethoxydiglycol in mice was 5500 mg/kg.[38] In rats and rabbits, it was 3.4 ml/kg and 2.0 ml/kg, respectively.[52] The intraperitoneal LD_{50} of Ethoxydiglycol in rats was 6310 mg/kg.[38] The intravenous LD_{50} in dogs was 3000 mg/kg and in cats, 5000 mg/kg.[38] Other investigators report intravenous LD_{50}s in mice, rats, and rabbits as 3.9, 2.9, and 0.9 ml/kg, respectively.[52]

The intraperitoneal LD_{50} of Dipropylene Glycol in rats and mice was 10 g/kg and 4600 mg/kg, respectively.[35] The intravenous LD_{50} in rats and dogs was 5800 mg/kg and 11,500 mg/kg, respectively.[35]

Inhalation Toxicity

Rats survived an 8-hour exposure to the saturated, room temperature vapors of Hexylene Glycol.[45]

Cutaneous Toxicity

Acute Studies

The cutaneous LD_{50} of Hexylene Glycol in rabbits and rodents was 13.2 g/kg.[38] A product formulation containing 5.0 percent Butylene Glycol had a cutaneous LD_{50} of >2 g/kg when tested in rabbits.[36]

The cutaneous LD_{50} of Ethoxydiglycol was 6 g/kg in rats[38] and 10.3 g/kg in rabbits.[53]

A product formulation containing 7.2 percent Dipropylene Glycol produced a cutaneous LD_{50} of >2 g/kg when tested in rabbits.[44]

Subchronic Studies

A product formulation containing 3 percent Butylene Glycol was applied daily at 500 mg/kg to the clipped intact and abraded skin of each of 8 albino rabbits for 4 weeks. A control group of 8 rabbits remained untreated. All of the animals survived the duration of the study. Clinical observations of compound-related importance were confined to the skin, which had slight erythema with drying and flaking. No systemic effects as evidenced by microscopic tissue examination were attributable to the test material.[54]

Skin Irritation

Primary Irritation

Undiluted Butylene Glycol produced no more than minimal skin irritation when tested under occlusion on the skin of rabbits for 24 hours[55] or daily for 4 consecutive days.[56]

Undiluted Hexylene Glycol produced moderate irritation when 465 or 500 mg was applied to the skin of rabbits for 24 hours.[38] A 24-hour application of 1.84 g/kg undiluted Hexylene Glycol to the skin of rabbits caused mild edema and erythema.[57]

Undiluted Ethoxydiglycol was a mild irritant when applied to rabbit skin (500 mg for 24 hours).[38] According to Rowe,[57] it is a nonirritant to rabbits.

Undiluted Dipropylene Glycol caused mild irritation when 500 mg was applied to rabbit skin for 24 hours.[38]

Several product formulations containing 5.0 to 21.4 percent Butylene Glycol, 1.0 to 1.6 percent Hexylene Glycol, 1.0 percent Ethoxydiglycol, or 7.2 percent Dipropylene Glycol were tested for 24 hours under occlusion on rabbit skin (Leberco Labs).[36,44,58-64] The products produced no irritation to moderate irritation, depending upon the particular formulation tested. The degree of irritation did not correlate with the concentration of glycol.

Cumulative Irritation

A daily dose of 0.5 ml of a paste mask product formulation containing 2 percent Ethoxydiglycol was applied to the backs of 3 albino rabbits for 14 consecu-

tive days. Each treatment site was rinsed with warm tap water 30 minutes after treatment. There was slight erythema 24 hours after the initial application that had disappeared by 48 hours. There were no other signs of irritation.[42]

Ocular irritation

According to NIOSH,[35] 505 mg of undiluted Butylene Glycol applied to the rabbit eye was an irritant. No irritation was observed when 0.1 ml of undiluted Butylene Glycol[65] or a 40 percent aqueous solution of Butylene Glycol[66] was instilled into 1 eye of each of 6 rabbits.

Irritation was severe when 93 mg undiluted Hexylene Glycol was instilled into the eyes of rabbits,[38] and Rowe[57] reported that this glycol caused corneal damage in a rabbit. A 25 percent aqueous solution of Hexylene Glycol caused no ocular irritation when tested in the rabbit.[67]

Moderate toxic effects were found in the eyes of rabbits instilled with 500 mg undiluted Ethoxydiglycol. Mild effects were caused by 125 mg.[38]

Laillier et al.[68] studied the ocular effects of Ethoxydiglycol and other chemicals using the rabbit. The chemicals were applied to a series of 4 animals at application frequencies of 1, 3, 6, 7, and 13 times over periods of 2, 4, 7, 26, and 58 hours. The chemicals were used either pure or as a 25 percent dilution in distilled water in 0.1 ml volumes. Ocular edema was measured by the following formula:

$$\frac{\text{mg dry tissue weight}}{\text{mg wet tissue weight}} \times 100$$

In addition, aqueous humor and conjunctival content were assayed for effects 1 hour after Evans blue solution was injected into the rabbit's marginal ear vein. Ethoxydiglycol was very irritating to the rabbit's eye in this assay system (Table 3).

Undiluted Dipropylene Glycol is an irritant in the rabbit eye in an amount of 510 mg.[35]

Several product formulations containing 5.0 to 21.35 percent Butylene Glycol, 1.0 percent Hexylene Glycol, 1.0 to 2.0 percent Ethoxydiglycol, or 7.2 percent Dipropylene Glycol produced no more than minimal, transient irritation when instilled into the eyes of rabbits.[36,42,44,69-72] Another product formulation containing 1.6 percent Hexylene Glycol produced mild to moderate irritation in the eyes of rabbits.[73] This formulation had also produced mild to moderate irritation when applied to the skin of rabbits.

Clinical Assessment of Safety

Nutritional and Metabolic Studies

Tobin and associates[74] investigated the nutritional and human metabolic effect of Butylene Glycol. Three studies were conducted.

In the first experiment, the effect of Butylene Glycol and urea in the nutrition of 12 men and women was studied. The volunteers went through a 2-day depletion period in which nitrogen intake was 1.23 g/day. Caloric intake was evaluated and adjusted so that during the 4- to 7-day test periods subjects consumed diets with constant caloric content. Dietary variation was randomly distributed during

TABLE 3. Ocular Irritation in Rabbits by Measuring Tissue Edema: Ethoxydiglycol[68]

	No. of Instillations (4 Rabbits Each)	Time* (hours)	Conjunctivae (% Dry Weight)	Conjunctivae (μg Evans Blue/g Dry Weight)	Corneas (% Dry Weight)	Aqueous Humors (μg Evans Blue/ml)
Ethoxydiglycol (undiluted)	1	2	13.9 ± 0.8†	439 ± 88†	24.1 ± 1.2†	135.1 ± 69.1†
	3	4	12.7 ± 1.3†	439 ± 92†	21.2 ± 2.0†	21.7 ± 16.0†
	6	7	13.1 ± 0.6†	497 ± 168†	18.6 ± 1.9†	9.0 ± 4.9†
	7	26	16.4 ± 1.9†	906 ± 171†	17.1 ± 1.5†	10.9 ± 8.0†
	13	58	15.9 ± 1.0†	988 ± 283†	15.8 ± 1.4†	29.5 ± 22.9†
25% Ethoxydiglycol in distilled water	1	2	17.7 ± 1.1†	189 ± 28†	24.8 ± 1.3	3.3 ± 2.6†
	3	4	20.7 ± 0.8	91 ± 23	25.9 ± 1.5	0.8 ± 0.25
	6	7	18.6 ± 1.4	178 ± 34†	25.3 ± 1.2	11.6 ± 8.6†
	7	26	20.8 ± 0.4	177 ± 32†	25.5 ± 1.5	12.8 ± 11.9†
	13	58	19.4 ± 1.4	139 ± 27	27.1 ± 1.0	5.6 ± 3.0†

*Time in hours over which instillations made.
†Significantly different from controls (Student's *t*-test).
Mean ± 95% confidence limits.

the 4 experimental periods: 1 in which the glycol (15 g) was substituted isocalorically for starch in the diet, 1 in which starch without the glycol was ingested, 1 in which urea (4 g of nitrogen/day) was added to the diet, and the fourth and final period in which the glycol and urea were added to the diet. Butylene Glycol, as compared to starch, caused a significant decrease of urinary nitrogen excretion. Subjects fed urea or glycol plus urea had a significant increase in urinary excretion of nitrogen. The glycol did not increase fecal nitrogen excretion, but urea feeding did. Feeding the glycol or urea or the combination caused a less negative nitrogen balance than did the starch feeding. The glycol caused a lowering of blood glucose and no increase in blood ketones. The investigators concluded that Butylene Glycol can be used as a caloric source by human beings.

The second study investigated the effect of Butylene Glycol on endocrine function and its influence on glucose homeostasis. Twenty-seven women volunteered for a 15-day experiment in which one half were fed 40 g of Butylene Glycol per day for 5 days or a calorically equivalent quantity of sucrose for 5 days. At the end of 5 days, the diets were switched. Mean blood glucose concentrations and serum insulin concentrations were lower in the second and third weeks of ingestion. The glycol had no effect on triglyceride or cholesterol concentrations. Fasting insulin and growth hormone concentrations were somewhat increased by the glycol.

In the third study, 10 adult male and female volunteers were fed for 12 days 6 g of nitrogen per day, starch, and vitamin and mineral supplements. The Butylene Glycol was substituted isocalorically for sucrose to provide 10 percent of the total caloric intake. Glucose tolerance tests were performed on the sixth and twelfth days of the test. Glucose concentrations were normal, as were free fatty acid and growth hormone values. Serum insulin values and blood pyruvate and lactate values were normal, and β-hydroxybutyrate, acetoacetate and triglyceride values were likewise normal. Butylene Glycol was nontoxic in these tests.[74]

Skin Irritation/Sensitization

A Shelanski and Shelanski repeated insult patch test was conducted on 200 volunteers (80 male, 120 female) to assess the irritation and sensitization potentials of Butylene Glycol. The compound was diluted to 50 percent in water, and 0.9 ml of the mixture was applied under occlusion to sites on the upper arm. After 24 hours of contact, the patches were removed and the sites were graded on a scale of 0 (no reactions) to 4+ (erythema, edema, vesicles, and extensions beyond the site of contact). After 24 hours, the sites were reexamined. If no changes occurred, a second patch was reapplied to the same site. This cycle was repeated each Monday, Wednesday, and Friday. After the fifteenth application, sites were not treated for a 2-week period, and then 24-hour occlusive patches were applied to the same sites. Test areas were graded immediately and then at 24 and 48 hours after patch removal. The investigator reported visible skin change in one subject after applications 4–6 and in another after applications 13–15. No reactions were caused by the challenge patch. Butylene Glycol was a mild fatiguing agent in 2 of 200 test subjects. With statistical extrapolation, greater than 98 percent of the general population would not be sensitized to Butylene Glycol[19] (Table 4).

Undiluted Butylene Glycol was applied to the volar skin of the forearms or

TABLE 4. Clinical Skin Patch Tests with Butylene Glycol and Hexylene Glycol

Test Method	*Material Tested*	*Concentration (%)*	*No. of Subjects*	*Results*	*Reference*
24-hour single insult occlusive or semiocclusive patch	Butylene Glycol	100	37	Occlusive patch; no reactions	75
			39	Semiocclusive patch; 1 subject with mild irritation	
	Hexylene Glycol	100	37	Occlusive patch; minimal irritation (primary irritation index 0.11; max, 4.0)	76
			39	Semiocclusive patch; minimal irritation (primary irritation index 0.02; max, 4.0)	
Shelanski and Shelanski repeated insult patch test (24-hour occlusive patches 3 days/week for 15 induction patches; challenge patch after 2-week rest)	Butylene Glycol	50 (in water)	200	Mild skin irritation in 2 subjects; no sensitization	19

medial arms of 37 human subjects under occlusion and 39 subjects under semioccluded conditions for 24 hours. One subject in the semioccluded panel had evidence of mild irritation; no other reactions were observed in either panel[75] (Table 4). Hexylene Glycol was tested in an identical fashion, producing primary irritation indices of 0.11 (scale 0 to 4) for the occluded patch and 0.02 for the semioccluded patch. These scores are indicative of only minimal irritation[76] (Table 4).

Fisher[18] reported that cross-reactivity (sensitivity) may occur between Butylene Glycol and propylene glycol.

A number of product formulations containing 1 of the glycols at concentrations of 0.016 to 21.4 percent have also been tested for skin irritation and sensitization in humans (Table 5). In single insult occlusive patch tests, products containing 3.0 to 21.4 percent Butylene Glycol produced no more than minimal irritation.[77-80] Several multiple insult tests were conducted on products containing a glycol in which no irritation to moderate irritation was found depending upon the particular product tested. There was no correlation between the degree of irritation and the concentration of glycol (Table 5). Results indicative of irritation cannot be interpreted without knowledge of the other ingredients in a formulation. Of the 1087 subjects tested in skin sensitization assays (Schwartz-Peck and Draize-Shelanski tests), there were no reactions indicative of sensitization to any of the glycols (Table 5).

Photoreactivity

Four studies included exposure to ultraviolet light as a supplement to the Schwartz-Peck prophetic patch tests and Draize-Shelanski repeated insult patch tests on a nail lotion containing 5.0 percent Butylene Glycol[81] and on a shaving preparation containing 7.2 percent Dipropylene Glycol[82] (Table 5). The ultraviolet light exposure was to a Hanovia Tanette Mark I quartz lamp at a distance of 12 inches for 1 minute. This lamp has a wavelength coverage of 240 to 370 nM, with a peak at 365 nM. None of the subjects in the Schwartz-Peck tests had reactions when a single UV exposure was made after the second insult. The Draize-Shelanski tests included UV exposure after induction patches 1, 4, 7, and 10 and after the challenge patch; there were no reactions (Table 5).

Ocular Irritation

A drop of Butylene Glycol applied to the eyes of humans caused immediate severe stinging similar to that induced by propylene glycol. Irrigation with water brought rapid relief.[83]

When human subjects were exposed for 15 minutes to a vapor concentration of 50 ppm of Hexylene Glycol, ocular irritation occurred.[57]

Inhalation Toxicity

Nasal and respiratory discomfort occurred from a concentration of 100 ppm aerosolized Hexylene Glycol, and at 1000 ppm irritation of the eyes, nose, throat, and respiratory tract were noted.[57]

Industry Complaint Experience

A skin care product containing 1.6 percent Hexylene Glycol had 43 safety-related complaints in 4 years with 243 million units distributed.[97] A shaving preparation containing 7.2 percent Dipropylene Glycol had 7 safety-related complaints in 3 years with 2.3 million units sold; 2 of these were listed as "rash" and 5 as "irritated skin."[98]

SUMMARY

Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are viscous liquids used in the cosmetic industry as humectants, emulsifiers, plasticizers, and solvents. They are added to various types of cosmetic products at concentrations up to 50 percent. The Glycols also have many noncosmetic uses and have been given Direct and/or Indirect Food Additive status by the FDA.

Various animal species and man metabolize Butylene Glycol and use it as a source of calories. The results of acute, subchronic, and chronic oral toxicity studies using a variety of animal species indicate a low order of toxicity for the Glycols. Results of parenteral injection, inhalation, and acute and subchronic cutaneous toxicity studies likewise support a low order of toxicity. Butylene Glycol, Ethoxydiglycol, and Dipropylene Glycol caused minimal to mild irritation of rabbit skin, whereas Hexylene Glycol was moderately irritating. The Glycols produced mild to severe ocular irritation when tested in rabbits, and Hexylene Glycol produced the most severe irritation. Although undiluted Hexylene Glycol

TABLE 5. Clinical Skin Patch Tests with Product Formulations Containing Glycols

Test Method	*Material Tested*	*Concentration (%)*	*No. of Subjects*	*Results*	*Reference*
24-hour single insult occlusive patch	Eye shadow	21.35 Butylene Glycol	20	Minimal irritation	79
	Foundation makeup	16.0 Butylene Glycol	19	Minimal irritation. Also included semiocclusive patch with minimal irritation	78
	Mascara	8.0 Butylene Glycol	20	Minimal irritation	80
	Rouge	3.0 Butylene Glycol	20	No signs of irritation	77
"Soap chamber test:" 1 24-hour followed by 4 daily 6-hour applications in Duhring chambers on volar forearm	Personal cleanliness product	0.13 Hexylene Glycol (8% aqueous dilution of product containing 1.6%)	10	Moderate irritation	84
Cumulative irritancy test (daily 23-hour occlusive patch for 21 days)	Eye shadow	21.35 Butylene Glycol	10	Slight irritation; total composite score was 70/630 max	85
	Paste mask	2.0 Ethoxydiglycol	12	Essentially nonirritating; total composite score was 36/630 max	86
Schwartz-Peck prophetic patch test (open and closed 48-hour patches, repeated after 2 weeks)	Nail lotion	5.0 Butylene Glycol	104	No reactions; supplemental UV exposure at open patch after second insult produced no reactions	81
	Shaving preparation	7.2 Dipropylene Glycol	101	Mild irritation with closed patch in 6 subjects at first exposure and in 8 subjects at second; open patches and supplemental UV exposure after second insult produced no reactions	82
Draize-Shelanski repeated insult patch test (24- or 48-hour patches 3 days/week for 9 or 10 induction patches; challenge patch after 2-week rest)	Foundation makeup	16.0 Butylene Glycol	108	Mild irritation; no sensitization	87

	Nail lotion	5.0 Butylene Glycol	49	No irritation; no sensitization. Supplemental UV exposure after induction patches 1, 4, 7, and 10 and after challenge showed no photosensitization	81
	Rouge	3.0 Butylene Glycol	108	Slight irritation; no sensitization	88
	Eye makeup remover	1.0 Hexylene Glycol	103	Mild irritation; no sensitization	89
	Personal cleanliness product	0.048 Hexylene Glycol (3% aqueous dilution of product containing 1.6%)	52	Mild irritation with fatiguing during induction; 4 reactions on challenge at original site with 2 persisting and 3 reactions on challenge at alternate site with 1 persisting. Reactions at challenge consistent with induction irritation reactions. Test sites exposed to 30 minutes natural sunlight 24 hours after each application	90
	Personal cleanliness product	0.016 Hexylene Glycol (1% aqueous dilution of product containing 1.6%)	52	Mild irritation; no sensitization	90
		0.016 Hexylene Glycol (1% aqueous dilution of product containing 1.6%)	106	No significant irritation; no sensitization	91
	Paste mask	2.0 Ethoxydiglycol	213	Minimal irritation; no sensitization	92
	Body lotion	1.0 Ethoxydiglycol	93	Minimal irritation; no sensitization	93
	Shaving preparation	7.2 Dipropylene Glycol	50	Mild irritation with probable fatiguing; no sensitization. Supplemental UV exposure after induction patches 1, 4, 7, and 10 and after challenge showed no photosensitization	82
Controlled use test: 4 weeks	Mascara	8.0 Butylene Glycol	50	No reactions	94
	Shaving preparation	7.2 Dipropylene Glycol	59	No reactions	95
Controlled use test: 2 weeks	Personal cleanliness product	1.6 Hexylene Glycol	80	Minimal irritation	96

produced severe ocular irritation, a 25 percent aqueous solution produced no signs of irritation.

Feeding studies in man indicated that Butylene Glycol was metabolized and nontoxic. Single insult 24-hour skin patch tests on undiluted Butylene Glycol and undiluted Hexylene Glycol showed a very low order of primary skin irritation potential for these ingredients. In a repeated insult patch test, Butylene Glycol produced mild skin fatigue in 2 of 200 test subjects but no evidence of skin sensitization. A number of product formulations containing the Glycols at concentrations up to 21.4 percent have been tested in various human skin irritation and sensitization assays (Table 5). The degree of irritation produced depended upon the particular formation. There was no correlation between the degree of irritation and the concentration of the Glycol present in the formulation. There were no reactions indicative of skin sensitization to the Glycols in any of the 1087 subjects tested under skin sensitization assays. Supplemental exposure to ultraviolet light in some of the skin sensitization tests on product formulations produced no reactions suggestive of phototoxicity or photosensitization. Butylene Glycol and Hexylene Glycol were irritating to the human eye. And Hexylene Glycol was irritating to the respiratory tract at concentrations significantly higher than those generally found in cosmetic products.

CONCLUSION

Based on the available data, Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are safe as presently used in cosmetics.

ACKNOWLEDGMENT

Jeffrey Moore, MD, Scientific Analyst and writer, prepared the technical analysis used by the Expert Panel in developing this report.

REFERENCES

1. ESTRIN, N.F., CROSLEY, P., and HAYNES, C. (eds.). (1982). *Cosmetic Ingredient Dictionary*, 3rd ed. Washington, DC: Cosmetic, Toiletry and Fragrance Association.
2. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION. (CTFA). (Sept. 21, 1982). Submission of unpublished data. CTFA cosmetic ingredient chemical description: Dipropylene Glycol.* (CTFA Code 2-17-170)
3. FOOD CHEMICALS CODEX. (1981). 3rd ed. Washington, DC: National Academy Press.
4. WEAST, R.C. (ed.). (1979). *CRC Handbook of Chemistry and Physics*, 59th ed. Boca Raton, FL: CRC Press.
5. HAWLEY, G.G. (ed.). (1971). *The Condensed Chemical Dictionary*, 8th ed. New York: Van Nostrand Reinhold.
6. WINDHOLZ, M. (ed.). (1976). *The Merck Index*, 9th ed. Rahway, NJ: Merck and Co.
7. CTFA. (Sept. 21, 1981). Submission of unpublished data. CTFA cosmetic ingredient chemical description. Butylene Glycol.* (CTFA Code 2-17-175)

*Available upon request: Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Avenue, N.W., Washington, DC 20005.

8. CTFA. (Sept. 21, 1982). Submission of unpublished data. CTFA cosmetic ingredient chemical description. Hexylene Glycol.* (CTFA Code 2-17-176)
9. CTFA. (Sept. 21, 1982). Submission of unpublished data. CTFA cosmetic ingredient chemical description. Ethoxydiglycol.* (CTFA Code 2-17-172)
10. WAGNER, F.S. (1966). 1,3-Butylene Glycol. *Kirk-Othmer Encycl. Chem. Technol.*, 2nd ed. **10,** 660–7.
11. GOSSELIN, R.E., HODGE, H.C., SMITH, R.P., and GLEASON, M.N. (1976). *Clinical Toxicology of Commercial Products,* 4th ed. Baltimore, MD: Williams & Wilkins.
12. BUDKE, C.C., and BANERJEE, D.K. (1971). Glycols and polyhydric alcohols. Encycl. Indus. Chem. Anal. **12,** 533–607.
13. HOLMAN, N.W., and MUNDY, R.L. (1976). Analysis of ethylene glycol and glycoaldehyde in mouse plasma. Fed. Proc. **35**(3), 534.
14. CHAMPION, M.H. (1970). Collaborative study on the GLC determination of propylene glycol in cosmetics. J. Assoc. Offic. Anal. Chem. **53,** 82–4.
15. FURIA, T.E. (ed.). (1972). *CRC Handbook of Food Additives,* 2nd ed. Cleveland, OH: The Chemical Rubber Co.
16. CODE OF FEDERAL REGULATIONS (CFR). (1982). 21 CFR 173.220; 177.1200; 175.105; 177.1680; 177.1210; 178.2010; 176.180; 176.210; 178.3910; 176.200.
17. BALSAM, M.S., and SAGARIN, E. (eds.). (1972). *Cosmetics: Science and Technology.* New York: Wiley-Interscience.
18. FISHER, A.A. (1980). Reactions to popular cosmetic humectants. Part III. Glycerin, propylene glycol, and butylene glycol. Cutis **26**(3), 243–4, 269.
19. SHELANSKI, M.V. (Sept. 1974). Evaluation of 1,3-Butylene Glycol as a safe and useful ingredient in cosmetics. Cosmet. Perfum. **89,** 96–8.
20. HARB, N.A. (1974). 1,3-Butylene glycol as a humectant in cosmetic creams. Drug Cosmet. Ind. **115**(6), 48, 50, 58, 60.
21. FOOD AND DRUG ADMINISTRATION (FDA). (1981). Computer printout of cosmetic product formulations.
22. ROMSOS, D.R., BELO, P.S., and LEVEILLE, G.A. (Nov. 1975). Butanediol and lipid metabolism. Fed. Proc. **34**(12), 2186–90.
23. MEHLMAN, M.A., TOBIN, R.B., HAHN, H.K., KLEAGER, L., and TATE, R.L. (1971). Metabolic fate of 1,3-butanediol in the rat. Liver tissue slices metabolism. J. Nutr. **101**(12), 1711–8.
24. TATE, R.L., MEHLMAN, M.A., and TOBIN, R.B. (1971). Metabolic fate of 1,3-butanediol in the rat. Conversion to beta-hydroxybutyrate. J. Nutr. **101**(12), 1719–26.
25. MEHLMAN, M.A., TOBIN, R.B., and MACKERER, C.R. (Nov. 1975). 1,3-Butanediol catabolism in the rat. Fed. Proc. **34**(12), 2182–5.
26. MORRIS, H.J., NELSON, A.A., and CALVERY, H.O. (1942). Observations on the chronic toxicities of glycols. J. Pharmacol. Exp. Ther. **74,** 266.
27. LARSEN, V. (1958). The toxicity of 2-methyl-pentan-2,4-diol (hexyleneglycol) by chronic oral administration to rats and mice. Acta Pharmacol. Toxicol. **14,** 341.
28. GESSNER, P.K., PARKE, D.V., and WILLIAMS, R.T. (1960). Studies in detoxication 80. The metabolism of glycols. Biochem. J. **74**(1).
29. FELLOWS, J.K., LUDUENA, F.P., and HANZLIK, P.J. (1947). Glucuronic acid excretion after diethylene glycol monoethyl ether (carbitol) and some other glycols. J. Pharmacol. Exp. Ther. **89,** 210.
30. KHAWAJA, J.A., WALLGREN, H., USMI, H., and HILSKA, P. (Dec. 1978). Neuronal and liver protein synthesis in the developing offsprings following treatment of pregnant rats with ethanol or 1,3-butanediol. Res. Commun. Chem. Pathol. Pharmacol. **22**(3), 573–80.
31. AYERS, J.J., and ISGRIG, F.A. (1970). Comparisons of 1,3-butanediol and glycerol on several behavioral measures. Psychopharmacologia **16**(4), 290–304.
32. FRYE, G.D., CHAPIN, R.E., VOGEL, R.A., MAILMAN, R.B., and KILTS, C.D. (1981). Effects of acute and chronic 1,3-butanediol treatment on central nervous system function: A comparison with ethanol. J. Pharmacol. Exp. Ther. **216**(2), 306–14.
33. TSUKAMURA, M., and TSUKAMURA, S. (1968). Differentiation of mycobacteria by susceptibility to nitrite and propylene glycol. Am. Rev. Respir. Dis. **98**(3), 505–6.
34. HARB, N.A., and TOAMA, M.A. (May 1976). Inhibitory effect of 1,3-butylene glycol on microorganisms. Drug Cosmet. Ind. **118,** 40–1, 136–7.
35. NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). (1981). *Toxic Substances List.* Washington, DC: US Government Printing Office.
36. CTFA. (1980). Submission of unpublished data. CIR safety data test summary. Animal oral, dermal, and

ocular tests of nail lotion containing Butylene Glycol.* (CTFA Code 2-17-160).
37. CTFA. (April 22, 1978). Submission of unpublished data. CIR safety data test summary. Acute oral toxicity test of product containing Butylene Glycol.* (CTFA Code 2-17-79).
38. NATIONAL LIBRARY OF MEDICINE (NLM). (1982). Computerized data base.
39. CTFA. (1978–1979). Submission of unpublished data. CIR safety data test summary. Acute oral toxicity tests of skin care product containing Hexylene Glycol.* (CTFA Code 2-17-136).
40. LEBERCO LABORATORIES. (May 13, 1980). Submission of unpublished data by CTFA. Acute oral toxicity test of eye makeup remover containing Hexylene Glycol.* (CTFA Code 2-17-31).
41. LANG, E.P., CALVERY, H.O., MORRIS, H.J., and WOODARD, G. (1939). The toxicology of some glycols and derivatives. J. Ind. Hyg. Toxicol. **21,** 173.
42. CTFA. (Nov. 1, 1979). Submission of unpublished data. CIR safety data test summary. Acute oral, dermal, and ocular testing of product containing Ethoxydiglycol.* (CTFA Code 2-17-5).
43. LEBERCO LABORATORIES. (Dec. 16, 1980). Submission of unpublished data by CTFA. Acute oral toxicity test of body lotion containing Ethoxydiglycol.* (CTFA Code 2-17-27).
44. CTFA. (1977). Submission of unpublished data. CIR safety data test summary. Product containing Dipropylene Glycol.* (CTFA Code 2-17-166).
45. SMYTH, H.F., and CARPENTER, C.P. (1948). Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. **30,** 63.
46. HALL, D.E., LEE, F.S., AUSTIN, P., and FAIRWEATHER, F.A. (1966). Short-term feeding with diethylene glycol monoethyl ether in rats. Food Cosmet. Toxicol. **4**(3), 263–8.
47. GAUNT, I.F., COLLEY, J., GRASSO, P., LANSDOWN, A.B.G., and GANGOLLI, S.D. (1968). Short-term toxicity of diethylene glycol monoethyl ether in the rat, mouse, and pig. Food Cosmet. Toxicol. **6**(6), 689–705.
48. SCALA, R.A., and PAYNTER, O.E. (1967). Chronic oral toxicity of 1,3-Butanediol. Toxicol. Appl. Pharmacol. **10,** 160–4.
49. CTFA. (Jan. 6, 1977). Submission of unpublished data. CIR safety data test summary. Acute intraperitoneal toxicity test of Butylene Glycol.* (CTFA Code 2-17-77).
50. HEM, S.L., BRIGHT, D.R., BANKER, G.S., and POGUE, J.P. (1974–1975). Tissue irritation evaluation of potential parenteral vehicles. Drug Dev. Commun. **1**(5), 471–7.
51. WOODARD, G., JOHNSON, V.D., and NELSON, A.A. (1945). Acute toxicity of 2-methyl-2,4-pentanediol. Fed. Proc. Fed. Am. Soc. Exp. Biol. **4,** 142.
52. STENGER, E.G., AEPPLI, LISLOTT, MULLER, D., PEHEIM, E., and THOMANN, P. (1971). Zur Toxikologie des Athyleneglykol-Monoathylathers. Arzneim.-Forsch. **21,** 880.
53. CARPENTER, C.P. (1947). Cellosolve acetate. JAMA **135,** 880.
54. CTFA. (Feb. 12, 1975). Submission of unpublished data. Four-week subacute dermal toxicity study in rabbits.* (CTFA Code 2-17-71).
55. CTFA. (Dec. 6, 1976). Submission of unpublished data. CIR safety data test summary. Primary skin irritation test of Butylene Glycol.* (CTFA Code 2-17-76).
56. CTFA. (March 9, 1979). Submission of unpublished data. CIR safety data test summary. Rabbit skin patch test of Butylene Glycol.* (CTFA Code 2-17-75).
57. ROWE, V.K. (1963). Derivatives of glycols. In: Patty, F.A. (ed.). *Industrial Hygiene and Toxicology,* 2nd ed. New York: Interscience, Vol. 11, p. 1561.
58. CTFA. (Nov. 21, 1975). Submission of unpublished data. CIR safety data test summary. Primary skin irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-87).
59. CTFA. (Jan. 15, 1976). Submission of unpublished data. CIR safety data test summary. Primary skin irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-81).
60. CTFA. (Nov. 17, 1976). Submission of unpublished data. CIR safety data test summary. Primary skin irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-84).
61. CTFA. (Aug. 2, 1977). Submission of unpublished data. CIR safety data test summary. Primary skin irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-86).
62. CTFA. (1978–1979). Submission of unpublished data. CIR safety data test summary. Primary skin irritation tests of skin care product containing Hexylene Glycol.* (CTFA Code 2-17-134).
63. LEBERCO LABORATORIES. (Aug. 15, 1980). Submission of unpublished data by CTFA. Primary skin irritation test of eye makeup remover containing Hexylene Glycol.* (CTFA Code 2-17-29).
64. LEBERCO LABORATORIES. (Dec. 19, 1980). Submission of unpublished data by CTFA. Primary skin irritation test of body lotion containing Ethoxydiglycol.* (CTFA Code 2-17-25).
65. CTFA. (Dec. 6, 1976). Submission of unpublished data. CIR safety data test summary. Eye irritation test of Butylene Glycol.* (CTFA Code 2-17-74).

66. CTFA. (Dec. 29, 1977). Submission of unpublished data. CIR safety data test summary. Eye irritation test of Butylene Glycol.* (CTFA Code 2-17-73).
67. CTFA. (May 1, 1973). Submission of unpublished data. CIR safety data test summary. Eye irritation test of Hexylene Glycol.* (CTFA Code 2-17-94).
68. LAILLIER, J., PLAZONNET, B., DE DOUAREC, J.C., and GONIN, M.J. (1975, 1976). Evaluation of ocular irritation in the rabbit: Development of an objective method of studying eye irritation. Proc. Eur. Soc. Toxicol. **17,** 336–50.
69. CTFA. (Jan. 15, 1972). Submission of unpublished data. CIR safety data test summary. Eye irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-80).
70. CTFA. (Nov. 17, 1976). Submission of unpublished data. CIR safety data test summary. Eye irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-83).
71. LEBERCO LABORATORIES. (May 19, 1980). Submission of unpublished data by CTFA. Rabbit eye irritation test of eye makeup remover containing Hexylene Glycol.* (CTFA Code 2-17-30).
72. LEBERCO LABORATORIES. (Dec. 23, 1980). Submission of unpublished data by CTFA. Rabbit eye irritation test of body lotion containing Ethoxydiglycol.* (CTFA Code 2-17-26).
73. CTFA. (1978–1979). Submission of unpublished data. CIR safety data test summary. Rabbit eye irritation tests of skin care product containing Hexylene Glycol.* (CTFA Code 2-17-135).
74. TOBIN, R.B., MEHLMAN, M.A., KIES, C., FOX, H.M., and SOELDNER, J.S. (Nov. 1975). Nutritional and metabolic studies in humans with 1,3-butanediol. Fed. Proc. **34**(12), 2171–6.
75. CTFA. (Aug. 16, 1973). Submission of unpublished data. CIR safety data test summary. Human skin irritation test of Butylene Glycol.* (CTFA Code 2-17-78).
76. CTFA. (Aug. 16, 1973). Submission of unpublished data. CIR safety data test summary. Human skin irritation test of Hexylene Glycol.* (CTFA Code 2-17-95).
77. CTFA. (Feb. 27, 1974). Submission of unpublished data. CIR safety data test summary. Human skin irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-93).
78. CTFA. (Nov. 13, 1975). Submission of unpublished data. CIR safety data test summary. Human skin irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-88).
79. CTFA. (Jan. 15, 1976). Submission of unpublished data. CIR safety data test summary. Human skin irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-82).
80. CTFA. (Feb. 12, 1976). Submission of unpublished data. CIR safety data test summary. Human skin irritation test of product containing Butylene Glycol.* (CTFA Code 2-17-85).
81. CTFA. (1981). Submission of unpublished data. CIR safety data test summary. Prophetic patch and repeat insult patch tests of nail lotion containing Butylene Glycol.* (CTFA Code 2-17-161).
82. CTFA. (1978). Submission of unpublished data. CIR safety data test summary. Prophetic and repeated insult patch tests of product containing Dipropylene Glycol.* (CTFA Code 2-17-167).
83. GRANT, W.M. (1974). *Toxicology of the Eye,* 2nd ed. Springfield, IL: Charles C Thomas.
84. CTFA. (Feb. 1978). Submission of unpublished data. CIR safety data test summary. Human skin irritation test of personal cleanliness product containing Hexylene Glycol.* (CTFA Code 2-17-128).
85. HILL TOP RESEARCH. (Feb. 5, 1980). Submission of unpublished data by CTFA. Human cumulative irritancy test of product containing Butylene Glycol.* (CTFA Code 2-17-68).
86. HILL TOP RESEARCH. (July 16, 1979). Submission of unpublished data by CTFA. The study of cumulative irritant properties of a series of test materials.* (CTFA Code 2-17-6).
87. CTFA. (March 4, 1977). Submission of unpublished data. Allergic contact sensitization test of product containing Butylene Glycol.* (CTFA Code 2-17-70).
88. HILL TOP RESEARCH. (Nov. 3, 1976). Submission of unpublished data by CTFA. Repeated insult patch test of ten samples. Rouge containing Butylene Glycol.* (CTFA Code 2-17-72).
89. TESTKIT LABORATORIES. (July 31, 1980). Submission of unpublished data by CTFA. Repeated insult patch test of eye makeup remover containing Hexylene Glycol.* (CTFA Code 2-17-28).
90. CTFA. (July 1976). Submission of unpublished data. CIR safety data test summary. Repeated insult patch test with sun exposure of personal cleanliness product containing Hexylene Glycol.* (CTFA Code 2-17-126).
91. CTFA. (Jan. 1978). Submission of unpublished data. CIR safety data test summary. Repeated insult patch test of personal cleanliness product containing Hexylene Glycol.* (CTFA Code 2-17-125).
92. CTFA. (July 1979). Submission of unpublished data. CIR safety data test summary. Repeated insult patch testing of product containing Ethoxydiglycol.* (CTFA Code 2-17-3).
93. TESTKIT LABORATORIES. (March 31, 1981). Submission of unpublished data by CTFA. Repeated insult patch test of body lotion containing Ethoxydiglycol.* (CTFA Code 2-17-24).
94. CTFA. (March 29, 1976). Submission of unpublished data. Clinical use test.* (CTFA Code 2-17-69).

95. CTFA. (1978). Submission of unpublished data. CIR safety data test summary. Human use test of shaving preparation containing Dipropylene Glycol.* (CTFA Code 2-17-168).
96. CTFA. (Sept. 1981). Submission of unpublished data. CIR safety data test summary. Human use test of personal cleanliness product containing Hexylene Glycol.* (CTFA Code 2-17-124).
97. CTFA. (Feb. 26, 1982). Submission of unpublished data. Industry complaint experience on skin care product containing Hexylene Glycol.* (CTFA Code 2-17-137).
98. CTFA. (June 11, 1982). Submission of unpublished data. Industry complaint experience on shave preparation containing Dipropylene Glycol.* (CTFA Code 2-17-169).

2016 FDA VCRP Data

Rosa Canina Fruit Extract

03B - Eyeliner	1
03C - Eye Shadow	165
03D - Eye Lotion	4
03F - Mascara	1
03G - Other Eye Makeup Preparations	2
05A - Hair Conditioner	9
05C - Hair Straighteners	2
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	7
05G - Tonics, Dressings, and Other Hair Grooming Aids	22
05H - Wave Sets	1
05I - Other Hair Preparations	5
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	13
07A - Blushers (all types)	14
07B - Face Powders	30
07C - Foundations	3
07I - Other Makeup Preparations	1
09B - Mouthwashes and Breath Fresheners	1
10A - Bath Soaps and Detergents	8
10E - Other Personal Cleanliness Products	2
12A - Cleansing	11
12C - Face and Neck (exc shave)	17
12D - Body and Hand (exc shave)	4
12F - Moisturizing	8
12G - Night	4
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	2
12J - Other Skin Care Preps	3
Total	**342**

Rosa Canina Bud Extract (No FDA Data)

Rosa Canina Flower

07B - Face Powders	1
12C - Face and Neck (exc shave)	2
12F - Moisturizing	1
12G - Night	1
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	2
Total	**8**

Rosa Canina Flower Extract

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

03E - Eye Makeup Remover	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	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	**24**

Rosa Canina Flower Powder (No FDA Data)

Rosa Canina Fruit

02A - Bath Oils, Tablets, and Salts	1
07I - Other Makeup Preparations	1
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	1
Total	**4**

Rosa Canina Fruit Juice (No FDA Data)

Rosa Canina Leaf Extract

05A - Hair Conditioner	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07E - Lipstick	1
10E - Other Personal Cleanliness Products	1
12F - Moisturizing	1
12J - Other Skin Care Preps	2
Total	**7**

Rosa Canina Seed (No FDA Data)

Rosa Canina Seed Extract

01A - Baby Shampoos	1
01B - Baby Lotions, Oils, Powders, and Creams	2
03B - Eyeliner	2
03F - Mascara	3
03G - Other Eye Makeup Preparations	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07E - Lipstick	10
07I - Other Makeup Preparations	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	3
12F - Moisturizing	9
Total	**36**

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. Lange, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 25, 2016

SUBJECT: Updated Concentration of Use by FDA Product Category: *Rosa canina*-Derived Ingredients

Concentration of Use by FDA Product Category – *Rosa canina*-Derived Ingredients*

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

Ingredient	Product Category	Maximum Concentration of Use
Rosa Canina Fruit Extract	Bath oils, tablets and salts	0.0075%
Rosa Canina Fruit Extract	Other bath preparations	0.1%
Rosa Canina Fruit Extract	Eye shadow	0.001%
Rosa Canina Fruit Extract	Eye lotion	0.0002-0.2%
Rosa Canina Fruit Extract	Eye makeup removers	0.0015%
Rosa Canina Fruit Extract	Other eye makeup preparations	0.02%
Rosa Canina Fruit Extract	Perfumes	0.0015%
Rosa Canina Fruit Extract	Powders (dusting and talcum)	0.01%
Rosa Canina Fruit Extract	Hair conditioners	0.00015-0.1%
Rosa Canina Fruit Extract	Hair sprays Aerosol Pump spray	 0.0002% 0.25%
Rosa Canina Fruit Extract	Rinses (noncoloring)	0.00003-0.0017%
Rosa Canina Fruit Extract	Shampoos (noncoloring)	0.000009-0.005%
Rosa Canina Fruit Extract	Tonics, dressings and other hair grooming aids	0.00015-0.25%
Rosa Canina Fruit Extract	Wave sets	0.00015-0.0006%
Rosa Canina Fruit Extract	Hair dyes and colors	0.0014%
Rosa Canina Fruit Extract	Hair lighteners with color	0.00003%
Rosa Canina Fruit Extract	Face powders	0.001-0.002%
Rosa Canina Fruit Extract	Foundations	0.0015-0.03%
Rosa Canina Fruit Extract	Lipstick	0.0015%
Rosa Canina Fruit Extract	Makeup bases	0.0015%
Rosa Canina Fruit Extract	Rouges	0.002%
Rosa Canina Fruit Extract	Other makeup preparations	0.001-0.0015%
Rosa Canina Fruit Extract	Bath soaps and detergents	0.0001-0.004%
Rosa Canina Fruit Extract	Deodorants Not spray Aerosol	 0.0000014% 0.00003%
Rosa Canina Fruit Extract	Other personal cleanliness products Not spray	 0.00025%
Rosa Canina Fruit Extract	Skin cleansing (cold creams, cleansing lotions, liquid and pads)	0.0075-0.015%
Rosa Canina Fruit Extract	Face and neck products	

	Not spray	0.00019-0.2%
Rosa Canina Fruit Extract	Body and hand products Not spray	 0.0003-0.1%
Rosa Canina Fruit Extract	Moisturizing products Not spray	 0.0015-0.2%
Rosa Canina Fruit Extract	Night products Not spray	 0.0001-0.01%
Rosa Canina Fruit Extract	Paste masks and mud packs	0.0002%
Rosa Canina Fruit Extract	Skin fresheners	0.02%
Rosa Canina Fruit Extract	Other skin care preparations	0.02%
Rosa Canna Flower	Aftershave lotions	0.009%
Rosa Canina Flower	Other skin care preparations	0.5%
Rosa Canina Flower Extract	Perfume	0.01%
Rosa Canina Flower Extract	Hair conditioners	0.001%
Rosa Canina Flower Extract	Hair sprays Pump sprays	 0.001%
Rosa Canina Flower Extract	Shampoos (noncoloring)	0.0001%
Rosa Canina Flower Extract	Tonics, dressings and other hair grooming aids	0.0001%
Rosa Canina Flower Extract	Lipstick	0.04%
Rosa Canina Flower Extract	Paste masks and mud packs	0.001%
Rosa Canina Fruit	Shaving cream (aerosol, brushless and lather)	0.0003%
Rosa Canina Seed Extract	Mascara	0.1%
Rosa Canina Seed Extract	Hair conditioners	0.1%
Rosa Canina Seed Extract	Shampoos (noncoloring)	0.00029%
Rosa Canina Seed Extract	Tonics, dressings and other hair grooming aids	0.029%
Rosa Canina Seed Extract	Lipstick	1.5%
Rosa Canina Seed Extract	Body and hand products Not spray	 0.0005%

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

Information collected in 2015

Table prepared July 2, 2015

Updated January 21, 2016: Rosa Canina Fruit Extract moisturizing products high concentrations changed from 5% to 0.2%; indoor tanning preparations deleted

Updated March 2, 2016: Rosa Canina Fruit Extract eye lotion high concentration changed from 1.8% to 0.2%; face and neck products high concentration changed from 7% to 0.2%

Updated April 25, 2016: Rosa Canina Flower Extract deleted 3% face and neck product

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 20, 2016

SUBJECT: Rosa Canina Flower Extract

Consumer Product Testing Co. 2010. Repeated insult patch test of a lip balm containing 0.04% Rosa Canina Flower Extract.

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

Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT: [redacted]

ATTENTION: [redacted]

TEST: Repeated Insult Patch Test
Protocol No.: 1.01

TEST MATERIAL: Lip Balm – ENG045857-0.1.1.0, LSH4-28-1
Contains 0.04% Rosa Canina Flower Extract

EXPERIMENT REFERENCE NUMBER: CI0-0185.02

Reviewed by: Richard R. Eisenberg, M.D.
Medical Director
Board Certified Dermatologist

Approved by: Michael Caswell, Ph.D., C.C.R.C., C.C.R.A.
Director, Clinical Evaluations

Approved by: Joy Frank, R.N.
Executive Vice President, Clinical Evaluations

Date: March 12, 2010

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

Consumer Product Testing Co.
EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study Number: C10-0185.02

The Consumer Product Testing Company, Incorporated (CPTC) Quality Assurance Unit (QAU) is responsible for monitoring the conduct, content and reporting of all clinical laboratory studies that are conducted at CPTC.

This study has been conducted in accordance with ICH Guideline E6 for *Good Clinical Practice*, the requirements of 21 CFR Parts 50 and 56, other applicable regulations, CPTC Standard Operating Procedures, and the approved Study Protocol.

The CPTC QAU has reviewed all data, records, and documents relating to this study and also this Final Report. The following QAU representative signature certifies that all data, records, and documents relating to this study and also this Final Report have been reviewed and are deemed to be acceptable, and the study conforms to all of the requirements as indicated above.

Quality Assurance Representative

3/18/10
Date

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: One hundred thirteen (113) qualified subjects, male and female, ranging in age from 17 to 76 years, were selected for this evaluation. One hundred six (106) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] and over.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material: Lip Balm – ENG045857-0.1.1.0, LSH4-28-1

Study Schedule:

Panel #	Initiation Date	Completion Date
20100016	January 18, 2010	March 1, 2010
20100020	January 25, 2010	March 4, 2010

[a]With parental or guardian consent

Methodology:

The upper back between the scapulae served as the treatment area. Approximately 0.2 g of the test material, or an amount sufficient to cover the contact surface, was applied to the 1" x 1" absorbent pad portion of a clear adhesive dressing. This was then applied to the appropriate treatment site to form a semi-occlusive patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period. It was noted that due to inclement weather, numerous subjects were unable to report as scheduled. They were instructed to report on the following test day.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications were discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of twenty-four hours following each Tuesday and Thursday removal, and forty-eight hours following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic twenty-four and seventy-two hours post-application. For Panel 20100016, it was noted that due to inclement weather, the final evaluation was conducted one hundred twenty hours post application.

Methodology (continued):

Evaluation Criteria (Erythema and additional Dermal Sequelae):

0	=	No visible skin reaction	E	=	Edema
0.5	=	Barely perceptible	D	=	Dryness
1	=	Mild	S	=	Staining
2	=	Moderate	P	=	Papules
3	=	Marked	V	=	Vesicles
4	=	Severe	B	=	Bullae
			U	=	Ulceration
			Sp	=	Spreading

Erythema was scored numerically according to this key. If present, additional Dermal Sequelae were indicated by the appropriate letter code and a numerical value for severity.

Results:

The results of each participant are appended (Table 1).

Observations remained negative throughout the test interval.

Subject demographics are presented in Table 2.

Summary:

Under the conditions of this study, test material, Lip Balm – ENG045857-0.1.1.0, LSH4-28-1, did not indicate a potential for dermal irritation or allergic contact sensitization.

Table 1
Panel #20100016

Individual Results

Lip Balm – ENG045857-0.1.1.0, LSH4-28-1

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	120 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	DID NOT COMPLETE STUDY										
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0[W]	0	0
11	0	0	0	0	0	0	0	0	0	0[W]	0	0
12	0	0	0	0	0	0	0	0	0	0[W]	0	0
13	0	0	0	0	0	0	0	0	0	0[W]	0	0
14	0	0	0	0	0	0	0	0[m]	0[W]	0	0	0
15	0	0	0	0	0	0	0	0	0	0[W]	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0[W]	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0[W]	0	0
25	DID NOT COMPLETE STUDY											
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
m = Additional makeup day granted at the discretion of the clinic supervisor
W = Inclement weather. Subject unable to report as scheduled.

Table 1
(continued)
Panel #20100016

Individual Results

Lip Balm – ENG045857-0.1.1.0, LSH4-28-1

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	120 hr
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	---DNC---	
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0[W]	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0[W]	0	0
37	0	0	0	0	0	0	0	0	0	0[W]	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	----------DID NOT COMPLETE STUDY----------										
41	0	----------DID NOT COMPLETE STUDY----------										
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0[W]	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0[W]	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	-	0	0	0	0	0	0	0	0	0[W]	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
W = Inclement weather. Subject unable to report as scheduled.
DNC = Did not complete study
- = Subject not present for supervised removal

Table 1
(continued)
Panel #20100020

Individual Results

Lip Balm – ENG045857-0.1.1.0, LSH4-28-I

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0[W]	0	0	0	0
2	0	0	0	0	0	0	0	0[W]	0	0	0	0
3	0	0	0	0	0	0	0	0[W]	0	0	0	0
4	0	0	0	0	0	0	0	0[W]	0	0	0	0
5	0	0	0	0	0	0	0	0[W]	0	0	0	0
6	0	0	0	0	0	0	0	0[W]	0	0	0	0
7	0	0	0	0	0	0	0	0[W]	0	0	0	0
8	0	0	0	0	0	0	0	0[W]	0	0	0	0
9	0	0	0	0	0	0	0	0[W]	0	0	0	0
10	0	0	0	0	0	0	0	0[W]	0	0	0	0
11	0	0	0	0	0	0	0	0[W]	0	0	0	0
12	0	0	0	0	0	0	0	0[W]	0	0	0	0
13	0	0	0	0	0	0	0	0[W]	0	0	0	0
14	0	0	0	0	0	0	0	0[W]	0	0	0	0
15	0	0	0	0	0	0	0	0[W]	0	0	0	0
16	0	0	0	0	0	0	0	0[W]	0	0	0	0
17	0	0	0	0	0	0	0	0[W]	0	0	0	0
18	0	0	0	0	0	0	0	0[W]	0	0	0	0
19	0	0	0	0	0	0	0	0[W]	0	0	0	0
20	0	0	0	0	0	0	0	0[W]	0	0	0	0
21	0	0	0	0	0	0	0	0[W]	0	0	0	0
22	0	0	0	0	0	0	0	0[W]	0	0	0	0
23	0	0	0	0	0	0	0	0[W]	0	0	0	0
24	0	0	0	0	0	0	0	0[W]	0	0	0	0
25	0	0	0	0	0	0	0	0[W]	0	0	0	0
26	0	0	0	0	0	0	0	0[W]	0	0	0	0
27	0	0	0	0	0	0	0	0[W]	0	0	0	0
28	0	0	0	0	0	0	0	0[W]	0	0	0	0
29	0	0	0	0	0	0	0	0[W]	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
W = Inclement weather. Subject unable to report as scheduled

Table 1
(continued)
Panel #20100020

Individual Results

Lip Balm – ENG045857-0.1.1.0, LSH4-28-1

Subject Number	Induction Phase									Virgin Challenge Site	
	24*hr	1	2	3	4	5	6	7	8	9	24*hr	72 hr
30	0	0	0	0	0	0	0	0[W]	0	0	0	0
31	0	0	0	0	0	0	0	0[W]	0	0	0	0
32	0	0	0	0	0	0	0	0[W]	0	0	0	0
33	0	0	0	0	0	0	0	0[W]	0	0	0	0
34	0	0	0	0	0	0	0	0[W]	0	0	0	0
35	0	0	0	0	0	0	0	0[W]	0	0	0	0
36	0	0	0	0	0	0	0	0[W]	0	0	0	0
37	----------DID NOT COMPLETE STUDY----------											
38	0	0	0	0	0	0	0	0[W]	0	0	0	0
39	0	0	0	0	0	0	0[W]	0	0	0	0	0
40	0	0	0	0	0	0	0	0[W]	0	0	0	0
41	0	0	0	0	0	0	0	0[W]	0	0	0	0
42	0	0	0	0	0	0	0	0[W]	0	0	0	0
43	0	0	0	0	0	0	0	0[W]	0	0	0	0
44	----------DID NOT COMPLETE STUDY----------											
45	0	0	0	0	0	0	0	0[W]	0	0	0	0
46	0	0	0	0	0	0	0	0[W]	0	0	0	0
47	0	0	0	0	0	0	0	0[W]	0	0	0	0
48	0	0	0	0	0	0	0	0[W]	0	0	0	0
49	0	0	0	0	0	0	0	0[W]	0	0	0	0
50	0	0	0	0	0	0	0[W]	0	0	0	0	0
51	0	0	0	0	0	0	0	0[W]	0	0	0	0
52	0	0	0	0	0	0	0	0[W]	0	0	0	0
53	0	0	0	0	0	0	0	0[W]	0	0	0	0
54	0	0	0	0	0	0	0	0[W]	0	0	0	0
55	0	0	0	0	0	0	0[W]	0	0	0	0	0
56	0	0	0	0	0	0	0	0[W]	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
W = Inclement weather. Subject unable to report as scheduled

Table 2
Panel #20100016

Subject Demographics

Subject Number	Initials	Age	Sex
1	SV	45	F
2	CA	33	F
3	WP	51	F
4	EF	56	F
5	LB	57	F
6	MM	68	F
7	CL	69	F
8	RM	33	F
9	JM	44	F
10	JC	42	M
11	WB	37	M
12	TW	37	F
13	MS	29	F
14	SL	17	F
15	PM	45	F
16	LV	58	M
17	MV	49	F
18	JR	64	F
19	DW	45	F
20	DC	28	F
21	DM	17	F
22	PD	40	F
23	MD	66	F
24	MP	70	F
25	TI	57	M
26	MT	50	F
27	TR	31	F
28	PT	48	F
29	ST	53	M

Table 2
(continued)
Panel #20100016

Subject Demographics

Subject Number	Initials	Age	Sex
30	MD	45	F
31	JT	22	M
32	JL	58	M
33	ML	24	M
34	YO	37	F
35	IM	43	F
36	MD	27	F
37	MA	38	M
38	FJ	47	F
39	HJ	51	M
40	EB	64	F
41	MA	69	F
42	CF	55	F
43	SR	59	M
44	LR	44	F
45	DR	17	F
46	BG	37	F
47	BW	52	F
48	JR	22	M
49	JR	52	M
50	MV	49	F
51	KT	20	M
52	KR	33	M
53	AL	33	F
54	MV	29	F
55	MA	29	F
56	TU	62	F
57	PK	20	M

Table 2
(continued)
Pancl #20100020

Subject Demographics

Subject Number	Initials	Age	Sex
1	WH	69	M
2	JF	26	M
3	WF	56	F
4	GA	69	F
5	RD	28	F
6	TD	36	F
7	MD	18	F
8	KS	39	F
9	NJ	19	F
10	ST	33	F
11	KG	30	F
12	RD	73	M
13	RF	53	F
14	WL	52	F
15	DB	28	F
16	FR	65	F
17	IM	34	F
18	EE	66	F
19	YS	31	F
20	JF	72	F
21	LF	67	F
22	ML	43	F
23	CB	51	F
24	MC	31	M
25	JR	23	F
26	AQ	62	F
27	JQ	57	F
28	JC	42	F
29	KM	39	M

Table 2
(continued)
Panel #20100020

Subject Demographics

Subject Number	Initials	Age	Sex
30	DB	49	M
31	DS	71	F
32	SS	51	F
33	EF	38	F
34	TF	61	F
35	GV	44	F
36	LJ	45	F
37	WC	54	M
38	CB	45	F
39	CR	43	F
40	JP	69	F
41	FZ	22	F
42	DD	41	F
43	AG	49	M
44	DM	44	F
45	AD	57	M
46	YG	34	F
47	CD	51	F
48	NP	64	M
49	BQ	75	F
50	DM	76	F
51	CR	57	F
52	PG	47	F
53	AP	76	F
54	MC	27	M
55	AL	63	F
56	VB	70	F

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 21, 2016

SUBJECT: Rosa Canina Flower Extract

TKL Research. 2012. Repeated insult patch test of a lip liner containing 0.018% Rosa Canina Flower Extract.

Institute d'Expertise Clinique. 2008. In-use test under dermatological control: night cream containing 0.005% Rosa Canina Flower Extract.

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

TKL RESEARCH

REPEATED INSULT PATCH TEST

TKL STUDY NO. DS109311/109711-2

[redacted] STUDY NO. DT046755

CONDUCTED FOR:

[redacted]

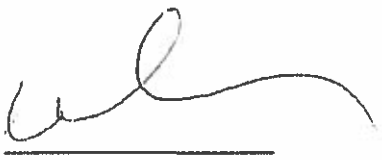
DATE OF ISSUE:

February 24, 2012

Version 1.0

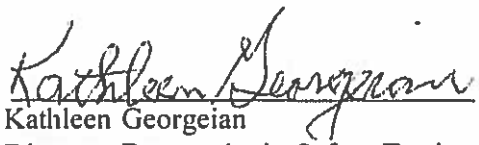
SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6I The report accurately reflects the raw data for this study.

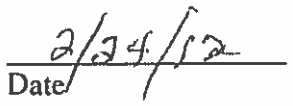


2/24/12

Jonathan S. Dosik, MD
Dermatologist
Principal Investigator
Date



Kathleen Georgeian
Director, Dermatologic Safety Testing



Date

Michelle Medina
Manager, Dermatologic Safety Testing

2/24/12
Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the stmi of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

---

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/1 35/95)" -- ICH Harmonized Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY
Repeated Insult Patch Test

SPONSOR
[redacted]

STUDY MATERIAL
ROSA CANINA FLOWER EXTRACT 0.018% Lip liner

DATE STUDY INITIATED
December 19, 2011

DATE STUDY COMPLETED
February 03, 2012

DATE OF ISSUE
February 24, 2012

INVESTIGATIVE PERSONNEL
Jonathan S. Dosik, MD - Dermatologist
Principal Investigator

Kathleen Georgeian
Director, Dermatologic Safety Testing

Michelle Medina
Manager, Dermatologic Safety Testing

CLINICAL SITES
TKL RESEARCH, INC
48 South Franklin Turnpike
Ramsey, NJ 07446

TKL RESEARCH, INC
1255 Broad Street
Bloomfield, NJ 07003

SUMMARY

One study material, ROSA CANINA FLOWER EXTRACT 0.018% Lip liner, was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. Two hundred two (202) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to ROSA CANINA FLOWER EXTRACT 0.018% Lip liner.

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 200 completed subjects. In the absence of any sensitization reactions in this sample size (200 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 to 70 years of age, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding;
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated; and/or
6. Were participating in another study or had been recruited to participate in another study concurrently.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 Description of Study

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2]

Following the 9th evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the 6th week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

To be considered a completedcase, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK1

DAY	ACTIVITIES
1[3]	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK2

DAY	ACTIVITIES
1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK3

DAY	ACTIVITIES
1-6	Same as Week 2

WEEK4

DAY	ACTIVITIES
1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU patches
3	Staff graded MU induction sites at MU visit
2-7	Rest Period

WEEK5

DAY	ACTIVITIES
1-7	Rest Period

WEEK6

DAY	ACTIVITIES
1	Staff applied patches

[3] Study flow starting with Week 1, Day 1, was altered when enrollment occurred on Wednesday or Friday. Study flow could be altered if a holiday occurred during the study.

2 Subject removed patches

3 Staff graded sites

4 Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

SYMBOL		REACTION
-	=	No reaction
?	=	Minimal or doubtful response, slightly different from surrounding normal skin
+	=	Definite erythema, no edema
++	=	Definite erythema, definite edema
+++	=	Definite erythema, definite edema and vesiculation

SPECIALNOTATIONS

E	=	Marked/severe erythema
S	=	Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p	=	Papular response > 50%
pv	=	Papulovesicular response > 50%
D	=	Damage to epidermis: oozing, crusting and/or superficial erosions
I	=	Itching
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Not applied
NP	=	Not patched (due to reaction achieved)
N9G	=	No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : ROSA CANINA FLOWER EXTRACT 0.018% Lip liner
Amount Applied : 0.2 g

4.2 Storage, Handling, and Documentation of Study Material

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material was kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 Application of Study Material

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 Description of Patch Conditions

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patches are secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pads are affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours.

Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred Rechallenge procedure involves the

application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of TKL.

7.0 RESULTS AND DISCUSSION

Two hundred twenty-three (223) subjects between the ages of 18 and 70 were enrolled and 202 subjects completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition.

Number enrolled:		223
Number discontinued:		21
Lost to follow-up:	12	
Voluntary withdrawal:	5	
Other reason: (Disrespectfultostudystaff)	4	
Number completed:		202

Source: Table 1, Appendix I

There were no adverse events reported.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to ROSA CANINA FLOWER EXTRACT 0.018% Lip liner.

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

Draize JH, Woodward G, Calvary HO. Methods for the study of irritation and toxicology of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 82: 377-390.

Lanman BM, Elvers WB, Howard CS. The role of human patch testing in a product development program. Joint Conf Cosmet Sci Toilet Goods Assoc 1968; 135-145.

Marzulli FN, Maibach HI. Contact allergy: predictive testing in man. Contact Dermatitis 1976; 2:1.

Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980:41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

INSTITUT D'EXPERTISE CLINIQUE

IEC JAPAN - IEC SINGAPORE - IEC KOREA - IEC BULGARIE - IEC ESPAGNE - IEC AFRIQUE DU SUD - IEC CHINA - IEC INDIA

REPORT: ACCEPTABILITY STUDY

EV0803-0477

IN-USE TEST UNDER DERMATOLOGICAL CONTROL

CLINICAL STUDY FOR THE APPRAISAL OF THE CUTANEOUS ACCEPTABILITY OF A COSMETIC INVESTIGATIONAL PRODUCT, APPLIED UNDER NORMAL CONDITIONS OF USE, FOR 4 WEEKS, IN THE ADULT SUBJECT

INVESTIGATIONAL PRODUCT: ROSA CANINA FLOWER EXTRACT 0.005% Night Cream- batch n° FIC1 16/05/2008
EXPERIMENTAL PROTOCOL: N° 080950PE - Version 1, of 27 May 2008

REPORT: N° 080950RDT - Version 1, of 31 July 2008

START OF OBSERVATIONS: 27 May 2008
END OF OBSERVATIONS: 3 July 2008

STUDY MONITOR	RESPONSIBLE FOR THE STUDY	INVESTIGATOR
[redacted]	Mrs G. GIROUD Ph.D. in Physiology I.E.C. 88, boulevard des Belges 69006 LYON - FRANCE	Dr. B. BISBAL, M.D. Dermatologist Address of Investigation: I.E.C. 88, boulevard des Belges 69006 LYON - FRANCE

Document of 40 pages

AUTHENTICATION

The study subject of the present report was conducted under my responsibility, in compliance with standard and specific experimental protocols, in accordance with the standard operating procedures of the Clinical Research Centre, and in the spirit of the general principles of the Good Clinical Practices published by I.C.H. (Topic E6: CPMP/ICH/135/95).

All observations and numerical data obtained during this study are reported in the present document.

31/07/08

Dr. Brigitte BISBAL, M.D.
Dermatologist Investigator
and
Study Director

I have read this report, I certify that these data are an accurate reflection of the results obtained and I agree with its content.

31/07/08

Geraldine GIROUD
Responsible for the Study

PERSONNEL INVOLVED IN THE REALISATION OF THE STUDY

President General Director Name: J.P. GUILLOT Senior Toxicologist- Pharmacologist (Eurotox Registered Toxicologist) Address: Route de Bibost 69690 Bessenay - France ☎: +33 (0) 4.74.70.93.39	Deputy General Director Name: E. CAMEL Pharm. D., D.B.A. in Skin Biology and Cosmetology, Senior Toxicologist (Eurotox Registered Toxicologist) Address: 88, boulevard des Belges 69006 Lyon - France ☎: +33 (0) 4.72.69.89.61

Administration, Finance and Human Resources Director Name: Y. POHLMANN D.U.E.L. in English Address: 88, boulevard des Belges 69006 Lyon - France ☎: +33 (0) 4.72.69.70.91	Head for the Management of Clinical Studies and Consumer Tests Name: E. MARQUIS Master in Biochemistry Post graduate in Industrial Cosmetology (I.P.I.L.) Address: 88, boulevard des Belges 69006 Lyon - France ☎: +33 (0) 4.72.69.89.73

Head of Clinical Safety Studies Name: B. GRANGER Post graduate in "Metabolism, Endocrinology and Nutrition", and Training to Clinical Trials Address: 88, boulevard des Belges 69006 Lyon - France ☎: +33 (0) 4.72.69.89.70	Responsible for Management of the Volunteers Name: S. GUILLOT General Marketing Certificate of Education from the "Chambre de Commerce et d'Industrie" Address: 88, boulevard des Belges 69006 Lyon - France ☎: +33 (0) 4.72.69.90.92

Investigator (Study Director) Name: Dr. B. BISBAL, M.D. Post Graduate in Dermatology Address: 88, boulevard des Belges 69006 Lyon - France ☎: +33 (0) 4.72.69.89.60	Responsible for the Study Name: G. GIROUD Ph.D. in Physiology Address: 88, boulevard des Belges 69006 Lyon - France ☎: +33 (0) 4.72.69.77.42

Technician Name: M. DELEGLISE Address: 88, boulevard des Belges 69006 Lyon - France ☎: +33 (0) 4.72.69.89.68

INSTITUT D'EXPERTISE CLINIQUE

Head office: route de Bibost, 69690 Bessenay - France
Phone: +33 (0) 4.74.70.93.39- Fax: +33 (0) 4.74.70.94.98

ENGLISH SUMMARY OF THE REPORT

SPONSOR: [redacted]

INVESTIGATIONAL PRODUCT: ROSA CANINA FLOWER EXTRACT 0.005% Night Cream- batch n° FICI 16/05/2008)

EV0803-0477

ACCEPTABILITY STUDY: IN-USE TEST UNDER DERMATOLOGICAL CONTROL

CLINICAL STUDY FOR THE APPRAISAL OF THE CUTANEOUS ACCEPTABILITY OF A COSMETIC INVESTIGATIONAL PRODUCT, APPLIED UNDER NORMAL CONDITIONS OF USE, FOR 4 WEEKS, IN THE ADULT SUBJECT

STUDY OBJECTIVE	To appraise the cutaneous acceptability of a cosmetic investigational product, applied under the normal conditions of use, in the adult subject.	
TYPE OF STUDY	Acceptability study ("in-use test"), under Dermatological control, in "open".	
INCLUSION CRITERIA SPECIFIC TO THE STUDY *(in addition to the general criteria)*	. *Number of subjects:* 50 . *Sex:* female . *Origin:* Caucasian . *Age:* 45 to 65 years old . *Face skin:* all types . *"Sensitive" skin:* about 50% . *"Healthy subjects with history of atopy":* 20 to 25%* maximum	. *Other:* subject presenting with cutaneous slackening problems on the face as well as wrinkles and fine lines on the eye contours (according to the specific photographic scale provided by the Sponsor - N°E0503 - Annexe 1 - VI). **proportion currently admitted for the French*
METHODOLOGY	- Application modalities of the investigational product: . *areas:* face and neck (insisting on the eye contours) . *frequency and duration:* once a day (in the evening) for 4 weeks . *application conditions:* by the subject him/herself, at home (starting on DO and ending on D27), under the normal conditions of use (as much as is necessary) - Modalities of evaluations of the cutaneous acceptability: - cutaneous clinical examinations by the Dermatologist Investigator on DO and on D28 - questionnaire including a daily log to be filled in by the subject	

RESULTS AND CONCLUSION

STUDIED POPULATION

Number of subjects recruited	74
Number of subjects who came to I.E.C.	57
Number of subjects included by the Dermatologist Investigator	50
Number of subjects discontinued from the study	2
Number of subjects for the analysis ofthe results	48

The physical characteristics of the subjects are summarized in the following table:

Subjects		Face skin nature		Sensitivity		Healthy subjects with history of atopy
Number	:48	Normal	: 2 (4 %)	Face skin	: 25 (52%)	3 (6 %)
Females	:48 (100%)	Mixed Oily	:8(17%)			
Males	: 0 (0 %)	Oily	:1 (2 %)			
Mean age	: 57.6	Mixed Dry	:15(31%)			
Age min	:46	Dry	: 21 (44 %)			
Age max	: 65	Very Dry	:1 (2 %)			

All these subjects presented with cutaneous slackening problems on the face as well as wrinkles and fine lines on the eye contours.

CONCLUSION

Analysis of the results obtained revealed a very good acceptability of the investigational product in 41 out of the 48 subjects who took part in the whole study.

6 out of the 7 other subjects (with a "sensitive" or with a dry tendency skin) indicated having presented with discomfort (prickling in particular), associated in one of them with a redness, which intensity (very slight to slight), duration (a few seconds or minutes for the majority) and frequency of appearance (after a few applications of the beginning of the study only for 5 subjects) are rather frequently encountered with this type of investigational product (with an anti-wrinkle/anti-ageing aim) studied under these conditions.

2 subjects (of whom one previously cited) indicated having presented with an eye watering during the whole study or a slight palpebral swelling in the morning following the first few applications. These phenomena are sometimes encountered with anti-wrinkle products studied under these conditions (insisting on the eye contours).

One of these subjects also indicated having observed a few "small pimples" during 2 days of the 1st week of the study. This isolated and liminal reaction, which imputability to the investigational product seems doubtful, remains without any particular significance.

It should be noted that no abnormal clinical sign was noted, by the Dermatologist Investigator, after the 4 weeks of use.

The synthesis of the reactions noted during the study is shown in the table below (in % of the subjects questioned):

	Frequency of reaction
Reactions noted during the whole study	15% (7/48)
Reactions observed by the Dermatologist Investigator	0% (0/48)
Reactions reported by the subjects *. discomfort only* *. irritation(+ discomfort and palpebral swelling)* *. "small pimples" +discomfort*	15% (7/48) *8% (4148)* *4% (2148)* *2% (1/48)*
Reactions that needed to modifY significantly the frequency or to stop the applications	0% (0/48)
Reactions which can be considered as "pertinent"*	4% (2/48)
Reactions considered as adverse events linked to the investigational product	0% (0/48)
Reactions considered as serious adverse events linked to the investigational product	0% (0/48)

* *conclusion based on the analysis of the nature, of the duration, of the intensity, of the frequency and of the appearing time of the reactions.*

The CUTANEOUS ACCEPTABILITY of the investigational product designated as "ROSA CANINA FLOWER EXTRACT 0.005% Night Cream- batch n° F1C1 16/05/2008)" can be judged, on the whole, GOOD, after repeated applications, under normal conditions of use, once a day for 4 consecutive weeks, to the face (insisting on the eyes contours) and neck skin, by 48 female adult subjects, from 46 to 65 years old, of all skin types, presenting with cutaneous slackening problems as well as wrinkles and fine lines on the eye contours and of whom 52% with a "sensitive" skin.

Lyon,

31/07/08

Dr. B. BISBAL, M.D.
Dermatologist Investigator
and
Study Director

31/07/08

G. GIROUD Ph.D. in
Physiology Responsible
for the Study

This study was conducted by INSTITUT D'EXPERTISE CLINIQUE (I.E.C.), registered by the French Ministry of Health, under the number 22056 MHC, and managed by Mr. J.P. GUILLOT, Senior Toxicologist (Eurotox Registered Toxicologist).

QUALITY CONTROL

This study was conducted in conformity with the standard operating procedures of the Clinical Research Centre, the signed protocol and in the spirit of the general principles of the Good Clinical Practices published by I.C.H. (Topic E6: CPMP/ICH/135/95).

The quality control of the clinical studies, which are not considered as interventional studies from the law n° 2004-806 dated 9 August 2004, is carried out periodically. It is designed to ensure that all critical phases (investigational product applications and examinations or measurements) of a particular study type are controlled, at least once a quarter, for the studies carried out during this time period. Dates of these quality controls and study type concerned are given below.

The results of these quality controls were reported to the Dermatologist Investigator and to the General Management.

Types of study	Dates of quality controls	Dates of reports to the Dermatologist Investigator	Dates of reports to the General Management
. Identical study:	27 June 2008	30 June 2008	7 July 2008
. Miscellaneous:	Elbow fold:		
	27 June 2008	30 June 2008	7 March 2008
	TUOR:		
	16 July 2008	17 July 2008	24 July 2008
. Raw data:	10 July 2008	11 July 2008	18 July 2008

This report has been controlled by I.E.C. Quality Unit, it is an accurate account of the procedures followed, and accurately records the original raw laboratory data generated in this study.

	Date of quality control	Date of report to the Dermatologist Investigator	Date of report to the General Management
Report (vs. Compiled data):	29 July 2008	29 July 2008	29 July 2008

31/07/08

Signature:

Cecile AUZEAU
Quality Executive Manager

Date:

1. INTRODUCTION

The study consists in the application of the investigational product(s) under normal conditions of use, to at least 50 adult subjects for 4 weeks. The target panel of the study depends on the tested investigational product(s) nature.
It is carried out on cosmetic products whose safety had been assured by a toxicologist, with the aim to further confirm safety of these products which will be used by a large number of consumers under normal or reasonably foreseeable use conditions.

2. EXPERIMENTAL DESIGN

2.1. STUDY OBJECTIVE

To appraise the cutaneous acceptability of a cosmetic investigational product, applied under the normal conditions of use, in the adult subject.

2.2. STUDY RELEVANCE

Cutaneous irritation can be defined as an attack of skin integrity, with lesions to the epidermis and coming from an inflammatory reaction of the dermis, expressed by macroscopically visible phenomena, mainly redness (erythema), up to cedema.

In man, the "in-use" ("acceptability" test) test perfomled under Dermatological control (subjects individually examined by a Dermatologist Investigator), enables to check the absence of discomfort and/or irritation reactions (functional and physical signs) linked to the investigational product(s) applied for 3 weeks at least, under the normal conditions of use, in at least 20 subjects with specific inclusion criteria.

2.3. PRINCIPLE

ACTIONS	DO	D27	D28
Final admission by the Dermatologist Investigator (inclusion and non-inclusion criteria)	X		
Individual clinical examination of each subject by the Dermatologist Investigator (functional and physical signs)	X		X
Applications of the investigational product(s) by the subject at home	[_____]		
Tolerance questionnaire including a daily log to be filled in by the subject at home (application frequency, application number, nature, location, intensity, duration and period of appearance of the reactions)	[_____]		

2.4. INVESTIGATIONAL PRODUCT

Designation	Night Cream
Formula	ROSA CANINA FLOWER EXTRACT 0.005%
Batch n°	FICI 16/05/2008
Physical form	tick emulsion
I.E.C. identification code	080950 009032
Analytical control	The Sponsor will guarantee the conformity of the investigational product(s) with the labelling and will provide the investigational laboratory with information (colour, physical form). For this type of study, no analytical dosage will be made and neither stability, nor absorption of the investigational product(s) will be evaluated by I.E.C..
Colour	white
Packaging	porcelain pot
Quantity supplied	110 x 50 ml
Date of receipt	23 May 2008
Storage	Under lock and key, protected from heat (between + 5° C and + 25° C) and light. the unused investigational products will be destroyed at the end of the study. A sample of the investigational product(s) will be kept in the concerned facility for 6 months as of the date of dispatch of the final report. From this date and unless advised of the contrary by the Sponsor, the investigational product(s) will be destroyed.

2.5. SUBJECTS

2.5.1. Principle of selection, recruitment, admission and inclusion

The procedure for selection, recruitment and admission of a subject who accepted to pmiicipate in this study, after signed informed consent form, was elaborated to give him/her clear and precise information, enabling him/her to appreciate the aim and the consequences of his/her consent.

This procedure included, in particular:
- a preliminary interview during which the objective and the protocol of the study was explained to the subject, the study timetable, the indemnity amount, as well as the possible benefits, the constraints linked to the study and the foreseeable risks even in case of stop of the study before its normal end;
- the signature of an informed consent form by the subject: he/she was thus able to make his/her decision completely freely taking the conditions proposed into account;
- the notification of his/her taking over by the insurance in civil liability subscribed independently by the Sponsor and I.E.C., once the subject was definitely admitted in the study by the Dermatologist I nvestigator.

The subject recruited for this study was previously selected by the M.D. in charge of recruitment, on the basis of a medical examination performed for the inclusion in the panel of I.E.C. (medical examination, based on the general inclusion and general non-inclusion criteria defined in the I.E.C. procedures).
The final inclusion of the subject in the present study was determined by the Dermatologist Investigator, Study Director, from a pre-study medical auto-questionnaire and from a clinical medical examination specific to the study, performed just before its start, on the basis of the inclusion and non-inclusion criteria specific to the study, as well as the prohibition and restriction concepts defined in the protocol.

2.5.2. Number of subjects requested for the study

The number of valid cases in the study must be of 50 according to the request of the Sponsor. A valid case was defined as a subject who has completed a full procedure (complete application duration with all examinations planned).
Justification: at least 20 subjects are frequently used for in-use tests and is considered as sufficient number to be able to draw valid conclusions.
The subjects were registered and allocated in progressive order of their selection on their arrival.

2.5.3. Inclusion criteria

2.5.3.1. General inclusion criteria in the I.E.C. database

- Origin: Caucasian
  Justification for origin: the white colour of Caucasians' skin allows easier evaluation of the cutaneous reactions.

- Weight: based on the scales proposed by the Metropolitan Insurance Company.

- Understanding of the language spoken in the research center: subject able to read the documents they are presented with and to hold to what they are explained.

- Social cover: subject having medical coverage (private medical aid, social welfare, government health service, ... For people who have not a social cover: the subject should have a fixed abode).

Note: all these general inclusion criteria are a preliminary condition to be enrolled in I.E.C. panel and consequently are not systematically reported in the case report form specific to the performed study.

2.5.3.2. Inclusion criteria specific to the study

These criteria were evaluated on the basis of a questionnaire and clinical examination listed in the case report form.

- Age: 45 to 65 years old.

- Sex: female.

- Origin: Caucasian.

- Skin type: all types.

- Subject presenting with cutaneous slackening problems on the face as well as wrinkles and fine lines on the eye contours (according to the specific photographic scale provided by the Sponsor - N°E0503 - Annexe 1 -V I).

- "Sensitive" skin: about 50% of the panel.
This criterion should be put in concrete form by a positive answer to the following question: "do you have any abnormal and repeated reactions to the face (tightness, prickling, itching, redness,...)?"
to care products;
to hygiene products (soap, ...);
to the environment during a major part of the year (cold, wind, sun ...);
to others (water, clothes contact, shaving, ...).

- "Healthy subject with family or personal history of atopy, without any progressive or recent clinical features of atopic disease": a maximum of 20 to 25% of the panel (proportion which can be admitted in the study depending on the recruitment modalities, unless contrary specifications are given by the Sponsor: this percentage corresponds to a currently admitted proportion for this population).
For this, the subject should present with :
either TWO familial past history (among: mother, father, brother(s) and sister(s)) for the following affections: (I) atopic dem latitis, (2) allergic asthma in the lst part of life, (3) recognised pollinosis, (4) derma-respiratory syndrome;
or personal past history (at least ONE criterion) among the following affections: (1) constitutional eczema, mostly appearing during the childhood and mostly located into the skin folds, (2) recurrent periodic asthma in the childhood or pre-teenage years (no asthma crisis should have occurred during the last 6 months), (3) recurrent periodic (chronic) conjunctivitis, (4) documented (allergological examination +prick tests) or non-documented pneumallergen related (pollens, acaridae, animals) allergic rhinitis.

2.5.4. Non-inclusion criteria

2.5.4.1. General non-inclusion criteria in the I.E.C. database

- Subject deprived from liberty by a judiciary or administrative decision, sick subject m situation of emergency.

- Under age or of age subject protected by law, as well as those admitted to sanitary or social facilities, ever since the research can be performed in another manner.

- Subject being an I.E.C.'s employee.

- Subject who cannot be contacted in case of emergency.

Health condition: these selection criteria will be strictly adhered to, m order to minimise risks to the subject (criteria evaluated on the basis of a questionnaire):

Subject either pregnant or breastfeeding mother, or not using a medically acceptable contraceptive method;

Subject having undergone organ excision (kidney, lung, spleen, liver ...), an organ transplant, a skull concussion with extended loss of consciousness in the last 5 years or with present after-effects;

Subject having at least one of the following disorders: cardiovascular, pulmonary, digestive, neurologic, psychiatric, genital, urinary, haematological or endocrine;

Subject having or being in the course of a long-term treatment, in particular with antihistaminics, corticoids, beta blockers (including eye lotion) and/or desensitisation;

Subject having an asthma crisis;

Subject having a background of drug intolerance (in particular local or general anaesthetics, or antibiotics) or of allergy to products for professional use, such as colophony, rubber (gloves, adhesives, plasters);

Subject having *a skin disease,* and in particular: urticaria, cedema, eczema, recurrent herpes, herpes zoster having erupted in the last 3 months, pityriasis versicolor, common acne with a sudden rise of inflammation or nodular or kystic acne, psoriasis, ichthyosis, lichen planus, chronic lupus erythematosis, keloid scars, severe pigmentation disorders (vitiligo, chloasma, multiple lentigines, numerous or congenital nevi, especially if they are of large size), hyperhidrosis, dorsal hyperpilosity;

Subject having a disease ofthe immune system or under immunosuppressive treatment;

Subject smoking more than the equivalent of 10 cigarettes a day or consuming more than 3 glasses of alcoholic drink a day.

Note: all these general non-inclusion criteria are a preliminary condition to be enrolled in I.E.C. panel and consequently are not systematically reported in the case report form specific to the peljormed study.

2.5.4.2. Non-inclusion criteria specific to the study

These criteria were evaluated on the basis of a questionnaire and clinical examinations listed in the case report form:

- Subject having refused to give his/her agreement by not signing the informed consent form.

- Subject not meeting with the above-mentioned inclusion criteria.

- Subject not covered by a medical insurance or without a fixed abode.

- Subject not having respected:
  the prohibition concerning the simultaneous acceptance of several biomedical research projects,
  the grace period during which a person may not be involved in any other biomedical research projects: subject having participated in an acceptability study in the last week and/or in a sensitisation study in the last 3 months and/or in a photo-irritation or photo-sensitisation study in the last 4 months.

- Subject of whom the health condition has changed since the inclusion visit in the I.E.C. database and/or makes, in the Dermatologist Investigator judgement, the subject ineligible or places the subject at undue risk (if the potential subject is under the care of a physician, approval to participate may be sought from that physician, at the Dermatologist Investigator's discretion and/or in accordance with regulatory requirements):
  Subject either pregnant or breastfeeding mother, or not using a medically acceptable contraceptive method;
  Subject having undergone organ excision, an organ transplant, a skull concussion with extended loss of consciousness in the last 5 years or with present after-effects;
  Subject having a disease of the immune system or under immunosuppressive treatment;
  Subject having had an asthma crisis during the last 6 months;

Subject having been at least one of the following disorders: cardiovascular, pulmonary, digestive, neurologic, psychiatric, genital, urinary, haematological, endocrine or immunologic;
Subject having or being in the course of a long-term treatment, in particular with antihistaminics, corticoids, beta blockers (including eye lotion) and/or desensitisation;
Subject having a background of drug intolerance (in particular local or general anaesthetics, or antibiotics) or of allergy to products for professional use, such as colophony, rubber (gloves, adhesives, plasters);
Subject having *a skin disease,* and in particular: urticaria, cedema, eczema, recurrent herpes, herpes zoster having erupted in the last 3 months, pityriasis versicolor, common acne with a sudden rise of inflammation or nodular or kystic acne, psoriasis, ichthyosis, lichen planus, chronic lupus erythematosis, keloid scars, severe pigmentation disorders (vitiligo, chloasma, multiple lentigines, numerous or congenital nevi, especially if they are of large size), hyperhidrosis, dorsal hyperpilosity;
Subject smoking more than the equivalent of 10 cigarettes a day or consuming more than 3 glasses of alcoholic drink.

- Subject having macroscopic traces of irritation or any other abnormality on the concerned areas of product application which could interfere in the analysis of the results.

- Subject having taken, in the past 3 months, medical treatment which is, in the Dermatologist Investigator judgement, inconsistent with the participation in the study and that thus makes him/her ineligible, in particular for anti-inflammatories applied on the test area within the 2 weeks before the beginning of the study and corticoids during the month before the beginning of the study.

- Subject currently receiving anti-allergy injections, with final injection within the last 8 days, or expecting to begin injections during the study.

- Subject having had a febrile illness: more than 24 hours of fever within the 8 days prior to the first application of the investigational product.

- Subject being vaccinated in the last month preceding the start of the study or expecting to be vaccinated during the study.

- Subject having modified his/her cosmetic habits (on the areas concerned by the study) during the last 2 weeks.

- Subject having applied a cosmetic product (other than the usual cleanser) on the areas concerned by the study, on the inclusion day of the study.

- Subject having a skin recently exposed to sunlight (natural or artificial), or having followed heliotherapy in the last 2 weeks.
- Subject having undergone plastic surgery to the concerned area

- Subject having undergone anti-wrinkle / depigmenting / anti-blemishes physical or chemical treatment (peeling, injections...) to the concerned area during the 12 months before the stmiing day of the study

- Subject in pre-menopause period and prone to phenomenon of sudden flush.

- Subject having modified their cosmetic habits on the studied areas during the 2 weeks before the starting day of the study.

-Subject having applied anti-wrinkle cares or cosmetic products containing A.H.A. (or derivates) or retinol during the 4 weeks before the starting day of the study.

- Subject having followed, during the 3 months before the starting day of the study, a medical treatment (either oral or topical) containing tretinoin or isotretinoin.

- Subject having already suffered from irritation or allergy to A.H.A..

- Subject having applied cosmetic or pharmaceutical products (other than their usual cleanser and eventually toner) to the face skin during the 48 hours before the starting day of the study.

-Subject having applied make-up products on the starting day of the study.

2.5.5. Prohibition and Restriction

Aspirin, products containing aspirin, anti-inflammatory drugs, antibiotics or antihistaminics or systemic steroids by general route, were forbidden throughout the duration of the study (paracetamol accepted). Vaccination was not permitted during the whole study. No other cosmetic of anti-wrinkle or anti-ageing type, except soap and water or the usual cleansing/make up removing products, should be used on the skin throughout the duration of the study. The subject could go on using only his/her usual day moisturising, eye and lips make up products, if he/she felt like it (in this case, this was precised in his/her questionnaire).
Moreover, the subject should prevent any solar exposure during the study, apart from his/her usual habits. The investigational product(s) should not be applied on the last day of study.

2.6. METHODOLOGY

2.6.1. Modes of application

The applications of the investigational product were performed by the subject him/herself (at home), in replacement of the one he/she generally uses and according to the following indications:

Application area	face and neck (insisting on the eye contours)
Quantity	as much as necessary*
Frequency	once a day (in the evening)
Duration	4 consecutive weeks
Application conditions	under normal conditions of use, on a clean skin.

* Weighing of the products at the beginning and at the end of the observations.

2.6.2. Removal of subjects from study or data analysis

Reasons for which a subject could be discontinued from the clinical study or withdrawn from the data analysis will be one of the following:
- Adverse event,
- Serious adverse event,
- Concomitant treatment(s) incompatible with the study,
- Consent withdrawal by the subject*,
- Lost to follow up,
- Emergence of a non-inclusion criterion,
- Decision of the Study Director/Dermatologist Investigator,
- Violation ofthe protocol.

**All the subjects will be informed of the fact that they can willingly and freezy withdraw their consent for participating in the study, if they wish to do so.*

Any discontinuation in the participation of a subject during the study was mentioned in the report and the reasons for this discontinuation were precised.
Any premature discontinuation linked to an Adverse Event or a Serious Adverse Event has to be followed-up (until final outcome). If complementary tests were necessary, a study amendment was written.
If the number of discontinuation or non presentations at the beginning of the study is higher than 10%, the subjects were replaced so that the data are available in at least 90% of the subjects, except if this discontinuation is due to an intolerance to the investigational product.

2.6.3. Observations and clinical examinations

2.6.3.1. Appraisal of the cutaneous acceptability by the Dermatologist Investigator

The cutaneous examinations were carried out by the Dermatologist Investigator, before the start of use (DO) of the investigational product(s) and after the 4 weeks of application (D28).

The cutaneous acceptability was assessed, by the Dermatologist Investigator, on the basis, on the one hand, of clinical examinations of the skin allowing to observe the physical signs (erythema, oedema, dryness, desquamation ...) linked to the use of the investigational product(s), and on the other hand, an interrogation making possible to evaluate the functional signs (prickling, tightness, heat sensation, ...) completed by a questionnaire including a daily log filled in by the subject at home and given back to the Dermatologist Investigator the last day of the study (detailing the application frequency, application number, nature, location, intensity, duration and period of appearance of the reaction).

2.6.3.2. Adverse events

2.6.3.2.1 Definition

An adverse event (AE) was defined as:

- any unfavourable and unintended event or degradation of the medical conditions (in comparison with those noted during the initial examination), occurring during the period of application of the investigational product(s) (between the inclusion in the study and the end of the study), not related to the investigational product(s) application: disease, accident, food intoxication, ...
- any reaction or event related to the application of the investigational product(s) (definitely related (very probable or certain), probably related, possibly related or unlikely related (doubtful)) or unrelated to investigational product(s) application, which by its nature, its intensity or its appearance frequency leads to a modification of the application modalities of the investigational product(s) (rhythm, quantity, application area, ...), and/or a discontinuation from the study (withdrawal of the consent by the subject or discontinuation on decision of the Dermatologist Investigator).

As of I.E.C. knows that AE occurred, the Sponsor was informed of the AE either immediately for a serious adverse event (see§ 2.6.3.2.4.) or within 48 hours for a non-serious adverse event.
The AEs should be collected in the appropriate form at the end of the case report f01m along with the date of onset, site and duration of event, any action taken, outcome and an assessment of causality and severity. If the AE was on going on the final visit, the Dermatologist Investigator had to follow-up the event until complete outcome.

2.6.3.2.2 Causality

The Dermatologist Investigator assessed the relationship (causality) of an AE to the investigational product(s) according to the following definitions.

- **Definitely related (very probable or certain)**
  No uncertainty about the relationship between the event and investigational product(s) application.
  The event followed a definite reasonable temporal sequence from the time of the investigational product(s) application and improved upon stopping the dose of the investigational product(s). A re challenge was positive. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject. The event followed a known response pattern to the investigational product(s).

- **Probably related**
  High degree of certainty about the relationship between the event and investigational product(s) application.
  The event followed a reasonable temporal sequence from the time of the investigational product(s) application and improves upon stopping the dose of the investigational product(s). The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject.

- **Possibly related**
  Unlikely but cannot rule out with certainty the relationship between the event and investigational product(s) application.
  The event may follow a reasonable temporal sequence from the time of the investigational product(s) application. The event may have been produced by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.

- Unlikely related (doubtful)
  Clinical event has an unlikely relationship with the investigational product(s) application.
  There is no reasonable temporal association between the investigational product(s) and the suspected event and the event could have been reasonably produced by the subject's clinical state or other modes of therapy administered to the subject.

- Unrelated (not linked)
  Clinical event is clearly not due to investigational product(s) application.
  There is no reasonable temporal relationship between the investigational product(s) application and the suspected event (e.g., event occurs before investigational product(s) application) or no reasonable causality, such as an accident, which cannot remotely be related to study participation (injuries sustained in a car accident).

2.6.3.2.3 *Severity*

The Dermatologist Investigator assessed the severity of each AE according to the following definitions:

Slight

Subject is aware (fully or partly) of the sign or symptom, but it is easily tolerated and does not interfere at all with the subject's daily activity.

Mild

Subject is aware of the sign or symptom, but it is rather well tolerated and does not interfere with the subject's daily activity.

Moderate

Event causes discomfort enough to interfere with the subject's usual activities.

Severe

Incapacitating; subject is unable to perform usual activity.

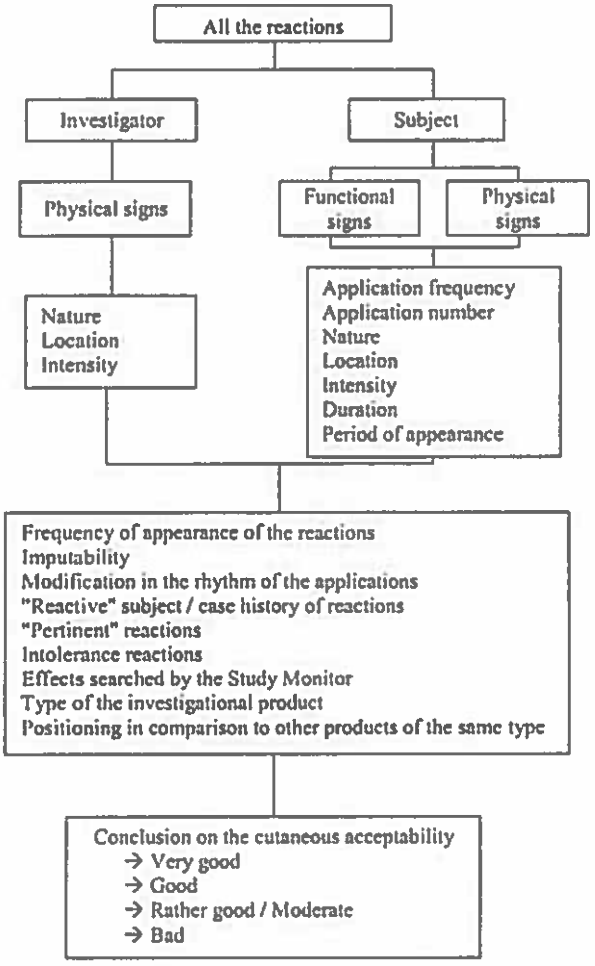
2.6.3.2.4 *Serious Adverse Events*

A serious adverse event (SAE) is defined as any adverse event, regardless of cause or relationship to the investigational product(s), which:

- Resulted in death.
- Was life-threatening (i.e., an event which, in the view of the Dermatologist Investigator, placed the subject at immediate risk of death from the reaction as it occurred; it did not refer to an event which hypothetically might have caused death if it were more severe).
- Required hospitalisation or prolonged hospitalisation.
- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly.
- Also considered an SAE is any other important medical event that jeopardised the subject or required intervention to prevent one of the outcomes listed in this definition above.

2.7. DATA ANALYSIS AND INTERPRETATION OF THE RESULTS

The results obtained were collected, analysed and interpreted by the Dermatologist Investigator, based on the normal conditions of use and the effects searched by the Sponsor, according to the following schematic drawing.



2.8. REGULATION, CONFIDENTIALITY AND LEGAL FORMALITIES

2.8.1. Regulations

The study was performed in agreement with the most recent recommendations of the World Medical Association (Declaration of Helsinki - 1964, and last amendment in force).

This study being carried out on cosmetic product(s) and being "non interventional", was not directly subjected to the application field of the French law of 20 December 1988 relative to the protection of people undergoing biomedical research (Huriet-Serusclat law) and its successive modifications of which the last one in the law n° 2004-806, dated 9 August 2004 - JORF of 11 August 2004 (included in the public health code at articles L1221 and following and decree n° 2006-447 of 26 April 2006).

However, this study was carried out in the spirit of this/the French modified Huriet law (law of 20 December 1988 relative to the protection of people undergoing biomedical research and its successive modifications of which the last one in the law n° 2004-806, dated 9 August 2004 - JORF of II August 2004, included in the public health code at articles L1221 and following and decree n° 2006-447 of26 April 2006), except for the information to the French National Card Index for people undergoing biomedical research, for the advice of the "Comite de Protection des Personnes" and the submission to competent authorities, which were not required.

2.8.2. Confidentiality

Any information regarding the health condition of the subjects and the results of the clinical examinations, performed before the start of treatment, for their recruitment, their selection and inclusion, were submitted to the rules of the medical secrecy according to Article 226-13 and following of the French Penal Code and to the Code of medical deontology (Decree n° 95-1000, dated 6 September 1995): in no case this information was given to the Sponsor with their identity.
To ensure preservation of the subjects' anonymity, they were identified by a code number using 5 letters (and 2 numbers if necessary when the letter code is already given to another subject), corresponding to the first 3 letters of their name, then the first 2 letters of their first name, and for the study, by a number corresponding to their inclusion order in the study.
At the end of the study, the page named "Subject Identification Form", in which the name and address ofthe subject were mentioned, was taken from the case report form and destroyed.
Should the raw data be sent to the Sponsor, the confidential data of the informed consent form, as well as of the information sheet, were masked.
The Dermatologist Investigator/Institution should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority(ies).
The Monitor(s), the Auditor(s), the IRB/IEC, and the Regulatory Authority(ies) are granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations (law n° 78-17 dated 6 January 1978, relative to data processing, files and freedom, updated by the law n° 2004-806 dated 6 August 2004 regarding the protection of people for the declaration to the C.N.I.L.) and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.

2.8.3. Legal formalities

2.8.3.1. Insurance of I.E.C.

I.E.C. benefits of an insurance to guarantee its civil liability vis-a-vis the subjects for studies

2.8.3.2. Insurance of the Sponsor

The Sponsor suscribed an insurance to guarantee its civil liability vis-a-vis the subjects.

2.8.3.3. Information sheet and informed consent form

An information sheet was given to each subject, in order to inform him/her, in particular of:
- the aim of the research, its methodology and its duration;
- the possible benefits, the constraints linked to the study and the foreseeable risks, even in case of stop of the research before its end, the modes of application ofthe investigational product(s);
- the non-inclusion period, the amount of the compensation, the possibility for him/herself to check the exactitude of the data contained in his/her medical file and their subsequent destruction.

Prior to a subject's participation in a study:
- The subject dated and signed the information sheet and the informed consent form, with full knowledge of the facts. The information sheet and a copy of the signed and dated informed consent form was kept by the subject.
-The Dermatologist Investigator dated and signed the informed consent form.

2.8.3.4. Data recording and archiving

Raw data were defined as original records and certified copies of original records of clinical / instrumental findings and observations (hand-written data, printing tickets, pictures, digital recordings, samples...) directly input in the case report form (constituted, paginated and stapled before the stmi of the study) or in another specific software / folder / file. Raw data are then synthesised in compilation documents, which are mainly informatic files and enable either direct analysis of the data, or transfer to a more specific software (video/image analysis, statistical analysis...). If corrections of the raw data or of the compilation were required, the person in charge of the correction should state the reason, date and sign, according to the investigator's SOP (the original entry must remain legible).

All raw data (case report forms, questionnaires if any), as well as the original documents of the compilation, of the final protocol (amendments if any), of the final report (all different versions and/or amendments if any) and ofthe statistical analysis if any, are kept in the archives for 10 years at the following addresses:

For the 2 to 6 months following despatch of report:
I.E.C., 88, boulevard des Belges, 69006 Lyon- France
For the following years: in the premises of ARCHIV'ALPHA
Head office: 9, rue Edmond Poillot- 28000 Chartres- France.

Once this period is over, the Sponsor will be contacted regarding its archives. No archive destroying will be done without the written and signed agreement from the Sponsor.

3. RESULTS

3.1. PROTOCOL COMPLIANCE

- The mean amount of investigational product applied during the study by the whole panel, with individual data for each subject, are reported in Table I in appendix. Taking into account the individual data, it was not necessary to exclude subject from the results analysis.

- 19 subjects presented with a deviation to protocol concernmg application number and/or application frequency (see Table II in appendix).

- Analysis of the results was carried out on 48 valid cases instead of the 50 as stated in the protocol.

These deviations did not affect, in a notable way, the quality or the interpretation of the results obtained.

3.2. SUBJECTS

Number of subjects recruited	74
Number of subjects who came to I.E.C.	57
Number of subjects included by the Dermatologist Investigator	50
Number of subjects discontinued from the study: -Non related adverse event - Non related serious adverse event - Related adverse event - Related serious adverse event -Concomitant treatment(s) incompatible with the study - Consent withdrawal by the subject - Lost to follow up - Emergence of a non- inclusion criterion - Decision of the Dermatologist Investigator -Violation of the protocol	2 1 (n° 44) 0 0 0 0 0 1 (n° 28) 0 0 0
Number of subjects for the analysis of the results	48

The physical characteristics of the subjects are summarized in the following table (see details by subject in table III in appendix):

Subjects		Face skin nature		Sensitivity		Healthy subjects with history of atopy
Number	:48	Normal	: 2 (4 %)	Face skin	: 25 (52%)	3 (6 %)
Females	:48 (100%)	Mixed Oily	: 8 (17 %)			
Males	: 0 (0 %)	Oily	:1 (2 %)			
Mean age	: 57.6	Mixed Dry	:15(31%)			
Age min	:46	Dry	: 21 (44 %)			
Age max	: 65	Very Dry	:1 (2 %)			

All these subjects presented with cutaneous slackening problems on the face as well as wrinkles and fine lines on the eye contours.

The dates of clinical examinations as well as the dates of first and last applications are detailed in Table IV in appendix I.

3.3. OBSERVATIONS AND CLINICAL EXAMINATIONS

3.3.1. Appraisal of the cutaneous (and ocular) acceptability of the investigational product

(see table V in appendix)

3.3.1.1. By the Dermatologist Investigator

After the 4 weeks of application of the investigational product, the Dermatologist Investigator did not observe any physical sign linked to its use in the 48 subjects examined.

3.3.1.2. By the Subject

7 subjects indicated having felt and/or observed, during the study, the following clinical signs:

Subject no	Nature	Location	Intensity	Duration	Period of appearance	Emergence after application
01 (s) very dry skin	prickling	whole face	slight	a few seconds	D0	a few minutes
					D1	
	tightness			a few minutes	D2	
					D3	
		forehead	very slight	a few seconds	D4	
		whole face			D5 and D6	
18 (s) dry skin	prickling	nose wings	very slight	a few seconds	D1 to D25	a few minutes
21 # p	eye watering	Right eye	moderate	a few minutes	D0	a few minutes
			Marked		D1 to D27	
25 (s) P mixed dry skin	prickling	cheeks / cheekbones	very slight	a few hours	D0 and D1	in the morning
	redness	chin				
	palpebral swelling	both eyes	slight			
	prickling	cheeks / cheekbones	very slight	a few seconds	D2	
	redness	cheeks / cheekbones				
	palpebral swelling	both eyes		a few hours	D2 to D4	

(s) : "sensitive" face skin
 # : case history of reactions linked to cosmetic products
P : reaction considered as "pertinent".

Subject no	Nature	Location	Intensity	Duration	Period of appearance	Emergence after application
27 (s) # mixed oily skin	prickling	cheeks / cheekbones	very slight	a few seconds	D1 to D6	immediately
29 mixed dry skin	prickling	eye contours nose wings	slight very slight slight	a few seconds	D1to D3 D4 and D5 D66	immediately
31 mixed dry skin	burning sensation	eye contours and both eyes eye contours	very slight	a few seconds	D1 D2, D3, D11 and D12	immediately
	"small pimples"	cheeks / cheekbones		2 days	D6 and D7	a few hours

(s) : "sensitive" face skin
 # : case history of reactions linked to cosmetic products

- Cutaneous signs felt and/or observed:
  . no **88%**

- Ocular signs felt and/or observed:
  . no **94%**

- Best tolerated product:
  . usual product 27% (4/15•)
  . no difference 67% (10/15•)
  . investigational product 7% (1/15•)

•regular users of this type of product.

3.3.2. Investigational product- related adverse events

(see table VI in appendix)

During the study, none of the subjects presented with any adverse event linked to the investigational product.

3.3.3. Positioning of the investigational product (acceptability), in comparison to products of the same type tested by I.E.C.

The synthesis of the results obtained from the I.E.C. Database, for all the in-use tests performed with products of the same type, is presented in the table hereunder.

Conclusion on the investigational product	% of products concerned	Global% of reactions	Nature of reactions(%)
Very good acceptability	11%	0%	Discomfort : 0% Irritation : 0% Acneiform : 0% Allergy: 0% Others: 0%
Good acceptability	76%	20%	Discomfort : 11% Irritation : 4% Acneiform : 2% Allergy: 0% Others: 3%
Rather good / Moderate acceptability	3%	52%	Discomfort: 39% Irritation : 4% Acneiform : 4% Allergy: 0% Others: 5%
Bad acceptability	10%	38%	Discomfort : 20% Irritation : 8% Acneiform : 0% Allergy: 0% Others: 10%

N.B.: statistical data obtained fi'om 1997 to 2007, on about 6750 products tested by I.E.C., of which 379 anti-wrinkles/eye contour products.

4. DISCUSSION AND CONCLUSION

Analysis of the results obtained revealed a very good acceptability ofthe investigational product in 41 out of the 48 subjects who took part in the whole study.

6 out of the 7 other subjects (with a "sensitive" or with a dry tendency skin) indicated having presented with discomfort (prickling in particular), associated in one of them with a redness, which intensity (very slight to slight), duration (a few seconds or minutes for the majority) and frequency of appearance (after a few applications of the beginning of the study only for 5 subjects) are rather frequently encountered with this type of investigational product (with an anti-wrinkle/anti-ageing aim) studied under these conditions.

2 subjects (of whom one previously cited) indicated having presented with an eye watering during the whole study or a slight palpebral swelling in the morning following the first few applications. These phenomena are sometimes encountered with anti-wrinkle products studied under these conditions (insisting on the eye contours).

One of these subjects also indicated having observed a few "small pimples" during 2 days of the 1st week of the study. This isolated and liminal reaction, which imputability to the investigational product seems doubtful, remains without any particular significance.

It should be noted that no abnormal clinical sign was noted, by the Dermatologist Investigator, after the 4 weeks of use.

The synthesis of the reactions noted during the study is shown in the table below (in % of the subjects questioned):

	Frequency of reaction
Reactions noted during the whole study	15% (7/48)
Reactions observed by the Dermatologist Investigator	0% (0/48)
Reactions reported by the subjects *. discomfort only* *. irritation (+ discomfort and palpebral swelling)* *. "small pimples" +discomfort*	15% (7/48) *8% (4/48)* *4% (2/48)* *2% (1/48)*
Reactions that needed to modify significantly the frequency or to stop the applications	0% (0/48)
Reactions which can be considered as "pertinent"*	4% (2/48)
Reactions considered as adverse events linked to the investigational product	0% (0/48)
Reactions considered as serious adverse events linked to the investigational product	0% (0/48)

* *conclusion based on the analysis of the nature of the duration of the intensity, of the frequency and of the appearing time of the reactions.*

The CUTANEOUS ACCEPTABILITY of the investigational product designated as " ROSA CANINA FLOWER EXTRACT 0.005% Night cream - batch n° F1C1 16/05/2008)" can be judged, on the whole, GOOD, after repeated applications, under normal conditions of use, once a day for 4 consecutive weeks, to the face (insisting on the eyes contours) and neck skin, by 48 female adult subjects, from 46 to 65 years old, of all skin types, presenting with cutaneous slackening problems on the face as well as wrinkles and fine lines on the eye contours and of whom 52% with a "sensitive" skin.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 24, 2016

SUBJECT: Comments on the Draft Report: Safety Assessment of *Rosa canina*-derived Ingredients as Used in Cosmetics (prepared for the March 31-April 1, 2016 CIR Expert Panel meeting)

Key Issue

Rosa Canina Flower Oil (an essential oil) was included in the concentration of use survey (no uses reported). Is there a reason why it is not included in the report?

Search Strategy - Searching only PubMed is not a sufficient search strategy for a plant-derived ingredient. Publications on the composition of plants are often not included in PubMed. A simple Google search such as "what is the composition of Rosa canina leaf" will often identify useful information such as the two attached papers:

Ghazghazi H, Miguel MG, Hasnaoui, et al. 2010. Phenols, essential oils and carotenoids of *Rosa canina* from Tunisia and their antioxidant activities. *African Journal of Biotechnology* 9(18): 2709-2716.

Hosni K, Kerkenni A, Medfei W. 2010. Volatile oil constituents of *Rosa canina* L.: Quality as affected by the distillation method. *Organic Chemistry International*, Article 621967.

Additional Considerations

Composition/Impurities, Rosa Canina Fruit - In the description of the percentages of minerals in rose hip tea (reference 13), it is not clear what the percentages represent. The percentage of the mineral that was originally found in the dried rose hips?

Cosmetic Use, Summary - The maximum use concentrations need to be updated with the information provided on March 2, 2016. The concentration of 7% Rosa Canina Fruit Extract in face products was an error and is no longer the maximum use concentration reported.

Table 3 - The title of Table 3 indicates that it includes an acetone extract, but only "tea" is shown in the table. Where is the information about the acetone extract?