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Safety Assessment of Hypericum Perforatum-derived Ingredients as Used in Cosmetics

CIR EXPERT PANEL MEETING

SEPTEMBER 10-11, 2012

Cosmetic Ingredient Review
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February 22, 2013

MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Subject: Draft Final Amended Report for *Hypericum perforatum*-derived ingredients as used in cosmetics

In December the Panel issued, for public comment, a tentative amended safety assessment with a safe in the present practices of use conclusion. The Panel had examined new data provided for *Hypericum perforatum*-derived ingredients (the common name for this plant is St. John's wort) and found the data sufficient to find these ingredients to be safe as used. The Panel also determined that the now available data were adequate to address the safety of three additional *Hypericum perforatum*-derived ingredients.

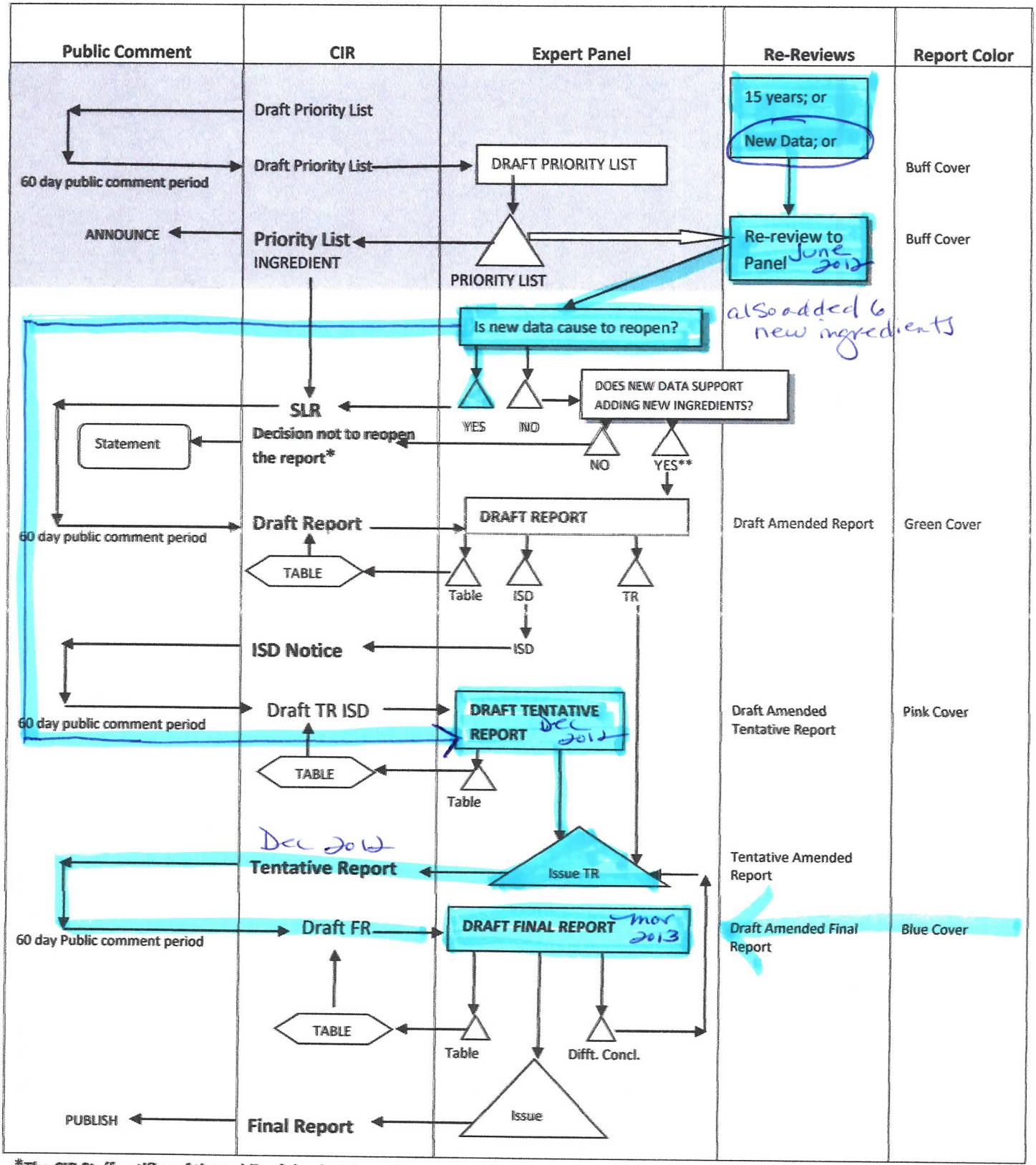
Comments were submitted by the Personal Care Products Council's CIR Science and Support Committee along with use concentration data. Council comments have been addressed and all new data incorporated.

The Panel should review the draft final amended report and confirm that the discussion and the conclusion reflect the Panel's thinking. Then the Panel is to issue a final amended report.

1101 17th St., NW, Suite 412 Washington, DC 20036-4702
Phone 202.331.0651 FAX 202.331.0088 http://www.cir-safety.org

Hypericum Perforatum Ingredients – Mar 2013

SAFETY ASSESSMENT FLOW CHART



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision

▭ Document for Panel Review

⇨ Option for Re-review

History of *Hypericum perforatum* (St. John's Wort)– Derived Ingredients

2001 - CIR Expert Panel published its review of the safety of Hypericum Perforatum Extract and Hypericum Perforatum Oil, concluding that the available data were insufficient to support the safety of these 2 ingredients and identifying a list of 7 data needs.

- Current concentration of use data;
- Function in cosmetics;
- Photosensitization and phototoxicity data using visible light (550-610 nm; 5-10 J);
- Gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures;
- Dermal reproductive/developmental toxicity data;
- Skin irritation/sensitization data in humans on Hypericum perforatum oil; and
- Ocular irritation data, if available.

June, 2012 – The Panel examined the summaries of new data submitted by industry to address the data needs. The Panel decided to reopen the safety assessment to examine the data possibly change the conclusion.

December, 2012 - The Panel found that there is enough new data to find *H. perforatum* safe in the present practices of use. The Panel issued a Tentative Amended Report.

March, 2013 – The Panel examines the Draft Amended Report and issues a Final Amended Report.

St. John's Wort Transcripts
December, 2012
DAY 1

Dr. Belsito's Team

MR. ANDERSEN: A little St. John's Wort will help that.

DR. BELSITO: Yeah, right. The next one is hypericum perforatum-derived ingredients. So, we looked at some new data in June and agreed that it likely addressed some of the insufficiencies in 2001 and we're going to go ahead and open this up and add in all the hypericum people that were out there. So, a total of eight ingredients.

And so, here we are. So, we have some issues here. Hypericum is a photosensitizer. Quercetin is an impurity and we'll probably want to eventually as we get around to dealing with this deal with it in some way.

Sensitization and irritation at concentration of use -- I guess, here's where I ran into problems. And I had emailed Alan at one point about this, because it's the old issue where these are not 100 percent. They're available as 2 to 25 percent of active ingredient, and then are the percentages -- Carol, giving us .2 of 2 percent, or is it .2 percent?

DR. EISENMANN: They are supposed to be giving me the concentration of named ingredients. So it's not just supposed to be the hypericum perforatum part and not the solvent part.

DR. BELSITO: Okay, so when -- let me --

DR. EISENMANN: That's what I tell them to give me.

DR. BELSITO: -- confirm this. When they say that they're using .2 percent hypericum it's .2 percent hypericum that's in there and not .2 percent of a 2 percent extract.

DR. EISENMANN: That's what they're supposed to be telling me.

DR. BELSITO: That's what they're supposed to.

DR. EISENMANN: Yes.

DR. BELSITO: So this is actual concentration of the actual ingredient.

DR. EISENMANN: Yes.

DR. BELSITO: Thank you. So, I don't know that we have sensitization and irritation data to cover the maximum use. We have .03 as the highest, right?

MS. BRESLAWEC: Dr. Belsito, the new use information had a maximum concentration of .07 percent which is down from the 5 percent maximum listed in the draft report.

DR. BELSITO: Okay.

DR. LIEBLER: Is that Wave 2?

MS. BRESLAWEC: Yes, Wave 2.

DR. BELSITO: How did I miss Wave 2?

DR. LIEBLER: I missed part of the wave.

DR. SNYDER: I didn't miss that part of the wave.

DR. BELSITO: Well, Paul, you're exonerated there. Okay, so .007 is --

MS. BRESLAWEC: .07.

DR. BELSITO: .07 is the max. And the max -- and clearly hypericum is not going to be present in levels of 1 percent in an extract of .07 of hypericum as a whole. And a 1.1 percent extract of hypericum was not photosensitizing, and that's in there.

Yeah, I've got Wave 2 printed out, I just failed to note it in my notes because I did the botanicals first and then I had to go back and re-look at them when I got Wave 2 with concentrations, and just missed that.

So, I -- you know --

MR. ANDERSEN: Don, you've also got photosensitization data in which the extract was tested at 1.1 percent.

DR. BELSITO: No, no, no.

MR. ANDERSEN: It was not photosensitizing, so --

DR. BELSITO: Right, yeah. I mean.

MR. ANDERSEN: It's also not sensitizing.

DR. BELSITO: Right, yeah. No. I'm happy with that.

And I guess probably the likelihood that any other botanical would have sufficient amounts of hypericum that it would throw it over when mixed together would be small. In the past, when we're concerned about, I think it was thujone we mentioned that when mixed with other botanicals that could contain this, they should remain under a certain limit. So if we're concerned about quercetin, we should say that.

I also queried Ann-Marie Appie about this and if in the case of hypericum I don't think it's important because it really doesn't contain a lot of essential oils. But as we look at botanicals, some of which will contain essential oils like eugenol and IC-eugenol, apparently the IFRA regulations on concentrations of use would pertain to total in a cosmetic ingredient, not just a fine fragrance -- assuming that the manufacturer was actually using it as a fragrance ingredient.

However, if they weren't using it as a fragrance ingredient -- if they were using it as an emollient or some other thing, a solvent, then even though it contained a fragrance material like eugenol it would not count, which I thought was sort of interesting.

And I wish there were some way that -- and that's an IFRA issue, I don't think it's a RIFM issue. But I just wanted to point that out to you that, you know -- and it's very funny because I just actually saw a product that contained lavender, lovengila, and it was listed as fragrance- free. I swear to god. And you smelled this thing and it quite clearly smelled like lavender but obviously the lovengila was added by the manufacturer for purposes other than the fact that it had an odor.

DR. LIEBLER: Maybe they meant no extra cost, so the fragrance part is free. (Laughter)

DR. BELSITO: But I just thought I'd point that out. So anyway, you know, yeah. Sure. Let's go ahead safe as used.

DR. LIEBLER: I think the hypericum content in the mixture is low enough that at the maximum use concentration for the mixture that hypericum content is way below the photosensitization level. So, I think we're okay there.

DR. BELSITO: Well, needs to be part of the discussion.

DR. LIEBLER: Correct.

DR. BELSITO: That 1 percent was not a photosensitizer, not a sensitizer of the hypericum.

DR. LIEBLER: Right, but.1 percent was.

DR. BELSITO: Yeah, and that, you know -- quercetin will be low, given the low concentration of use below threshold of toxicologic concern I think is how we phrased it. But when formulated with other botanicals that may contain quercetin, manufacturers should be aware of it to keep it as low as possible.

I don't know what else in the discussion. I mean there aren't, again, a lot of essential oils so I don't think that was an issue for this one.

MR. ANDERSEN: Well, I would expect we'd go through each of the previous data insufficiencies and now note that we have those data.

DR. BELSITO: Right.

MR. ANDERSEN: Just for the record.

DR. BELSITO: Okay.

MS. BECKER: In the Council comments they suggested that the callus culture extract is not appropriate here. It's got a different extraction method and doesn't -- it's not the same as the others, and they're suggesting that it be removed and we have no argument.

DR. BELSITO: That's sort of callous of them, though.

It's fine. It's okay, I don't care.

DR. LIEBLER: Dr. Belsito will be charged one time-out. (Laughter)

DR. BELSITO: I'm fine removing it. So, we're going to remove the callus extract. Safe as used, discussion, on photosensitization on hypericum but it's going to be low in the actual cosmetic product. Quercetin will be even lower, caution when combining with other botanicals that may contain quercetin, and address all the other data insufficiencies and how they work -- how they were satisfied for us.

Anything else?

DR. SNYDER: Page 4, that's not a carcinogenicity study, so --

DR. BELSITO: Pardon?

DR. SNYDER: That Page 4.
DR. BELSITO: Oh, I didn't realize (inaudible) -- Page 4.
DR. SNYDER: Page 4 under "Carcinogenicity". That's not a carcinogenicity study, so we need to --
DR. BELSITO: Panel Book 12, Page 4?
DR. SNYDER: It's actually -- yeah. Panel Book would be correct. Oh, I'm sorry. Page 6.
DR. BELSITO: Panel Book 14 Page 6.
DR. SNYDER: Yes, correct.
MR. ANDERSEN: So, what is it?
DR. BELSITO: It's an anti-carcinogenicity study.
DR. SNYDER: No, it's just a modulation of a pathway, a PKC pathway. It deals with anti-inflammatory, anti-tumor. It's not really a carcinogenicity study.
DR. LIEBLER: I don't think it belongs there at all.
DR. BELSITO: So what would you do? Pharmacologic effects, or?
DR. SNYDER: That would be fine.
MS. BECKER: Okay.
DR. SNYDER: Or, just under other studies, something.
MR. ANDERSEN: We're trying to remove that heading.
DR. BELSITO: What, "Other"?
MR. ANDERSEN: Yes.
DR. BELSITO: Pharmacologic effects.
MR. ANDERSEN: Yeah, that sounds much better.
DR. BELSITO: Anything else, Paul?
DR. SNYDER: No.
DR. BELSITO: Okay. Any other comments? Okie-doke.

Dr. Marks' Team

DR. MARKS: Okay. Let's go ahead and start the afternoon. And I believe we're up to the ingredients safety assessment of hypericum perforatum, otherwise St. John's Wort. And in 2001 an insufficient data conclusion was reached and in June of this year we reopened that. And had a number of insufficient data needs which many of them are met and let's just go down and make sure that -- where we're at at this point.

So, if you look on panel book page 2, there's bulleted needs and let's just go down there and we have the concentration, current concentration of use data. We have a table now with that. Functions in cosmetics, do we have that?

MS. BECKER: Yes.

DR. MARKS: Okay. I saw the list in there. Photosensitization of phototoxicity, that was still an issue for me since --

DR. SHANK: Me, too.

DR. MARKS: On page, panel book page 15, you see under hypericum and other constituents that there's clearly photosensitization and then there was even severe prolonged response with ear swelling. So, how do we get around the issue of phototoxicity? And this is being used at this point. There are uses as in page 27 table 4.

DR. SHANK: Well, we have some data on phototox but not photosensitization. And most of the studies are in UVA, UVB not visible. So, I think we still need photosensitization in the physical light.

DR. MARKS: Tom, Ron? Is that -- do you feel the same? Most of the photosensitization when you look at it occurs in the UVA range but when you do photo patch testing you're actually irradiating mainly with UVA. So, I'm not so much, I don't know if --

DR. SLAGA: Well, it's that one study in (inaudible) for photosensitization which resulted, there's a minimal after radiation but --

DR. MARKS: Right. That's right at the top of the page?

DR. SLAGA: -- swollen at all concentrations. That doesn't sound minimal to me.

DR. MARKS: So, would we want -- does it matter, in this case would you want to see it in humans? And is this -- one's an extract the other is the oil and the other one's constituents which I'm not sure what the constituents are there. Do we know? That's again on page 15.

DR. SHANK: Hypericin is the one they tested.

DR. MARKS: Yeah.

MS. BECKER: -- hypericin.

DR. MARKS: So, photosensitization?

MR. ANDERSEN: Jim, you always have the option since hypericin is a constituent of limiting the concentration to a level that wouldn't cause photosensitization. If you didn't exactly know what that level was, and I don't think these data are going to provide it, you could say and limit the hypericin to a level shown to not be photosensitizing. But the monkey back on the suppliers' back.

DR. MARK: Rons, Tom? Do you like that in the conclusion?

DR. SHANK: If hypericin is the only photosensitizing agent that would work. But do we know that?

MR. ANDERSEN: Whatever is in the oil, which is likely to be one group of things, and then the extract I would think would be another group of things, neither of those were photosensitizers. It's only when we've got purified hypericin that you got a positive result.

MR. ANSELL: Yeah, there's photosensitization on the extract using tape strip skin.

DR. SHANK: Was that invisible light?

MR. ANSELL: 320-400.

DR. SHANK: Okay, so not really.

MR. ANDERSEN: That gets into a discussion of what's visible versus; the 390-400 is blue light. You can see just barely that it's blue. Or violet.

DR. HILL: So the 98 insufficiency specifically said 550-610 nanometer. Do we know why that range was set? I still hadn't been able to sort that out.

MR. ANSELL: There's also photosensitization on the oil.

MR. ANDERSEN: Yeah. And that went up to --

MR. ANSELL: 290-2500 nanometer.

MR. ANDERSEN: Well, that's the entire spectrum.

MR. ANSELL: Yeah and then the minimal photosensitization in balb c 3 mice, balb c mice --

MS. BECKER: Okay, I'm looking at the --

MR. ANSELL: And that goes up to --

MS. BECKER: Sorry.

MR. ANSELL: -- just under 600.

MR. ANDERSEN: Got the original report here, too.

MS. BECKER: Yeah. I don't see anything in the discussion that said why you picked that range.

DR. SLAGA: Yeah. Why would they pick that range? I had a question about that but that doesn't really make sense.

DR. MARKS: They would be us, is that correct?

MS. BECKER: Yes.

DR. HILL: Okay. I can answer that question. On page -- well I've got the original report brought with me from last time and it says h. perforatum is a primary photosensitizer in animals because of the photo dynamic pigment hypericin. Hypericin causes photo activated damage by absorbing visible light in the 550-610 nanometer range. Maximum at 585. And so, that's where that -- it's written in the photosensitization section of the original report.

MR. ANDERSEN: So, focus was on that one chemical?

DR. HILL: It was indeed.

MS. BECKER: Right. There we go. Found it.

DR. HILL: And the concern seems to be oxidative damage to capillary walls.

DR. MARKS: So, it's an interesting suggestion. You made, Alan, is can we have the level of hypericin below a photosensitizing phototoxic level or --

MR. ANSELL: Well, since the commercial products look like there's six separate studies perhaps it would be better to point out that when hypericin is isolated it may be sensitizing. Cause we seem to have human volunteer data, oral data which is hard.

DR. MARKS: Yeah. Where's the human data?

MR. ANSELL: Well, I'm looking at the summary on 34.

DR. MARKS: Yeah, okay. Eight subjects, right, that's with the oil.

MR. ANSELL: And then 48 human volunteers after an oral study but --

DR. MARKS: Yeah. Do we have an idea of how much, because in the hypericin photosensitization studies they were using concentrations up to one to one point five percent? I presume we don't know how much hypericin are in these extract?

MR. ANSELL: Yeah, we do.

MS. BECKER: Yeah, we do. Page 22 of panel book 22.

MR. ANDERSEN: What is it?

MS. BECKER: It's fourteen point five parts per million up to 18,000 parts per million depending on plant part.

MR. ANSELL: Yeah, Carol calculated that at the maximum use concentration the hypericin concentration would be two, one, two, two ten-thousandths of a percent.

DR. SHANK: Okay.

MR. ANSELL: 0002.

DR. SHANK: And it wasn't photosensitizing at point one percent?

MS. BECKER: Okay?

DR. MARKS: Yeah.

MS. BECKER: All right. Sounds like a fun paragraph in the discussion..

DR. MARKS: So, we'll put that -- so, now we've met that data need that we're not concerned about the hypericin photosensitizing phototoxic effects since the concentration is so low on the final. So, that would be in the discussion.

Gross pathology, histopathology in the skin, sounds like allergist discussing. Is that still an issue?

DR. SHANK: I had no -- no, I have no --

DR. MARKS: Okay. Reproductive developmental toxicity?

DR. SHANK: We have it.

DR. MARKS: Skin irritation sensitization?

DR. HILL: On the oil specifically is what's --

DR. MARKS: Yeah, the oil and now we get into like with the previous botanical. Do we want to include the oil with these other extracts? Which presumably are water extracts, is that correct? Let's see. How do they manufacture this?

MS. BECKER: See what we've got. Ethanol extract.

DR. MARKS: Oh, ethanol.

MS. BECKER: It's like all the other extracts. It could be any of the solid ones.

DR. MARKS: Yeah. So, do we want to eliminate the oil?

DR. HILL: To me that would make very good sense but that's just my opinion.

DR. MARKS: If we do, that eliminates that.

DR. HILL: It does indeed.

MR. ANDERSEN: Well, you've got the phototox study on the oil.

DR. MARKS: Uh-huh.

MR. ANDERSEN: Which, by definition says the oil itself wasn't a photosensitizer.

DR. SLAGA: Right.

DR. MARKS: Yeah, that's just --

MR. ANDERSEN: When you added light it didn't sensitize so --

DR. MARKS: Eight subjects, is that enough?

MR. ANDERSEN: Well, it's not a lot of one that's for sure.

DR. MARKS: What about the actual idea of including the oil with these other extracts?

DR. SHANK: I think it's all right because --

DR. MARKS: Okay.

DR. HILL: But there is no toxicology other than that phototox? I guess my only

comfort would be that if the concentrations of use are -- where's that? They're really low, aren't they?

DR. SHANK: Yes.

MS. BECKER: Yes. They're incredibly low.

DR. HILL: Yeah, that's -- point zero zero zero zero five percent.

MR. ANDERSEN: It's hard to keep track of all those zeros.

MS. BECKER: Yes.

DR. HILL: That's pretty low..

MR. ANDERSEN: I think the intent here, because the original safety assessment addressed the extract and the oil, I think that you can't bucket --

DR. HILL: Want to keep it --

DR. MARKS: Okay. Now, I still have, there's not much on sensitization other than these phototoxic which are small numbers. There's not a RIPT. There's no local lymph node assay is there? Let me see.

MS. BECKER: There's --

DR. SHANK: We have naked photosensitization. Doesn't that cover it?

DR. HILL: Interesting.

MS. BECKER: We've got dermal repro and developmental. We've got one human irritation test.

DR. MARKS: I guess if I put a hair dye on eight subjects and didn't see a reaction I would say that's not a sensitizer? Well, we'll see what Don says. I still would like to see -- I don't think it is a sensitizer.

MR. ANSELL: On the oil or --

MS. BECKER: On the oil.

DR. MARKS: Anything. Do we have any big numbers on any animal? Let me see here.

MR. ANSELL: We've got 16 humans topical. We have oral, whatever.

DR. MARKS: Yeah, oral.

MR. ANSELL: And dermal, mouse dermal coupled with the guinea pig 10 animals.

DR. MARKS: Okay. So, the backs of guinea pigs with tape supply. Was that at -- but was an adjuvant. There was no adjuvant added to that as guinea pigs. It wasn't a maximization?

MR. ANSELL: It says it was.

DR. MARKS: Does it?

MR. ANSELL: Well, I'm looking at the summary. An unpublished guinea pig maximization study, two sites.

DR. MARKS: Oh, okay.

MR. ANSELL: One point one percent extract at ten percent dilution for reduction and point one and one diluted in challenge. No sensitization. One site at induction given UVA.

DR. HILL: So, I'm looking at the -- maybe I'm looking at the wrong one. I'm looking at the original report and there's a section on sensitization and it has, not in humans but it has hypericum perforatum extract and let's see, in guinea pigs. Bueller test and then they have the oral tested maximization test in guinea pigs.

DR. MARKS: And that's, okay. And that was negative.

DR. HILL: Yes.

DR. MARKS: Okay.

DR. HILL: But I don't know why it wasn't captured in the --

DR. MARKS: In this.

MS. BECKER: We don't put the old data in the new reports.

DR. HILL: Okay.

DR. SLAGA: But the old report had genotoxicity for some -- this report doesn't have it. So, that's not a concern.

MR. ANSELL: But your summary as it includes the data includes all the data not just the new data or?

MS. BECKER: At the beginning of the report I got a summary of the old data and

then the summary has a summary of the new data.

MR. ANSELL: But the letter you sent on page 34 was just the new data that was submitted?

MS. BECKER: Right.

DR. HILL: Okay. Yes and it just has that one sentence in the original safety assessment so --

DR. MARKS: Okay. So, we have guinea pig.

DR. HILL: Guinea pig.

DR. MARKS: Okay. I think that's sufficient. There aren't a significant number of case reports that would raise a flag so --

DR. HILL: Concentration's really low.

DR. MARKS: Yeah. Concentrations are low so.

DR. SLAGA: Also, in the old report there was mixtures containing the extract and the oil were not irritants or --

DR. MARKS: Sensitizers, yeah. Okay. Looks like we've met all the needs, ocular irritation so, proceed with a safe?

DR. SLAGA: Okay.

DR. MARKS: And this would be a draft final amended report.

MS. BECKER: In the Counsel comments, they suggested that we should take out the callus culture extract. It's collected and processed differently than the rest of it and with probably does that really belong here?

DR. SHANK: Okay.

DR. MARKS: Okay.

DR. HILL: There were no reported uses either, right?

MS. BECKER: Right.

DR. HILL: Not that that matters but --

MR. ANDERSEN: Jim, since you're reporting on hypericum, this -- you should be approving a draft tentative or a tentative amended because it does need to go out for public comment. It's not a final.

DR. MARKS: Okay. Because what I have, the memo says this is a draft tentative amended. And so, it's --

MR. ANDERSEN: So, all your removing is draft.

DR. MARKS: Okay. Thank you. Any other comments? I'll move tomorrow that we issue a tentative amended. So, then once this goes out is it going to change from the draft final report?

MR. ANDERSEN: We take all of the editorial comments. Put them in. Remove the callus ingredient.

DR. MARKS: Right.

MR. ANDERSEN: So, it will be tweaked. But not changed.

DR. MARKS: So, a tentative amended report with a conclusion of safe. And with removing the callus culture extract.

MS. BECKER: Right.

DR. MARKS: The hypericum. Okay. Any other comments?

DAY TWO

DR. BERGFELD: …Moving ahead to Dr. Marks' presentation on hypericum perforatum.

DR. MARKS: In June of this year the Panel decided to reopen the safety assessment of hypericum perforatum or St. John's wort. There were a number of insufficient data needs that were outlined in 2001's report. Our team felt that these were met and that we could move forward with a tentative amended report with a conclusion of safe. There were add-ons that were suggested to the original ingredient, and we felt that all the add-ons, other than the callus culture extract, could be included in this reopened document. So I move that we issue a tentative amended report with a safe conclusion and with the added ingredients except for callus culture extract.

DR. BELSITO: Second.

DR. BERGFELD: Any other comments? Don?

DR. BELSITO: Again in the discussion, I think we need to point out that some of these extracts contain hypericin, which is a photosensitizer, but it would be low and below the level of photosensitization. And quercetin, which we've noted can be a hepatotoxic, but, again, would be quite low, below the threshold of toxicological concern in a finished cosmetic product.

DR. MARKS: We concur.

DR. BERGFELD: Thank you. Any other comments? I'll call for the vote then. All those in favor? Thank you. Unanimous. Moving on to the next botanical, Dr. Belsito.

Amended Safety Assessment of Hypericum Perforatum-Derived Ingredients as Used in Cosmetics

Status:	Draft Amended Report for Panel Review
Release Date:	February 22, 2013
Panel Meeting Date:	March 18-19, 2013

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, 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 F. Alan Andersen, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

1101 17th Street, NW, Suite 412 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢ cirinfo@cir-safety.org

TABLE OF CONTENTS

ABSTRACT

This is an amended safety assessment of seven hypericum perforatum-derived ingredients as used in cosmetics. One common name for this plant is St. John's wort. These ingredients function in cosmetics as skin-conditioning agents – miscellaneous and antimicrobial agents. The Panel reviewed relevant animal and human data related to the *Hypericum perforatum*-derived preparations. The Panel concluded that hypericum perforatum-derived ingredients were safe as cosmetic ingredients in the practices of use and concentration as described in this safety assessment.

INTRODUCTION

This is a tentative amended safety assessment of cosmetic ingredients derived from *Hypericum perforatum* L. One common name for this plant is St. John's wort. These ingredients function in cosmetics as skin-conditioning agents – miscellaneous and antimicrobial agents (Table 1). The seven ingredients in this safety assessment are:

- hypericum perforatum extract
- hypericum perforatum flower extract
- hypericum perforatum flower/leaf extract
- hypericum perforatum flower/leaf/stem extract
- hypericum perforatum flower/twig extract
- hypericum perforatum leaf extract
- hypericum perforatum oil

In 2001, the Cosmetic Ingredient Review (CIR) published a safety assessment of hypericum perforatum extract and hypericum perforatum oil as used in cosmetics,[1] finding insufficient data to determine that these ingredients were safe for use in cosmetics. Additional data needs were identified:

- Current concentration of use data;
- Function in cosmetics;
- Photosensitization and phototoxicity data using visible light (550-610 nm; 5-10 J);
- Gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures;
- Dermal reproductive/developmental toxicity data;
- Skin irritation/sensitization data in humans on Hypericum perforatum oil; and
- Ocular irritation data, if available.

Additional data have been submitted and are summarized below along with new data discovered in the literature. Data on the major constituents of *H. perforatum* are also included.

Since the original report was published, the name of hypericum perforatum extract was changed to hypericum perforatum flower/leaf/stem extract.[2] Since then, another ingredient named hypericum perforatum extract, defined as an extract of the whole plant, has been added to the *International Cosmetic Ingredient Dictionary and Handbook*.[3]

Original Safety Assessment

This is a summary of the data in the original safety assessment.

Hypericum perforatum extract is an extract of the capsules, flowers, leaves, and stem heads of the hypericum, H. perforatum. In 1998, it was reported to the FDA that hypericum perforatum extract and hypericum perforatum oil were used in 64 and 11cosmetic formulations, respectively.[1] One manufacturer reported that hypericum perforatum extract is used at concentrations of ≤5% and it was reported by another supplier that a mixture of hypericum perforatum extract and propylene glycol is used at concentrations of 1% - 10%. In 1984, hypericum perforatum extract and hypericum perforatum oil were reported to be used at concentrations of ≤5% and unknown concentrations, respectively.

Using male subjects, a single oral administration of hypericum extract resulted in a nonlinear increase, with increasing dose in the amount of hypericin or pseudohypericin appearing in the plasma, and the increase was statistically significant for hypericin. With long-term dosing of hypericum extract, steady state occurred after 14 days. The polyphenol fraction of H. perforatum had immunostimulating activity on the mononuclear phagocyte system and cellular and humoral immunity, and the lipophilic portion had immunosuppressive activity on cellular and humoral immune responses.

The oral LD_{50} values for rats and mice of mixtures containing hypericum perforatum extract were >20 ml/kg. The minimum lethal SC dose of *H. perforatum* using guinea pigs was 0.1 mL. The i.p. LD_{50} values of the polyphenol, lipophile, and water soluble fractions of *H. perforatum* were 780, 4300, and 2800 mg/kg, respectively. Signs of toxicity were observed in Awasi sheep fed H. perforatum flowers (4 g/kg) for 14 days. In a chronic study in which Long-Evans rats were fed H. perforatum (5%), average daily weight gain was statistically significantly decreased as compared to control animals. Mixtures containing hypericum perforatum extract and hypericum perforatum oil were not irritants (up to 5%) or sensitizers (up to 5%) in animals. *H. perforatum* is a primary photosensitizer in animals because of the pigment hypericin, which causes photoactivated damage by absorbing visible light. A mixture containing hypericum perforatum oil, butylene glycol, and water was not phototoxic. Mixtures containing hypericum perforatum extract (0.5%) and hypericum perforatum oil (0.1%)

were non- to slightly irritating, respectively, in rabbit eyes.

In an Ames test, a tincture of hypericum had mutagenic effects at (20 mg/100 µL suspension), which the researchers attributed to flavonols. However, the origin of the plant and the mode of preparation of the tincture were considered to play a role in the mutagenic potential. In another Ames test, *H. perforatum* (10 µL) had mutagenic activity; in testing fractions of three extracts, the mutagenic potential was found exclusively in quercetin, and hypericin was not mutagenic. Hypericum extract (500 µL) and hypericin were not genotoxic in UDS assays using primary rat hepatocytes. Hypericum extract (4.00 µL/mg) was not mutagenic in a cell transformation assay using Syrian golden hamster embryo cells, and it was not genotoxic in a mouse fur spot test or in a chromosome aberration test.

A mixture of Hypericum Perforatum Oil, butylene glycol, and water was not irritating in clinical studies. In human testing, hypericum extract did not appear to be toxic, although some undesirable drug effects were observed.

CHEMISTRY

Definition

The definitions and functions of these *H. perforatum*-derived ingredients are provided in Table 1.

Constituents

Constituents of *H. perforatum* are listed in Table 2.

H. perforatum flower contains not less than 0.08% of total hypericins expressed as hypericin calculated with reference to the dried drug.[4-6] Constituents of *H. perforatum* include:

- Phloroglucinol derivatives: 0.2-4%, depending on the age of the herbal drug, mainly hyperforin and its homologue adhyperforin, furanohyperforin;
- Naphthodianthrone: 0.06-0.4%, mainly pseudohypericin and hypericin, protohypericin, protopseudohypericin, cyclopseudohypericin, skyrin derivatives. The amount of pseudohypericin is about 2-4 times higher than that of hypericin.
- Flavonoids: 2-4%, mainly glycosides of the flavonol quercetin: hyperoside, rutin, isoquercitrin, quercitrin; also biflavones (I3,II8-biapigenin, amentoflavone);
- Procyanidines: e.g. procyanidine B2, tannins with catechin skeletal (6-15%);
- Xanthones: in trace amounts;
- Essential oil: 0.1-0.25%; the essential oil of dried flowering tops contains as main compounds 2-methyloctane (16%) and α-pinene (10.6%). In the essential oil of leaves of Indian origin 58 components were identified, α-pinene (67%) being dominant; the other components included caryophyllene, geranyl acetate and nonane (each about 5%);
- Other constituents: include small amounts of chlorogenic acid and other caffeoylquinic and p-coumaroylquinic acids, and also free amino acids.

The variation of hypericins, hyperforin, and flavonoids of different commercial *H. perforatum* extracts are provided in Table 3.

In a batch of St. John's wort extract capsules, the label stated that they contained 300 mg of extract and 900 µg of hypericin.[7] Analysis found that the contents actually weighed 444 ± 20 mg and contained 840 ± 56 µg of hypericin and 11 ± 0.63 mg of hyperforin.

Method of Manufacture

It was reported that cosmetic grade hypericum perforatum flower/leaf/stem extract is mostly extracted from the dried plant, but may occasionally be from fresh material.[2] The extraction solvents include: water/propylene glycol; propylene glycol; 86% ethanol; 50% butylene glycol; water; sunflower oil; olive oil; caprylic/capric triglycerides; or glycerin. Solids in these extracts measure 0.1% - 5%. The hypericin content from an 86% ethanol (3% solids) extract of fresh plant materials was reported to be 60 – 65 µg/mL and the hyperforin content was 240 – 900 µg/mL.

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 4).[8] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group.[9]

Hypericum perforatum extract was reported to be used in 32 leave-on products (up to 0.01%), 3 rinse-off products (no use concentration reported), and 1 baby product (no use concentration reported).

Hypericum perforatum flower was reported to be used in 1 leave-on product; maximum concentration of use was reported to be 0.005% in face and neck creams, lotions and powders.

Hypericum perforatum flower/leaf/stem extract is reported to be used in 49 leave-on products (up to 0.07% in body

and hand creams, lotions and powders) and in 25 rinse-off products (up to 0.00004% in shampoos and rinses), mostly in skin care products. The VCRP reports that it is also used in 2 products that are diluted for bath (no use concentration reported). There is one reported use in baby lotions, powders and creams.

Hypericum perforatum oil is reported to be used in 13 leave-on products and in 4 rinse-off products. Use concentration was only reported for skin preparations up to 0.00005%.

There were no reported uses or concentration of use for:

- Hypericum perforatum flower/leaf extract,
- Hypericum perforatum flower/twig extract,
- Hypericum perforatum leaf extract.

Hypericum perforatum flower and hypericum flower/leaf/stem extract are used at concentrations up to 0.07% in cosmetic products that may include loose powders of which airborne particles may be inhaled. The size distribution of the particles in cosmetic powders have not been reported. However, particles incidentally inhaled from cosmetic aerosols would likely 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.[10-15]

Non-Cosmetic

Oral therapeutic use *H. perforatum* was reported to be safe up to 900 mg/d (~13 mg/kg/d) for humans.[16]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Dermal/Percutaneous

HYPERICIN

Hypericin is absorbed through the intestinal epithelium by passive transcellular diffusion.[17]

There was no hypericin detected in the plasma of Balb/c mice after administration to the ear (0.1% - 1%).[18] The distribution of hypericin-related fluorescence in the skin after dermal administration (1%) was concentrated in the stratum corneum and epidermis with only faint fluorescence in the dermis observed. At lower concentrations (0.1% and 0.01%), the fluorescence was concentrated only in the stratum corneum and was faint in the epidermis.

Oral

HYPERICUM PERFORATUM EXTRACT

After a single oral dose of *H. perforatum* extract (300 mg; tablet form; 900 µg hypericin + pseudohypericin), the mean serum level in subjects (n = 12) of total hypericin + pseudohypericin was 43 ng/mL and the mean skin blister fluid level was 5.3 ng/mL at 6 h.[19] After steady-state administration (1 tablet, 3 x/d for 7 days) the mean serum level of total hypericin + pseudohypericin was 12.5 ng/mL and the mean skin blister fluid level was 2.8 ng/mL. The authors state that these skin levels are far below hypericin skin levels that are estimated to be phototoxic (>100 ng/ml).

After a single oral dose of a *H. perforatum* extract (1600 mg/kg in agarose gel; 1.35% isoquercitrin, 0.38% quercitrin, 3.26% rutin, 1.83% hyperoside) administered to male Sprague Dawley rats (n = 30; control n = 6), the quercetin plasma level increased rapidly and reached the maximum of about 700 ng/ml after 4 h.[20] After 24 hours, 50% of the Cmax was still measurable. In contrast the concentration level of isorhamnetin/tamarixetin increased much slower, the maximum was reached after 24 hours with a Cmax of 903 ng/mL. Repeated doses of *H. perforatum* extract (1600 mg/kg/d for 8 days) caused a continuous increase in the plasma levels of quercetin and isorhamnetin for 5 days, after that time the concentration remained constant.

Short-term *H. perforatum* extract (300 mg 3 x/d) oral administration to human subjects resulted in a selective induction of CYP3A activity in the intestinal wall.[7] *H. perforatum* did not alter the CYP2C9, CYPlA2, or CYP2D6 activities.

In 36 samples of breast milk from mothers (n = 5) who were taking *H. perforatum* extract (300 mg 3/d), hyperforin was present in the milk at 0.9% - 2.5% (infant hyperforin dose/kg body weight expressed as a percentage of the maternal hyperforin dose/kg body weight).[21] The plasma from two of the infants contained low levels of hyperforin (0.1 ng/mL).

Hyperforin was detected in the breast milk of a mother who took three *H. perforatum* extract pills (3 x 300 mg/d; 0.12% - 0.28% hypericins, ~4.5% hyperforin).[22] Hyperforin and hypericin were below the limits of detection in the infant's plasma.

CONSTITENTS

The half-lives for hypericin, pseudohypericin, hyperforin quercetin, and isohamnetin were similar whether *H. perforatum* extract (612 mg) was administered to subjects (n = 18) in one dose or daily for 14 days.[23]

The Cmax of hyperforin was ~ 370 ng/mL (~ 690 nM) at ~3 h after oral administration of an ethanol/water extract

of *H. perforatum* (0, 300 mg/kg; 5% hyperforin) to Sprague-Dawley rats (n = 5 for each sampling interval).[24] Blood samples were taken at 15 and 30 min and 1, 2, 4, 6, 8, and 24 h.

In humans, the maximum plasma levels of ~150 ng/ml hyperforin (~ 280 nM) were reached 3.5 h after oral administration of a *H. perforatum* ethanol/water extract.[24] In an open, single-dose, four-way crossover study, the same *H. perforatum* extract (300, 600, 1200 mg; in pill form) or a second extract (0.5% hyperforin) was orally administered to subjects (n = 6) for 8 days. Blood samples were taken at 0, 15, 30, and 45 min and 1, 1.5, 2.5, 3, 4, 6, 8, 10, 12, and 24 h on days 1 and 8. Washout period was 3 days.

In a second human double-blind study, placebo-controlled parallel-group study of *H. perforatum* extract (300, 600, 1200 mg; in pill form) or a second extract (0.5% hyperforin), the half-life and mean residence time were 9 and 12 h, respectively. Hyperforin pharmacokinetics were linear up to the 600 mg dose. Increasing the doses to 900 or 1200 mg resulted in lower Cmax and AUC values than those expected from linear extrapolation of data from lower doses. Plasma concentration curves in volunteers fitted well in an open two-compartment model. In the repeated dose study, there was no accumulation of hyperforin in the plasma. The estimated steady state of hyperforin in plasma was ~100 ng/ml (~180 nM).

Using human colonic Caco-2 cells as a model for human intestinal absorption, porcine capillary endothelial cells for the blood-brain barrier, and plexus choriodei epithelial cells for the blood-cerebrospinal fluid barrier, it was shown that orally ingested miquelianin (quercetin 3-O-beta-D-glucuronopyranoside; a flavonoid with antidepressant activity) could possibly cross all three barriers and reach the central nervous system.[25] The permeability coefficients of miquelianin were 0.4 +/- 0.19 x 10^{-6} cm/sec), 1.34 +/- 0.05 x 10^{-6} cm/sec, and 2.0 +/- 0.33 x 10^{-6} cm/sec, respectively.

Intravenous

HYPERCICIN

Intravenous administration of hypericin (2 mg/kg in 2% benzyl alcohol and saline) to rhesus monkeys (*Maccaca mulatta*; n = 3) had a mean peak plasma concentration of 142 ± 45 µM; elimination was bi-exponential with an average alpha half-life of 2.8 ± 0.3 h and terminal half-life of 26 ± 14 h.[26] Hypericin was not detected in the cerebrospinal fluid of any animal.

Anti-inflammatory Activity

HYPERICUM PERFORATUM FLOWER EXTRACT

H. perforatum flower extracts (a hydroalcoholic extract, a lipophilic extract, and an ethylacetic fraction) provoked a dose-dependent reduction of Croton-oil-induced ear edema in mice.[27] Inflammation was induced in the right ear of male albino Swiss mice (n = 10) by applying Croton oil, 80 mg dissolved in 15 mL vehicle with and without the test substances. The following vehicles were used: acetone for extracts, the ethylacetic fraction, hypericin, hyperforin dicyclohexylammonium (DCHA) salt, dicyclohexylamine and the relevant controls; ethanol:acetone (3:1, v/v) for hyperoside and its controls; ethanol:acetone (1:1, v/v) for adhyperforin, amentoflavone, isoquercitrin and the relevant controls. The left ear remained untreated. Control animals were treated only with Croton oil.

The doses that inhibited by 50% (ID_{50}) the Croton-oil-induced ear edema in mice had the following order of activity: lipophilic extract (ID_{50} = 220 mg/cm^2) > ethylacetic fraction (ID_{50} = 267 mg/cm^2) > hydroalcoholic extract (ID_{50} >1000 mg/cm^2). Amentoflavone (ID_{50} = 0.16 mM/cm^2), hypericin (ID_{50} = 0.25 mM/cm^2), hyperforin DHCA salt (ID_{50} = 0.25 mM/cm^2) and adhyperforin (ID_{50} = 0.30 mM/cm^2) had anti-inflammatory activity that was more potent or comparable to that of indomethacin (ID_{50} = 0.26 mM/cm^2), whereas isoquercitrin and hyperoside were less active (ID_{50} ~ 1 mM/cm^2). As dicyclohexylamine alone was inactive, the effect of hyperforin DHCA salt can be attributed completely to the phloroglucinol moiety. The pharmacological activity and phytochemical profile of the tested extracts and fractions suggest that different constituents are involved in the topical antiphlogistic property of *H. perforatum* in vivo.

Pharmacokinetic Effects

HYPERICIN

Hypericin demonstrated antiviral, anti-inflammatory, and antitumor effects on human leukocytes.[28] Radio-labeled human granulocytes, mononuclear cells, and lymphocytes were incubated in various concentrations of hypericin, with and without bovine serum albumin (BSA), for 10 or 30 min then stimulated with phorbol-12-myristate-13-acetate (TPA) and/or calcium ionphore A-23187. ^{3}H-labeled compounds were used to assay for leukotriene B_4 (LTB4) and prostaglandin B_2 (PGE_2) released from the cells by ELISA test kits. An inhibitory effect was observed at concentrations of < 0.4 µM and in the presence of low concentrations of TPA (0.16 - 0.32 µM). Thus, hypericin inhibits the release of LTB_4 but not of PGE_2. The authors suggested that this is possibly due to the inhibition of the PKC-mediated signaling pathway, which influences the arachidonic acid metabolism and the interleukin-1-alpha production, which resulted in an immunosuppressive effect.

In an open-label, fixed schedule study, subjects (n = 12) were administered Tolbutamide (CYP2C9), caffeine (CYPlA2), dextromethorphan (CYP2D6), oral midazolam (intestinal wall and hepatic CYP3A), and intravenous midazolam (hepatic CYP3A).[7] Blood and urine samples were taken before and during treatment. Subjects continued to take the *H. perforatum* extract for 14 days. There were no serious adverse events but some cases of hypoglycemia occurred during the study. The bioavailability of midazolam was reduced to 55% of the control value after 2 weeks of treatment. The authors

conclude that *H. perforatum* reduced the therapeutic efficacy of drugs metabolized by CYP3A and this effect should be anticipated during long-term administration.

Cytotoxicity and Protection

HYPERICIN AND QUERCETIN

In a test of the protective effect of quercetin, a natural antioxidant compound, on hypericin-induced cytotoxicity using human promyelocytic leukemia cells (HL-60), hypericin (10^{-5} mol/L) alone decreased cell survival to 21%.[29] The combination of quercetin (10^{-5} mol/L) increased survival to 46%. Lower concentrations of quercetin had no protective effect. The authors suggested that these results indicate that oxygen radicals can play a role in hypericin-induced phototoxic effects.

TOXICOLOGICAL STUDIES

Acute Toxicity

Intravenous

HYPERICIN

Intravenous administration of hypericin (2 mg/kg in 2% benzyl alcohol and saline) was well tolerated by rhesus monkeys (n = 3).[26] At a dose of 5 mg/kg, a transient severe photosensitivity rash was observed at 12 h that resolved within 12 days. Edema and a pruritic erythematous rash with evolution to eschar were observed on the face and light exposed skin. Mild anorexia and transient elevation in hepatic transaminases was observed.

Repeated Dose Toxicity

Oral – Non-Human

HYPERICUM PERFORATUM EXTRACT

H. perforatum extract (900 and 2700 mg/kg) was orally administered to rats and dogs daily for 26 weeks.[16] Decreased body weight; slight changes in the hemography; changes in the clinical-chemical parameters, which indicate a slight load damage to the liver and kidneys were observed in both dose groups. A mild hypertrophy of the zona glomerulosa of the adrenals was observed.

Oral – Human

HYPERICUM PERFORATUM EXTRACT

In a randomized, double-blind crossover study, *H. perforatum* extract (255 to 285 mg ; 900 μg hypericin content) orally administered to healthy male subjects (n = 12) three times/day for 13 days had no effect on vasoconstrictor responses of cutaneous blood flow (VR) or skin conductance response (SR).[30] VR and SR were measured before treatment and at 0.5, 3, and 5 h after the last dose was given. Systolic and diastolic blood pressure was monitored before the start of medication as well as on treatment days 11 and 14. *H. perforatum* extract, and the controls (25 mg amitriptyline, and placebo) were administered to the subjects with at least a 14-day wash out period between treatments.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Animal

HYPERICUM PERFORATUM EXTRACT

There were no reproductive or developmental effects observed in a two-generational study of *H. perforatum* extract using CD-1 mice (n = 20).[31] The female mice were administered *H. perforatum* (180 mg/kg in feed) for 2 weeks prior to mating through gestation. Body weight, body length, and head circumference (measurements taken from postnatal day 3 through adulthood) increases were similar between the two groups of offspring, regardless of gender. No differences in reaching physical milestones (i.e., teeth eruptions, eye opening, external genitalia) were noted between the two groups. Reproductive capability, perinatal outcomes, and growth and development of the second-generation offspring were unaffected by parental exposure to *H. perforatum* extract.

There were no clinical signs of maternal or developmental toxicity when pregnant Wistar rats (n = 15) were administered *H. perforatum* extract (36 mg/kg/d in saline; 0.4% hypericin) during gestation days 9 – 15.[32] Maternal toxicity was evaluated through: water and food intake, body weight gain, piloerection, locomotor activity, diarrhea and mortality. Animals were killed on day 21 of gestation and necropsied. The indices of implantation and resorption were calculated.

Examination of the livers, kidneys, hearts, lungs, brains, and small intestines of the pups of Wistar rats (n = 6) orally treated with *H. perforatum* extract (methanol extraction solution containing 0.3% hypericin; 0, 100, 1000 mg/kg/d) showed severe damage to the livers and kidneys of animals killed postnatally on days 0 and 21.[33] Three dams were treated starting 2 weeks prior to mating through 21 days of lactating. The other three were treated from delivery through 21 days of lactation. Maternal body weights, gestation time, number of live pups, and weight of pups at birth were similar between groups. The livers of newborn pups of dams in the low dose group treated before and during pregnancy showed focal hepatocyte damage was apparent, with vacuolization of cells. In the high dose group, these lesions were much more evident, with hepatocyte hyaline degeneration, lobular fibrosis, and disorganization of hepatocyte arrays. In the low dose group, the kidneys showed a

reduction in glomerular size with disappearance of Bowman's space and hyaline tubular degeneration and in the high dose group, these lesions were more severe. The same lesions, but much more diffuse and serious, were observed in pups killed after 21 days of lactating from dams that were exposed to the test material throughout pregnancy and lactation. The same lesions were evident also in pups that were exposed to the substance only through nursing.

There were no effects on maternal weight gain or gestation length nor any effect on offspring body weights (up to postnatal day 56) behavior, or whole and regional brain weights in Sprague-Dawley rats (n = 35) fed diets containing *H. perforatum* extract (0, 180, 900, 1800, 4500 ppm; 0, 0.18, 0.90, 1.80, 4.50 g/kg; 0.3% hypericin) from gestation day 3 to postnatal day 21.[34] Offspring body weights in the treated groups were lower than controls at post natal days 56 (180, 900, 1800 ppm groups) and 78 (180, 1800 ppm groups). Offspring were tested using the open field test, acoustic startle response test, complex maze test, Morris water maze test, and the elevated plus maze activity test.

There were no behavioral effects to the offspring of CD-1 mice (n = 45) orally administered *H. perforatum* extract (0.75 mg/g/d in feed; 0.3% hypericin) for 2 weeks before and through gestation.[31] There were also no effects on reproductive behavior or success in the next three generations of offspring. In the male pups, the treatment group weighed less than the controls. The offspring were tested with homing, locomotor activity, exploratory, forced swim, and anxiety tests.

HYPERICUM PERFORATUM FLOWER EXTRACT

The contractility of the vas deferens of Wistar rats exposed to the hydromethanolic extract of the flowering tops of *H. perforatum* (1 – 300 μg/mL; 0.3% hypericin) and hyperforin (10^{-8} – 10^{-4} M was inhibited in a concentration dependent manner.[35] Stimulation for the contractions was through electrical field stimulation or exposure to α-,β-methylene ATP. Hypericin, quercitrin rutin, and kaempferol did not inhibit phenylephrine induced contractions.

HYPERICIN

Sprague-Dawley rat embryos explanted into a culture of hypericin (0 – 142 ng/mL) for 2 days exhibited morphological changes when compared to controls starting at 71.0 ng/mL.[36] Embryos were explanted at gestational day 9.5 and were examined on day 11.5. The embryos exposed to high concentration of hypericin (71.0 and 142.0 ng/mL) had lower total morphological score and number of somites compared with the control group. There was a negative linear trend in total morphological score, yolk sac diameter, and number of somites, indicating a progressive reduction in these parameters with increasing concentration of hypericin. There were no differences detected in crown-rump length. There were no adverse effects up 28.4 ng/mL.

Human

The frequency of live births and premature births of women in Canada who were taking St. John's wort (*H. perforatum*; n = 54; average age = 32.6 ± 5.3) during their pregnancy were similar to those with no exposure (n = 108; average age = 32.5 ± 4.9).[37] Women were interviewed during pregnancy and followed for 5 – 7 years after birth. *H. perforatum* was consumed by 76% of the pregnant women during the first trimester, 5.5% during the first and second trimester, 7.3% during the entire pregnancy, and 9.1% during some combination of the second and third trimester. Their average daily dose as reported by the subjects was 615 mg among those using tablets. The dose could not be estimated for a few of the subjects because they took *H. perforatum* in the form of teas (3), tincture (1) or granules (1).

There were no differences in milk production, maternal adverse events, and infant weight over the first year of life observed when breastfeeding women (n = 33) were orally administered *H. perforatum* extract (704.9 ± 463.6 mg/day, no further characterization) compared to disease-matched controls (n = 101) and age- and parity-matched non-disease controls (n = 33).[38]

In 36 samples of breast milk from mothers (n = 5) who were taking *H. perforatum* extract (300 mg 3/d), hyperforin was present in the milk at 0.9% - 2.5%.[21] The plasma from two of the infants contained low levels of hyperforin (0.1 ng/mL). No side effects were seen in the mothers or infants. The authors conclude that these results add to the evidence of the relative safety of St. John's wort while breast-feeding.

Hyperforin was detected in the breast milk of a mother took three Hypericum extract pills (3 x 300 mg/d; 0.12% - 0.28% hypericum, ~4.5% hyperforin).[22] No clinical effects were observed in the mother and infant.

HYPERICUM PERFORATUM FLOWER EXTRACT

The above contractility experiment was repeated with segments (3 to 4 cm) of the epididymal part of the vas deferens taken from subjects (n = 15) who underwent prostatectomy (9 who were 60 to 72 years old) or orchiectomy (3 who were 28 to 35 years old). *H. perforatum* flower extract and hyperforin inhibited contractions stimulated by phenylephrine (3 x 10-6 M).[35] The IC_{50}s were 13.9 ± 2.0 and 0.45 ± 0.04 μM, respectively.

GENOTOXICITY

There were no new genotoxicity studies discovered or submitted.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Human

HYPERICUM PERFORATUM EXTRACT

In an irritation test (n = 18), a bath oil containing *H. perforatum* extract (concentration not provided; 50 µL) did not cause irritation and was similar to the control of distilled water.[39] The test material was administered to the volar surface of the arm under occlusion for 24 h. After an hour, the test areas were evaluated and the test substance re-administered for another 24 h and evaluated again. The evaluations were transepidermal water loss (TEWL), photometric measurements of skin erythema, and visual scoring.

Sensitization

No dermal sensitization studies were discovered or submitted.

Phototoxicity

Dermal Administration

HYPERICUM PERFORATUM EXTRACT

A product containing *H. perforatum* extract (1.1%) was not photosensitizing to the backs of guinea pigs when applied to tape-stripped skin.[40] The backs of the guinea pigs were irradiated (320-400 nm; 10.2 j/cm^2) for 5 consecutive days after the product (1, 5, 10, and 20% in distilled water; 0.011%, 0.055%, 0.11%, 0.22%) was administered. Two weeks later, the product (0.1% and 1%) was applied and the skin irradiated. The test sites were observed at 24 and 48 h.

Incubation in methanolic extract of *H. perforatum* (> 50 µg/mL; 0.3% hypericin-like derivatives) was phototoxic to human keratinocyte HaCaT cells in UVA light.[41] The cells were incubated for 4 h then irradiated (1 J/cm^2 UVA or 150 mJ/cm^2 UVB) for 3 h. The test substance was not phototoxic in UVB light.

HYPERICUM PERFORATUM OIL

H. perforatum oil (110 µg/ml) and an ointment containing hypericum oil (30 µg/ml) were not phototoxic when administered to subjects (n = 8) with skin types II and III and no history of skin disease or photosensitivity.[42] There was no change in the minimal erythema dose after administration of the test materials. There was an increase of the erythema-index after treatment with *H. perforatum* oil using a more sensitive photometric measurement. The light doses were 24, 48, 96, and 144 J/cm^2 (290 – 2500 nm) and the treated area was observed at treatment, and after 24 and 48 h.

HYPERICIN

Dermal administration of hypericin (n = 5-10; 0.1% - 1%) resulted in minimal photosensitization to the ears of Balb/c mice at the highest concentration.[18] Hypericin acetate (n = 5-10; 0.015% - 1.5%) induced more severe and prolonged response after irradiation characterized by intense erythema and ear swelling at all concentrations; skin damage was healed in 14 days with no scar formation. Residual photosensitization effects declined to almost non-detectable at day 7. Radiation exposure (586 and 589 nm) was performed 24 h after administration of the test material.

Oral Administration

HYPERICUM PERFORATUM EXTRACT

In an oral study of two different *H. perforatum* extracts (STW3, 80% ethanol extract, 612 mg, 1.4 mg hypericin; STW3-VI, 50% ethanol extract, 900mg, 1.75 hypericin), male subjects (n = 20) had no change in minimum erythema dose of irradiation after administration of the test substances for 2 weeks.[43] Plasma steady state of hypericin/pseudohypericin was obtained before day 14 of treatment. The UV dose was adjusted for skin type. Two adverse events were reported, both described as hypersensitivity to light in mild intensity

In the presence of a stable plasma concentration of hypericin (6.72 ng/ml) the minimal erythema dose (MED) values did not differ from controls.[44] H. perforatum extract (three 60 mg capsules) was orally administered twice daily for 2 weeks. Photosensitivity was tested before and after administration of the test material.

Oral administration of *H. perforatum* extract in a single dose (5400 and 10800 µg hypericin; n =12) or over 7 days (5400 µg initial dose, 2700 µg /d; n =24) did not increase dermal erythema or pigmentation when subjects were exposed to UVB, UVA, visible light, or solar simulated radiation.[45] There was no evidence of a phototoxic effect. Photo-testing was performed prior to first dose and 6 h after last administration of hypericin tablets. The post-administration erythema index and melanin index were similar to pre-administration measurements in all cases except for visible light where there was an increase in the erythema index in the single dose study at both dose levels.

The single dose (5400 and 10800 µg hypericin; n = 48) and steady state (5400 µg initial dose, 2700 µg /d hypericin; n = 24) studies were repeated with similar results.[46]

In Vitro

HYPERICUM PERFORATUM EXTRACT, HYPERICIN, AND PSEUDOHYPERICIN

H. perforatum extracts (0, 30, 40, 50, 60, 70, 90, 100 μg/mL) from three different sources and hypericin (0, 0.1, 0.3 μg/ml) were cytotoxic to human keratinocyte cells (HaCaT cells) after incubation and exposure to UVA radiation (250 – 700 mJ/cm^2) in a concentration- and UVA-dose dependent manner.[47] The cells were incubated in the test substances for 24 h, irradiated and then tested for viability using a neutral red assay. As for other constituents, quercetin was cytotoxic without radiation, rutin was phototoxic, and quercitrin had antiphototoxic properties. UVA irradiation by itself was not cytotoxic up to 1000 mJ/cm^2, where it was mildly cytotoxic.

Hypericin combined with *H. perforatum* extracts (plant parts not specified) or constituents exerted less phototoxicity than pure hypericin when exposed to HaCaT keratinocytes.[48] The keratinocytes were exposed to two *H. perforatum* extracts, (1) an ethanol re-extraction of residue following a chloroform extraction (3.35 μM hypericin and 124.0 μM total flavonoids); and (2) a chloroform extract (hypericin and flavonoids not detected) supplemented with hypericin (20 μM), and hypericin (20 μM). Each plate was exposed to ambient light provided by fluorescent light bulbs which supplied 5.2 ± 5% J/cm^2 after 30 min of exposure to the test materials at room temperature. The extracts showed 24% and 40% less phototoxicity to the keratinocytes, respectively, than to those exposed to hypericin.

In a neutral red uptake assay of HaCAT keratinocytes exposed to UVA light (320 – 400 nm) after incubation in hypericin (0.1, 0.5, 1 μM) for up to 60 min, there was a dose-dependent increase in DNA damage as irradiation dose increased.[49] However, the authors states that although the results show that the combination of hypericin and UVA light increased the genotoxic burden, when all factors are taken into account, the risk of significant photogenotoxic damage incurred by the combination of *H. perforatum* extracts and UVA phototherapy may be low in the majority of individuals.

Treatment with both photoactivated hypericin and pseudohypericin resulted in a dose-dependent inhibition of proliferation of human acute T leukemic lymphoma cells; non-photoactivated plant pigments had no effect on cell proliferation.[50] The IC_{50} of irradiated hypericin was 100 ng/mL and 200 ng/mL for pseudohypericin.

Ocular

HYPERICIN

Human lens epithelial cells incubated in hypericin (0.1-10 μM) and irradiated (4 J/cm^2 UVA or 0.9 J/cm^2 visible light) had increased necrosis and apoptosis.[51] Neither hypericin exposure alone nor light exposure alone reduced cell viability. The addition of the ocular antioxidants lutein and N-acetyl cysteine did not prevent the damage. The authors concluded that ingested *H. perforatum* extract is potentially phototoxic to the eye and could contribute to early cataractogenesis.

Photosensitized photopolymerization was induced in lens alpha-crystalline, isolated from calf lenses, after irradiation (> 300 nm, 24 mW/cm^2) in the presence of hypericin (5×10^{-5} M in 10 mM ammonium bicarbonate; pH 7.0).[52] Further analysis of the oxidative changes using mass spectrometry showed specific oxidation of methionine, tryptophan, and histidine residues, which increased with time of irradiation. Hypericin did not damage the lens protein without irradiation. Damage to alpha-crystalline could undermine the integrity of the lens directly by protein denaturation and indirectly by disturbing chaperone function. The authors suggest that in the presence of light, hypericin can induce changes in lens protein that could lead to the formation of cataracts.

Human retinal pigment epithelial (hRPE) cells exposed to hypericin (10^{-7} to 10^{-5} M) and irradiated (0.72 J/cm^2) reduced cell viability compared to untreated cells and cells that were either just exposed to the test material or irradiated.[53] Viability was measured by (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt) (MTS) and lactate dehydrogenase (LDH) assays after 1.5 h incubation in hypericin and irradiated for 1, 3, 5, and 10 min. The presence of hypericin in irradiated hRPE cells significantly changed the redox equilibrium of glutathione and a decrease in the activity of glutathione reductase. Increased lipid peroxidation as measured by the TBARS assay correlated to hypericin concentration in hRPE cells and visible light radiation.

The UVB irradiation of bovine lenses exposed to hypericin (10^{-6} M) caused an increase in focal length variability and protein leakage compared to lenses that were only UVB irradiated.[54] The lenses were placed in tissue culture wells and irradiated (0.2 j/cm^2) then followed for 7 days. Lenses treated with hypericin and irradiated had an increase in focal length variability as compared with the lenses that were only UVB-irradiated. Lenses without UVB irradiation had lower focal length variability than irradiated lenses. For non-hypericin-treated lenses, UVB-irradiated lenses had a larger variability (4.58 mm) than the unirradiated lenses (1.78 mm). The lenses incubated in elevated glucose concentrations had a focal length variability (3.23 mm) equivalent to that of the unirradiated hypericin-treated lenses (3.54 mm). The authors conclude that photo-oxidative damage by hypericin results in changes in the optical properties of the lens, protein leakage and finally cataract formation. This is evidence that people should protect their eyes from intense sunlight when taking *H. perforatum*-derived substances.

Using the data collected in questionnaires by the National Center for Complementary and Alternative Medicine (NCCAM) and Alternative Health/Complementary and Alternative Medicine Supplement (ALT; a total of 120,142,753 responses), an association between the use of *H. perforatum* among person 40 years of age and older and the presence of cataracts was reported to have an odds ratio of 1.59 (05% CI 1.02 – 2.46) or that persons with cataracts are 59% more likely

to report St. John's wort use.[55] The authors stated that hypericum perforatum may increase the risk of cataracts but the mechanism is not established.

CLINICAL USE

ORAL

There are many clinical studies of the oral use of *H. perforatum* extracts for effectiveness as an antidepressant and for safety. Table 5 is a summary of adverse effects that have been reported with the oral administration of *H. perforatum* extracts. Adverse events included: nausea, headache, dizziness abdominal pain, insomnia/sleep disturbance, cold symptoms, and diarrhea. Except for sleep disturbance, and to a lesser extent headaches, the adverse events were reported in low percentages of the subjects.

DERMAL

In a half-side comparison study of a cream with and without *H. perforatum* extract (1.5% hyperforin), there were four reported adverse events in three subjects that were classified as not serious but resulted in not finishing the study.[56] One subject developed contact eczema to the vehicle. In the subjects, all with atopic dermatitis, that finished the 4-week study (n = 18), both sides of the skin lesions improved, with fewer skin colonies of *Staphylococcus aureus* on the hypericum perforatum extract side on days 7, 14, and 28.

Case Studies

HYPERICUM PERFORATUM EXTRACT

A 45-year-old female subject developed large blisters that resolved with some hyperpigmentation after laser treatment at 532 nm at 1.5 J/cm^2.[57] She had received a previous treatment with no ill effects. It was discovered that the subject had started taking medication that contained St. John's wort (*H. perforatum*). Another treatment a month after stopping the medication resulted in no ill effects.

A case of an overdose of *H. perforatum* extract in a suicidal attempt of a 16-year-old girl resulted in seizures and confusion that resolved after 6 days.[58] It has been reported that the girl had taken up to fifteen 300 μg tablets/day for 2 weeks and 50 tablets just before hospitalization. After 6 days the EEG was normal and no further seizures occurred in the following 6 months.

A case of acute neuropathy was reported in a woman after taking powdered *H. perforatum* extract (500 mg/d) and exposure to sunlight.[59] The pain started after 4 weeks of use and increased over time and after sunbathing. Symptoms decreased with discontinuation of use after 3 weeks and disappeared after 2 months.

Two pregnant women taking *Hypericum* extract (not characterized as to plant part, 900 mg/day) had no signs of toxicity or other harmful effects.[60] The authors stated concern about the use of *H. perforatum* instead of an established effective treatment because safety of *H. perforatum* in pregnancy and lactation has not been established.

SUMMARY

Hypericum perforatum (St. John's wort)-derived ingredients function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; skin protectants; antioxidants, hair conditioning agents; and antimicrobial agents. New information has been submitted to meet the data needs of the insufficient conclusion of the previous report.

Since the original report was published, the name of hypericum perforatum extract was changed to hypericum perforatum flower/leaf/stem extract and hypericum perforatum extract is now defined as an extract of the whole plant.

Hypericum perforatum extract was reported to be used in 32 leave-on products, 3 rinse-off products, and 1 baby product up to 0.003%. Hypericum perforatum flower was reported to be used in 1 leave-on product; maximum concentration of use was reported to be 0.005%. Hypericum perforatum flower/leaf/stem extract is reported to be used in 49 leave-on products and in 25 rinse-off products, mostly in skin care products, and 2 products that are diluted for bath up to 0.07%. Hypericum perforatum oil is reported to be used in 13 leave-on products and in 4 rinse-off products. Use concentration was only reported for skin fresheners up to 0.00005%.

Hypericin, the most active constituent of *H. perforatum*, penetrated the stratum corneum and epidermis of mouse ear skin, with little evidence of penetration into the dermis at 1%, with less penetration into the skin at 0.1 and 0.01 %. Hypericin, pseudohypericin, hyperforin quercetin, and isohamnetin were observed in the plasma after oral administration of *H. perforatum* extract. Hyperforin was detected in human breast milk but not in the feeding infant's plasma in mothers that ingested hypericum perforatum extract.

Orally administered *H. perforatum* extract at 900 and 2700 mg/kg to rats and dogs resulted in signs of load damage to the liver and kidneys due to the high doses.

Orally administered *H. perforatum* extract at 255 to 285 mg to healthy male subjects three times/day for 13 days had no effect on vasoconstrictor responses of cutaneous blood flow or skin conductance response.

There was liver damage to the pups of rats orally treated with *H. perforatum* extract at 100 and 1000 mg/kg/d. Lower doses had no effects on rat and mice dams or pups and had no effect on the cognitive abilities of pups. Rat embryos

incubated in hypericin at 71.0 and 142 ng/mL had a negative linear trend in total morphological score, yolk sac diameter, and number of somites.

No effects were reported or observed in women who ingested *H. perforatum* during pregnancy nor any effects to their infants. No effects were observed in breast feeding infants of mothers who took *H. perforatum*.

There was inhibited contractile response in rat and human vas deferens exposed to *H. perforatum* up to 300 µg/mL. Human sperm had DNA denaturation when exposed to *H. perforatum* extract.

Hypericin demonstrated antiviral, anti-inflammatory, and antitumor effects to human leukocytes.

A bath oil with an unknown concentration of *H. perforatum* extracts was non-irritating to humans.

Dermal administration of hypericum perforatum extract was not photosensitizing to the backs of guinea pigs at 1.1%. *H. perforatum* oil in a product was not phototoxic to humans at 110 µg/mL. Hypericin at 0.1% and hypericin acetate at 0.015% caused more severe and prolonged dermal response when mouse skin was irradiated. Single dose and short-term oral administration of *H. perforatum* extract did not increase photosensitization in humans. Human keratinocyte cells incubated in *H. perforatum* extracts and constituents demonstrated increased cytotoxic and photogenotoxic effects when exposed to UVA.

Human and bovine ocular cells/lens epitheliums had increased apoptosis and reduced cell viability after incubation in hypericin and exposure to UVA.

A survey showed a connection between *H. perforatum* use and the development of cataracts.

Adverse events in oral efficacy clinical trials included: nausea, headache, dizziness abdominal pain, insomnia/sleep disturbance, cold symptoms, and diarrhea.

DISCUSSION

While an earlier safety assessment of hypericum perforatum extract and oil found the available data insufficient to support safety, additional data were submitted addressing the concentration of use and function in cosmetics, and providing photosensitization/phototoxicity, reproductive/developmental toxicity, irritation/sensitization, and ocular irritation data.

Although there are data gaps in this report, the relatedness of constituents, physicochemical properties, functions and concentrations in cosmetics allowed grouping these ingredients together and interpolating/extrapolating the available toxicological data to support the safety of the entire group.

The Panel did note that one constituent of these ingredients is hypericin. Hypericin has been shown to be a photosensitizer in visible light and to have possible teratogenic effects in a study using rats. Hypericin was reported to be present in the various plant parts at 5 – 18,000 ppm. Another constituent is quercetin. Quercetin may be genotoxic, and is reported to be in *H. perforatum* plant parts at 1000 – 20000 ppm. Because the maximum concentration of use in cosmetics that contain these *H. perforatum* extracts was reported to be 0.07%, the Panel concluded that the amount of exposure to these constituents would be below the level of toxicological concern.

The Panel discussed the issue of incidental inhalation exposure from face and neck powders. There were no inhalation toxicity data available. The sizes of a substantial majority of the particles of these ingredients, as manufactured, would be expected to be larger than the respirable range (i.e., aerodynamic equivalent diameters > 10 µm) and to aggregate and agglomerate to form much larger particles in formulation, and would not be respirable to any appreciable amount. Furthermore, particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used (at concentrations up to 0.07% in cosmetic products that may become airborne), the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for *H. perforatum*-derived ingredients to cause irritation and sensitization, systemic toxicity, and reproductive/developmental toxicity. They noted the lack of systemic toxicity at doses much higher than any cosmetic exposure in acute and subchronic oral exposure studies, little or no irritation or sensitization in multiple tests of dermal and ocular exposure. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The following eight *Hypericum perforatum*-derived ingredients were found safe in the present practices of use and concentration in cosmetics:

- Hypericum perforatum extract
- Hypericum perforatum flower extract
- Hypericum perforatum flower/leaf extract*
- Hypericum perforatum flower/leaf/stem extract
- Hypericum perforatum flower/twig extract*
- Hypericum perforatum leaf extract*
- Hypericum perforatum oil

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

TABLES

Table 1. The definitions and functions of the *H. perforatum*-derived cosmetic ingredients.

Ingredient CAS #	Definition	Function
Hypericum perforatum extract	The extract of the whole plant, *Hypericum perforatum.*	Skin-conditioning agent – miscellaneous
Hypericum perforatum flower extract	The extract of the flowers of *Hypericum perforatum.*	Skin-conditioning agent – miscellaneous
Hypericum perforatum flower/leaf extract	The extract of the flowers and leaves of *Hypericum perforatum.*	Skin-conditioning agent – miscellaneous
Hypericum perforatum flower/leaf/stem extract 84082-80-4	The extract of the flowers, leaves and stems of *Hypericum perforatum.*	Skin-conditioning agent – miscellaneous
Hypericum perforatum flower/twig extract	The extract of the flowers and twigs of *Hypericum perforatum.*	Antimicrobial agent; skin-conditioning agent – miscellaneous
Hypericum perforatum leaf extract	The extract of the leaves of *Hypericum perforatum.*	Skin-conditioning agent – miscellaneous
Hypericum perforatum oil 68917-49-7	The fixed oil obtained from St. John's Wort, *Hypericum perforatum.*	Skin-conditioning agent – miscellaneous

Table 2. Constituents found in *Hypericum perforatum*.[61]

Chemical	Plant part	Concentration (ppm)
(+)-Catechin	Plant	
(+)-Epicatechin	Plant	
(-)-Epicatechin	Plant	
(E)-beta-farnesene	Plant	0.5-9
(E)-ocimene	Plant	0.1-2.25
(Z)-ocimene	Plant	0.25-4.5
1(3)-11(8)-biapigenin	Flower	
1(3)-11(8)-biapigenin	Shoot	72.5
1,3,6,7-tetrahydroxyxanthone	Leaf	
1,3,6,7-tetrahydroxyxanthone	Plant	
2,2-dimethyl-7-isobutyl-2h,5h-pyrano-(4,3-b)-pyran-5-one	Plant	1.5-27
2,2-dimethyl-7-sec-butyl-2h,5h-pyrano-(4,3-b)-pyran-5-one	Plant	1-18
2-methyl-butenol	Plant	
2-methyl-decane	Fruit Essent. Oil	
2-methyl-decane	Leaf Essent. Oil	
2-methyl-decane	Shoot	
2-methyl-octane	Fruit Essent. Oil	
2-methyl-octane	Shoot	
2-methyl-octane	Leaf Essent. Oil	
5-methylheptan-2,4-dione	Plant	0.25-4.5
6-methyl-hept-5-en-2-one	Plant	1-18
6-methylheptan-2,4-dione	Plant	0.25-4.5
Acetophenone	Plant	0.1-2.25
Acylphloroglucinols	Plant	
Adhyperfolin	Flower	

Table 2. Constituents found in *Hypericum perforatum*.[61]

Chemical	Plant part	Concentration (ppm)
Adhyperfolin	Fruit	
Adhyperiforin	Plant	2000-19000
Alkanes	Shoot	
Alkanols	Shoot	
Alpha-amorphene	Plant	0.25-4.5
Alpha-campholenol	Plant	0.05-0.9
Alpha-cuprenene	Plant	16-288
Alpha-eudesmol	Plant	2.5-45
Alpha-humulene	Plant	1-18
Alpha-phellandrene	Plant	0.3-5.4
Alpha-pinene	Shoot Essent. Oil	
Alpha-pinene	Leaf Essent. Oil	
Alpha-pinene	Plant	13-245
Alpha-pinene	Fruit Essent. Oil	
Alpha-selinene	Plant	1-18
Alpha-terpinene	Plant	1-18
Alpha-terpineol	Plant	3-54
Alpha-terpinyl-acetate	Plant	0.1-1.8
Amentoflavone	Flower	100-500
Amentoflavone	Shoot	
Ar-curcumene	Plant	0.5-9
Ascorbic-acid	Leaf	
Ascorbic-acid	Seed	395
Ascorbic-acid	Shoot	16.5
Ascorbic-acid	Plant	1300
Beta-amyrin	Shoot	
Beta-bourbonene	Plant	0.25-4.5
Beta-carotene	Shoot	12.1
Beta-elemene	Plant	0.25-4.5
Beta-eudesmol	Plant	2-32
Beta-pinene	Fruit Essent. Oil	
Beta-pinene	Shoot	
Beta-pinene	Plant	335-6055
Beta-pinene	Leaf Essent. Oil	
Beta-selinene	Plant	1.5-27
Beta-sitosterol	Plant	
Beta-sitosterol	Shoot	
Biapigenin	Leaf	
Bicycloelemene	Plant	0.1-1.8
Borneol	Plant	0.15-2.7
Bornyl-acetate	Plant	0.2-3.6
Brenzcatechin	Plant	
Cadinene	Essential Oil	
Cadmium	Leaf	1-7

Table 2. Constituents found in *Hypericum perforatum*.[61]

Chemical	Plant part	Concentration (ppm)
Cadmium	Root	1-3
Cadmium	Plant	1-5
Caffeic-acid	Plant	1000
Caffeic-acid	Shoot	1000
Camphene	Plant	1-18
Carotene	Seed	165
Carotenoids	Plant	
Caryophyllene	Essential Oil	
Caryophyllene	Plant	26-468
Caryophyllene-epoxide	Plant	0.5-9
Catechins	Plant	
Ceryl-alcohol	Plant	
Chlorogenic-acid	Leaf	
Chlorogenic-acid	Plant	
Chlorophyll	Plant	
Choline	Leaf	
Choline	Plant	
Choline	Shoot	34-1000
Cineole	Essential Oil	
Cinnamic-acid	Plant	
Cis-trollixanthin	Flower	
Cyanidin	Plant	
Cyclopseudohypericin	Plant	
Cysteine	Plant	
Delta-cadinene	Plant	0.5-9
Dodecanol	Plant	
Elemol	Plant	0.25-4.5
Emodinanthranol	Plant	
Eo	Flower	2500
Eo	Shoot	700-1250
Eo	Seed	3300
Eo	Plant	500-9000
Fat	Seed	328000
Fenchol	Plant	0.25-4.5
Ferulic-acid	Plant	
Flavonoids	Flower	117100
Flavonoids	Shoot	70000-74000
Gaba	Plant	700
Gallic-acid	Plant	
Gamma-curcumene	Plant	0.5-9
Gamma-eudesmol	Plant	1.5-27
Gamma-terpinene	Plant	1.5-27
Gentisic-acid	Plant	
Geranial	Plant	0.35-6.3

Table 2. Constituents found in *Hypericum perforatum*.[61]

Chemical	Plant part	Concentration (ppm)
Geraniol	Plant	4-72
Geranyl-acetate	Plant	24-432
Glutamine	Plant	
Guaiol	Plant	1.5-27
Gurjunene	Plant	
Hexacosan-1-ol	Leaf	
Humulene	Essential Oil	
Humulene	Plant	
Hyperesin-1	Plant	
Hyperesin-2	Plant	
Hyperforin	Flower	27930
Hyperforin	Shoot	
Hyperforin	Plant	20000-45000
Hyperforin	Fruit	
Hyperforin	Leaf	
Hypericin	Cotyledon	14.5
Hypericin	Stem	40-210
Hypericin	Shoot	390-1780
Hypericin	Plant	5000-7000
Hypericin	Leaf	190-1950
Hypericin	Fruit	730
Hypericin	Flower	860-18000
Hypericin	Flower Essent. Oil	5-19
Hypericin	Essential Oil	2200
Hypericins	Plant	95-4660
Hypericodihydroanthrone	Plant	
Hyperifolin	Plant	
Hyperin	Plant	3500-5500
Hyperoside	Flower	6570
Hyperoside	Stem	
Hyperoside	Shoot	5000-40000
Hyperoside	Plant	3500-20000
Hyperoside	Leaf	
I3,ii8-biapigenin	Flower	100-500
I3,ii8-biapigenin	Plant	2600
I3,ii8-biapigenin	Flower	1000-5000
Imanin	Plant	
Imanin	Shoot	
Ishwarane	Plant	0.5-9
Isoferulic-acid	Plant	
Isohypericin	Plant	
Isoquercetin	Plant	
Isoquercitin	Plant	
Isoquercitrin	Flower	

Table 2. Constituents found in *Hypericum perforatum*.[61]

Chemical	Plant part	Concentration (ppm)
Isoquercitrin	Plant	3000
Isovalerianic-acid	Plant	
Isovaleric-acid-ester	Plant	
Kaempferol	Plant	
Kielcorin	Plant	
Kielcorin	Root	
Kilecorin	Plant	
Lead	Leaf	6-18
Lead	Plant	2-12
Lead	Root	4-5
Leucine	Plant	
Leucocyanidin	Plant	
Limonene	Fruit Essent. Oil	
Limonene	Shoot	
Limonene	Plant	5-90
Limonene	Leaf Essent. Oil	
Linalool	Plant	2.5-45
Lutein	Flower	
Luteolin	Plant	
Luteoxanthin	Flower	
Lysine	Plant	
Mangiferin	Plant	
Mangiferin	Shoot	
Mangiferin(sic)	Plant	
Mannitol	Plant	11000-20000
Methyl-2-decane	Plant	
Methyl-2-octane	Essential Oil	164000
Methyl-3-but-3-en-2-ol	Plant	
Methyl-geranate	Plant	0.3-5.4
Myrcene	Fruit Essent. Oil	
Myrcene	Leaf Essent. Oil	
Myrcene	Essential Oil	
Myrcene	Plant	10-190
Myrcene	Shoot	
Myricetin	Plant	
Myricetin-3-o-beta-d-glucoside	Plant	
Myristic-acid	Plant	
N-decanal	Essential Oil	
N-nonane	Fruit Essent. Oil	
N-nonane	Shoot	
N-nonane	Essential Oil	
N-nonane	Leaf Essent. Oil	
N-octanal	Essential Oil	
N-octanol	Essential Oil	

Table 2. Constituents found in *Hypericum perforatum*.[61]

Chemical	Plant part	Concentration (ppm)
N-undecane	Fruit Essent. Oil	
N-undecane	Leaf Essent. Oil	
N-undecane	Shoot	
Neo-alloocimene	Plant	0.3-5.4
Neral	Plant	0.35-6.3
Nerol	Plant	1-18
Neryl-acetate	Plant	1-18
Nicotinic-acid	Leaf	0.007-1200
Nonacosane	Plant	
Nonane	Plant	23-414
Nor-cyclopseudohypericin	Plant	
Novoimanin	Plant	
Novoimanin	Shoot	30000-40000
Oct-1-ene	Plant	1.5-17
Octacosan-1-ol	Leaf	
Opcs	Plant	
Ornithine	Plant	
P-coumaric-acid	Plant	
P-cymene	Plant	0.5-9
P-hydroxy-benzoic-acid	Plant	
Palmitic-acid	Plant	
Pectin	Plant	
Perflavit	Shoot	
Phenol	Plant	
Phlobaphene	Plant	
Phloroglucinol	Plant	
Phloroglucinol	Shoot	
Phytosterols	Plant	
Pinene	Essential Oil	
Pinol	Plant	0.05-0.9
Proanthocyanidins	Plant	120000
Procyanidins	Plant	
Proline	Plant	
Protein	Seed	181000-207000
Protohypericin	Plant	
Protopseudohypericin	Plant	
Provitamin-a	Plant	130
Pseudohypericin	Cotyledon	164.9
Pseudohypericin	Shoot	40
Pseudohypericin	Plant	
Pseudohypericin	Leaf	
Pseudohypericin	Flower	2260-5800
Pseudohypericodihydroanthrone	Plant	
Pyrogallol	Plant	

Table 2. Constituents found in *Hypericum perforatum*.[61]

Chemical	Plant part	Concentration (ppm)
Quercetin	Flower	1000
Quercetin	Plant	20000
Quercetin	Stem	
Quercetin	Shoot	
Quercetin	Leaf	
Quercetin-3-o-glucuronide	Plant	
Quercetin-3-o-glucuronide	Shoot	
Quercetin-3-o-xyloside	Plant	
Quercetin-3-o-xyloside	Shoot	
Quercitrin	Flower	3380
Quercitrin	Leaf	
Quercitrin	Plant	
Quercitrin	Shoot	3000-5240
Resorcynol	Plant	
Rhodan	Plant	
Rutin	Flower	1000-2800
Rutin	Leaf	2000-3000
Rutin	Stem	
Rutin	Shoot	10000
Rutin	Plant	16000
Saponin	Seed	
Scopoletin	Plant	
Selina-4,11-diene	Plant	0.15-2.7
Sitosterol	Plant	
Stearic-acid	Plant	
Tannins	Flower	162000
Tannins	Stem	18000
Tannins	Shoot	3300
Tannins	Plant	30000-160000
Tannins	Leaf	124000
Tannins	Seed	121000
Taraxasterol	Shoot	
Terpinen-4-ol	Plant	0.5-9
Terpineolene	Plant	1.5-27
Tetracosan-1-ol	Leaf	
Threonine	Plant	
Triacontan-1-ol	Leaf	
Trollichrome	Flower	
Umbelliferone	Plant	
Undecane	Plant	0.25-4.5
Vanillic-acid	Plant	
Violaxanthin	Flower	
Xanthones	Plant	12.8

Table 3. Parameters/characterization of various commercial *H. perforatum* extracts (these are assumed to be dietary supplements).[62]

Parameter	Value
LI 160	
Extraction solvent	80% methanol
DER	3-6:1, initially 4-7:1
Total hypericins	0.12-0.28%
Hyperforin	Approximately 4.5%
Flavonoids	Approximately 8.3%
Other	From several notes in publications it can be assumed that the content of hyperforin is in the range from 3 to 6%.
WS 5570	
Extraction solvent	80% methanol
DER	3-7:1
Total hypericins	0.12-0.28%
Hyperforin	3-6%
Flavonoids	≥ 6.0%
Other	The extraction solvent and the declared amount of hypericum of this extract are identical with that of LI 160.
Ze 117	
Extraction solvent	Solvents vary: 50% ethanol (m/m) or ethanol 49% m/m : 2-propanol (97.3:2.7)
DER	4-7:1
Total hypericins	0.2%
Hyperforin	nearly free of hyperforin (e.g. 0.07%)
Other	Information on the refinement of the extract in order to reduce the content of hyperforin is not available.
Hyperforat drops	
Extraction solvent	50% ethanol
DER	0.5:1
Total hypericins	2 mg/ml
Hyperforin	Not specified
Other	Liquid
STW 3	
Extraction solvent	50% ethanol
DER	5-8:1
Total hypericins	mean 0.2%
Hyperforin	mean 2%
Flavonoids	mean 9%
Esbericum	
Extraction solvent	60% ethanol
DER	2-5.5:1
Total hypericins	0.1%
Hyperforin	Not specified
Flavonoids	Not specified
STEI 300	
Extraction solvent	60% ethanol m/m
DER	5-7:1
Total hypericins	0.2-0.3%
Hyperforin	2-3%
Flavonoids	Not specified
LoHyp-57	
Extraction solvent	60% Ethanol
DER	5-7:1
Total hypericins	0.2-0.3%
Hyperforin	2-3%
Flavonoids	Not specified
STW3-VI	
Extraction solvent	80% Ethanol
DER	3-6:1
Total hypericins	Mean 0.2%
Hyperforin	Mean 2.0%
Flavonoids	Mean 9%

Table 3. Parameters/characterization of various commercial *H. perforatum* extracts (these are assumed to be dietary supplements).[62]

Parameter	Value
WS 5572	
Extraction solvent	60% ethanol
DER	2.5-5:1
Total hypericins	not specified
Hyperforin	4-5%, 5%, 1.5%
Calmigen	
Extraction solvent	Not specified
DER	Not specified
Total hypericins	0.3%
Hyperforin	Not specified
Hyperiforce	
Extraction solvent	not specified
DER	4-5:1 (shoot tips)
Total hypericins	0.5%
Hyperforin	not specified

DER- Dry extract ratio

Table 4. Frequency of use according to duration and exposure of *H. perforatum*-derived cosmetic ingredients.[8,9]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Hypricum perforatum extract		Hypericum perforatum flower extract		Hypericum perforatum flower/leaf/stem extract		Hypericum perforatum oil	
Total/range	**35**	**0.00005-0.01**	**1**	**0.005**	**76**	**0.00002-0.07**	**17**	**0.00005**
Duration of use								
Leave-on	32	0.00005-0.01	1	0.005	49	0.00002-0.07	13	0.00005
Rinse-off	3	NR	NR	NR	25	0.00002-0.00004	4	NR
Diluted for (bath) use	NR	NR	NR	NR	2	NR	NR	NR
Exposure type								
Eye area	5	NR	1	NR	1	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	NR	NR	NR	1	NR	1	NR
Incidental inhalation-powders	1	NR	NR	NR	1	NR	NR	NR
Dermal contact	31	0.00005-0.01	1	0.005	64	0.00002-0.07	16	0.00005
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	22	NR	NR	NR	12	0.00002-0.00004	1	NR
Hair-coloring	1	NR	NR	NR	NR	0.00002	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	4	NR	NR	NR
Baby	1	NR	NR	NR	1	NR	NR	NR

NR = Not reported; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 5. Reported adverse events in oral clinical trials.

Extract [1]	Daily dose	Adverse events	Reference
WS 5570	3 x 300 mg	n=21 of 186 Nausea (4.8%) , headache (1.6%), dizziness (2.2%), Abdominal pain (1.1%), insomnia (1.6%)	63
WS 5572	3 x 300 mg	Sinusitis, bronchitis, Common cold	64
Ze 117	2 x 250 mg	n=6 of 81 (7.4%) Abdominal pain (2), moderate diarrhea (1), moderate Melancholia (1), moderate acute deterioration of patient's condition (1), moderate dry mouth (1)	65
Ze 117	2 x 250 mg	8% of 240 subjects Only GI disturbances (5%) with an incidence greater than 2%	66
PM235, (Cederroth International AB, Sweden)	3 x 270 mg	n150 Mild, mainly headache, gastrointestinal symptoms	67
WS 5570	900 mg or 1800 mg	26.8% of 71 No "typical adverse events (except: 1 allergic reaction to sunlight → early study termination); 0.006 AE/d	68
Ze 117	2 x 250 mg	62 of 157 (39%) Dry mouth (13) , headache (3), sweating (2), asthenia (2), nausea (1)	69
STEI 300	3 x 350 mg	0.5 Events per subject (22%); n = 263 Most frequently reported adverse event: Nausea	70
STW3	612 mg	9.8% Related to study medication; n=123 Diarrhea (1) Serious adverse events that caused leaving the study (3) somatic disorder, cerebral hemorrhage, unrelated accident	71
LI 160	3x 300 mg	Adverse events: 38; n=163 Subjects with adverse events: 35.1% Adverse events possibly related to study medication: 24. Body as a whole (13), Gastro-intestinal system disorders (6), Autonomic nervous system disorders (10), Central & peripheral nervous system disorders (10), Skin and appendages disorders (9), Psychiatric disorders (2), Others (5)	72
WS 570	600 mg or 1200 mg (2 x 600 mg)	All adverse events. 49 (39.8%); n=123, 127 Serious events 1 (tendon rupture attributable to accidental injury). Ear and labyrinth disorders 3 (2.4%), Gastrointestinal disorders 24 (19.5%), General disorders and administration site conditions 2 (1.6%), Infection and infestations 7 (5.7%), Injury, poisoning and procedural complications 1 (0.8%), Investigations 1 (0.8%), Metabolism and nutrition disorders 1 (0.8%), Musculoskeletal and connective tissue disorder 1 (0.8%), Nervous system disorder 6 (4.9%), Psychiatric disorders 2 (1.6%), Renal and urinary disorders 1 (0.8%), Reproductive system and breast disorders 1 (0.8%), Respiratory, thoracic and mediastinal disorders 4 (3.3%), Skin and subcutaneous disorders4 (3.3%), Vascular disorders 1 (0.8%)	73
LI 160	3 x 300 mg	n=90; Most common adverse events: headache (42%), dry mouth (22%), nausea (20%), gastrointestinal upset (20%), sleepiness (18%)	74
LI 160	900 mg/d for 4 weeks, after this period no adequate response, new dose 1200 mg/d	n=98; Headache (41%), Abdominal pain (≥ 10%)	75
LI 160	900 to 1500 mg (3-5 x 300 mg)	n=~110 ; Diarrhea (21%), Nausea (19%), Anorgasmia (25%), Forgetfulness (25%), Frequent urination (27%), Sweating (18%), Swelling (19%)	76
WS 5570	900 mg (3 x 300 mg) – 1800 mg (3 x 600 mg)	n=~125; Upper abdominal pain (9.6%), Diarrhea (9.6%), Dry mouth (12.8%), Nausea (7.2%), Fatigue (11.2%), Dizziness (7.2%), Headache (10.4%), Sleep disorder (4%), Increased sweating (7.2%). Highest incidence: Gastrointestinal disorders (59 events in 42 subjects), Nervous system disorders (35 events in 29 subjects), 2 serious adverse events (psychic decompensation attributable to social problems, hypertensive crisis), both not caused by Hypericum	77
?	900 to 1800 mg/d	n=22-23; Sleep disturbance (54.8%), Anxiety (42.9%), Sexual problems (11.9%), Headaches (42.9%), Dizziness (11.9%), Tremor (19.1%), Sweating (16.7%), Dry mouth (38.1%), Muscle spasms (11.9%), Muscle or joint stiffness (19.1%), Urinary problems (16.7%), Difficulty digesting (19.1%), Nausea or vomiting (9.5%), Diarrhea (23.8%), Lack of appetite (23.8%), Heart palpitations (9.5%), Fatigue (45.2%), Pain (11.9%), Blurred vision (14.3%) 1 serious adverse reaction (acute manic reaction)	78
WS 5573	3 x 300 mg	WS 5573 (28.6% of 49 subjects) Bronchitis (3/1), Influenza-like symptoms (2/0), Cough (2/0), Infection (1/0)	79

Table 5. Reported adverse events in oral clinical trials.

Extract [1]	Daily dose	Adverse events	Reference
Ze 117	2 x 250 mg	8 % Hypericum, GI disturbances (5%)	[66]
Hyperiforce (provided by Bioforce AG, Roggwil, Switzerland)	3 x 1 tablet (standardized to either 0.17 mg, 0.33 mg, or 1 mg total hypericin per day)	n=114-119; There is no difference in AE with possible or probable causality in the 3 treatment-groups. Probable/Possible relation to study medication: Skin (0/3), Nerves (2/5), Psyche (1/1), Gastrointestinal tract (4/0), Organism as a whole (0/2)	[80]
LoHyp 57	2 x 400 mg	n=149 (withdrawn for AEs: 6)	[81]
STW3-VI	900 mg	n=129; Total AEs. 58 (17.2%); Related: 10 Gastrointestinal disorders (6), Ear and labyrinth disorders (1), Skin and subcutaneous tissue disorders (1)	[82]
LI 160	3 x 300 mg	n=165;37 % of the subjects Dry mouth (5%), drowsiness (1%), sleepiness (2%), dizziness (1%), lethargy (1%), nausea/vomiting (7%), headache (7%), constipation (5%), pruritus (2%)	[83]
LI 160	3 x 600 mg	23% of the subjects n=37 Dry mouth (3); gastric symptoms (5), tiredness/sedation (5), restlessness (6), tremor (2), dizziness (5), allergic skin reaction (1)	[84]
WS 5572	600 mg/1200 mg	17 subjects n=21 (13 with relation to hypericum) AEs frequency < 1% Skin irritation, pruritus, allergic exanthema, nervousness, restlessness, gastrointestinal disorders (4), diarrhea, insomnia	[85]

[1] – See Table 3 for parameters/characterizations of these extracts.
AE = Adverse event

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Personal Care Products Council
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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 2, 2013

SUBJECT: Updated Concentration of Use by FDA Product Category: *Hypericum perforatum*-Derived Ingredients

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Concentration of Use by FDA Product Category*

Hypericum Perforatum Flower/Leaf/Stem Extract
Hypericum Perforatum Oil
Hypericum Peforatum Callus Culture Extract
Hypericum Perforatum Extract
Hypericum Perforatum Flower Extract
Hyperiucm Perforatum Flower/Leaf Extract
Hypericum Perforatum Flower/Twig Extract
Hypericum Perforatum Leaf Extract

Ingredient	FDA Code†	Product Category	Maximum Concentration of Use
Hypericum Perforatum Flower/Leaf/Stem Extract	05D	Permanent waves	0.00002%
Hypericum Perforatum Flower/Leaf/Stem Extract	05E	Rinses (noncoloring)	0.00004%
Hypericum Perforatum Flower/Leaf/Stem Extract	05F	Shampoos (noncoloring)	0.00004%
Hypericum Perforatum Flower/Leaf/Stem Extract	06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.00002%
Hypericum Perforatum Flower/Leaf/Stem Extract	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00002%
Hypericum Perforatum Flower/Leaf/Stem Extract	12C	Face and neck creams, lotions and powders not spray	0.003%
Hypericum Perforatum Flower/Leaf/Stem Extract	12D	Body and hand creams, lotions and powders not spray	0.07%
Hypericum Perforatum Flower/Leaf/Stem Extract	12F	Moisturizing creams, lotions and powders not spray	0.00002%
Hypericum Perforatum Flower/Leaf/Stem Extract	12H	Pastes masks and mud packs	0.00002%
Hypericum Perforatum Flower/Leaf/Stem Extract	12J	Other skin care preparations rinse-off	0.00005% 0.00002%
Hypericum Perforatum Oil	12J	Other skin care preparations	0.00005%
Hypericum Perforatum Extract	12C	Face and neck creams, lotions and powders not spray	0.003%

Hypericum Perforatum Extract	12J	Other skin care preparations	0.00005-0.01%
Hypericum Perforatum Flower Extract	12C	Face and neck creams, lotions and powders not spray	 0.005%

*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

†Product category codes used by FDA

Information collected in 2012

Table prepared October 25, 2012

Updated January 2, 2013: Hypericum Perforatum Extract: 12J added high concentration 0.01%

VCRP Data for Hypericum Perforatum (St. John's Wort)

01B - Baby Lotions, Oils, Powders, and Creams	999002189	HYPERICUM PERFORATUM EXTRACT	1
03D - Eye Lotion	999002189	HYPERICUM PERFORATUM EXTRACT	1
03F - Mascara	999002189	HYPERICUM PERFORATUM EXTRACT	2
03G - Other Eye Makeup Preparations	999002189	HYPERICUM PERFORATUM EXTRACT	2
05A - Hair Conditioner	999002189	HYPERICUM PERFORATUM EXTRACT	1
05F - Shampoos (non-coloring)	999002189	HYPERICUM PERFORATUM EXTRACT	1
07I - Other Makeup Preparations	999002189	HYPERICUM PERFORATUM EXTRACT	1
12A - Cleansing	999002189	HYPERICUM PERFORATUM EXTRACT	1
12C - Face and Neck (exc shave)	999002189	HYPERICUM PERFORATUM EXTRACT	6
12D - Body and Hand (exc shave)	999002189	HYPERICUM PERFORATUM EXTRACT	7
12F - Moisturizing	999002189	HYPERICUM PERFORATUM EXTRACT	5
12G - Night	999002189	HYPERICUM PERFORATUM EXTRACT	2
12I - Skin Fresheners	999002189	HYPERICUM PERFORATUM EXTRACT	3
12J - Other Skin Care Preps	999002189	HYPERICUM PERFORATUM EXTRACT	2
			35

03D - Eye Lotion	999002190	HYPERICUM PERFORATUM FLOWER EXTRACT	1

01B - Baby Lotions, Oils, Powders, and Creams	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
02B - Bubble Baths	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
03D - Eye Lotion	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
05A - Hair Conditioner	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
05F - Shampoos (non-coloring)	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	9
05I - Other Hair Preparations	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	2
07I - Other Makeup Preparations	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
10A - Bath Soaps and Detergents	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
10E - Other Personal Cleanliness Products	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
11A - Aftershave Lotion	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	3
11E - Shaving Cream	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
12A - Cleansing	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	8
12C - Face and Neck (exc shave)	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	7
12D - Body and Hand (exc shave)	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	7
12F - Moisturizing	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	9
12G - Night	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	4
12H - Paste Masks (mud packs)	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	4
12I - Skin Fresheners	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
12J - Other Skin Care Preps	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	10
13B - Indoor Tanning Preparations	84082804	HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT	1
			73

05G - Tonics, Dressings, and Other Hair Grooming Aids	68917497	HYPERICUM PERFORATUM OIL	1
11A - Aftershave Lotion	68917497	HYPERICUM PERFORATUM OIL	1
11G - Other Shaving Preparation Products	68917497	HYPERICUM PERFORATUM OIL	1
12A - Cleansing	68917497	HYPERICUM PERFORATUM OIL	2
12C - Face and Neck (exc shave)	68917497	HYPERICUM PERFORATUM OIL	2
12D - Body and Hand (exc shave)	68917497	HYPERICUM PERFORATUM OIL	4
12F - Moisturizing	68917497	HYPERICUM PERFORATUM OIL	1
12H - Paste Masks (mud packs)	68917497	HYPERICUM PERFORATUM OIL	1
12J - Other Skin Care Preps	68917497	HYPERICUM PERFORATUM OIL	3
13A - Suntan Gels, Creams, and Liquids	68917497	HYPERICUM PERFORATUM OIL	1
			17

07C - Foundations	977009963	ST JOHNS WORT (HYPERICUM PERFORATUM)	1
12C - Face and Neck (exc shave)	977009963	ST JOHNS WORT (HYPERICUM PERFORATUM)	1
12J - Other Skin Care Preps	977009963	ST JOHNS WORT (HYPERICUM PERFORATUM)	1
Combined with HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT			3

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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 3, 2013

SUBJECT: Comments on the Tentative Report on *Hypericum perforatum*-Derived Ingredients

Key Issues

In the Discussion, it is misleading to state that hypericin has been shown "to have teratogenic effects in studies using rats." The report text only includes one rat embryo culture study of hypericin. There are no *in vivo* developmental studies of hypericin included in the report.

The Discussion also states that quercetin is phototoxic. Where are the data that indicate that quercetin is phototoxic? Quercetin is an antioxidant and the abstract of the following study suggests that quercetin is protective of the phototoxic effects of hypericin.

Mirossay A, Onderková H, Mirossay L, Sarisský M, Mojzis J. 2001. The effect of quercetin on light induced cytotoxicity of hypericin. Physiol Res. 50(6):635-637.

Abstract

Protective effect of quercetin, a natural antioxidant compound, on hypericin-induced cytotoxicity was studied in human promyelocytic leukemia cells (HL-60). Hypericin (10(-5) mol x l(-1)) alone significantly decreased cell survival to 21% that found in the controls, whereas in combination with quercetin (10(-5) mol x l(-1)) this decrease was diminished to 46%. Lower concentrations of quercetin had no protective effect. These findings indicate that oxygen radicals can play an important role in hypericin-induced phototoxic effects.

Please consider the botanical template provided by the CIR SSC when completing CIR reviews of plant-derived ingredients. This report should also include some basic information about the plant, e.g., what type of plant it is, what does it look like, where does it grow, and the report should include some information on historic uses of this plant. Please see the reference books in Carol Eisenmann's office for this information. If this information was in the original CIR report, it should be mentioned in the summary of the original safety assessment.

If available, for each study in the report please include the type of extract, e.g. plant parts and extraction solvent, studied.

p.1, Abstract, Introduction, p.9, Summary - The Abstract, Introduction and Summary all state that the *Hypericum perforatum*-derived ingredients function as skin-conditioning agents - humectants,

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skin protectants; antioxidants and hair conditioning agents, although these functions are not listed in Table 1. These functions all need to be removed from the rest of the report as they are the functions listed for Hypericum Perforatum Callus Culture Extract which was removed from the report.

Additional Comments

p.1, Abstract - As much of the data in the report are on *Hypericum perforatum* preparations used as dietary supplements, rather than stating "data related to the ingredient" it should state "data related to *Hypericum perforatum*-derived preparations."

p.1, throughout report - Except when part of an INCI name, *Hypericum perforatum* or *H. perforatum* should be italicized. As there are multiple species of Hypericum, it is not correct to refer to extracts of *Hypericum perforatum* as "hypericum extracts." Please either use L. after *Hypericum perforatum* consistently throughout the report, or do not use it.

p.1 - In the summary of the original safety assessment, please provide some indication of the doses that were associated with adverse effects, or the highest dose that was not associated with any adverse effects.

p.1 - The meaning of "LP LD_{50}" in the last paragraph is not clear. Perhaps "LP" should be"IP"?

p.2 - Please correct the spelling of "naphtodianthrones" and "chloregenic acid".

p.3, 9 - There are no reported uses in "skin fresheners" in the new concentration of use information. In the new concentration of use survey, Hypericum Perforatum Oil was reported to be used in "Other skin care preparations" not skin fresheners.

p.3 - It does not make sense to state that the ingredients are used in powders and then precede to discuss potential exposure from use in sprays.

p.3 - It is not clear what was studied in reference 20 (rat oral pharmacokinetic study). A level of quercitrin is given, and then it gives values for quercetin in the plasma.

p.3 - The study showing effects of *Hypericum perforatum* on the metabolism of other drugs should be moved to the Pharmacokinetic Effects section.

p.4 - The last sentence under the Constituents subheading needs to state what the values represent.

p.5 - Please revise the following: "^{3}H-labeled compounds were assayed for leukotriene B_4...". It was likely the culture medium not the "compounds" that were assayed for leukotrienes and prostaglandins.

p.5 - Was methanol really used as the dosing solution in the developmental study of Hypericum Perforatum Extract (reference 30)? It was more likely the extraction solvent.

p.5 - When discussing rodent studies, please use "lactation" rather than "breastfeeding".

p.6 - In the rat embryo culture study of hypericin (reference 35), please indicate what concentration had no effects.

p.12-18, Table 2 - Please sort this table by plant part.

p.21, Table 5 - In the description of reference 64 it states "moderate acute deterioration"? What was observed to deteriorate?

p.21, Table 5, reference 78 - The following line is in the table twice "WS 5573 (28.6% of 49 subjects)".