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

CIR EXPERT PANEL MEETING

JUNE 10-11, 2013

May 17, 2013

MEMORANDOM

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

At the March, 2013 meeting, the Panel concluded that *Hypericum perforatum*-derived ingredients were safe as used in cosmetics. However, the Panel did not issue a final report and instead tabled the report so that a new boilerplate addressing the concern of constituents having an additive effect when multiple botanical ingredients are used in a single cosmetic product could be included.

The staff recognized that this would be a good time to also look at the boilerplate language of the pesticides/heavy metals and aflatoxin boilerplates, since we also want formulators to not create a problem with these potential toxicities when more than one botanical is used. We decided to incorporate all of these issues into one botanical boilerplate. We also developed language to use in the Abstract.

The proposed generic boiler plate language is attached. The language as applied to this safety assessment (in the Abstract and the Discussion) is marked in the draft final amended report.

Comments were submitted by the Personal Care Products and have been addressed. Updated use data have been received from FDA. There were no significant changes. The Use section and table have been updated.

The Panel is to review the Discussion, including the boilerplate language and make appropriate edits to reflect the Panel's thinking. A final report is to be issued.

Botanical Abstract/Discussion Framework

SENTENCE for ABSTRACT

Because formulators may use more than one botanical ingredient in a formulation, caution was urged to avoid reaching levels of concern for constituent chemicals and impurities such as pesticides.

Keep in mind the 150 word limit of the Abstract.

GUIDANCE for DISCUSSION

The basic framework has three parts:

1) An overview of the general issue that multiple botanical ingredients in a single formulation can contribute, cumulatively, to the total concentration of substances of concern in the formulation, including pesticides, heavy metals, aflatoxin, or constituents of concern (e.g., pulegone);
2) [Constructed by the writer] One or more paragraphs to be used in the discussion describing the constituent(s) of concern for the botanical ingredient(s); include endpoints, amounts in the plant/extract, previous CIR report conclusions, limits or other restriction specified by the Panel, and
3) Three paragraphs to choose from that provide the framework for discussion language as appropriate.

Opening Paragraph

NOTE: Delete aflatoxin from the second sentence and delete the last sentence if no suggestion of aflatoxin contamination has been made for the particular botanical (group).

Formulators must minimize the overall concentrations of impurities and constituents of concern when more than one botanical ingredient is used in a cosmetic formulation. A cosmetic formulation may contain multiple botanical ingredients, each of which can contribute to the total concentration of pesticides, heavy metals, aflatoxins, or other substances of concern in the botanical ingredients. As a result, industry must employ the procedures necessary to limit the concentrations of pesticide residues and heavy metals that result from combining botanical ingredients in the entire finished product, NOT just to each of the component ingredients in the formulation. This principle also applies to aflatoxin (≤ 15 ppb limit as corresponding to "negative" aflatoxin content by the USDA) and to those constituents of concern in botanical ingredients that might be purified or synthesized and added directly as ingredients to the overall formulation.

Then Use One of the Following:

1) If no limit is placed on the constituent(s) of concern, and the TTC approach was not applied:

{Example Discussion Paragraph}

The Panel noted 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 rat embryos. Hypericin was reported to be present in samples of various parts of the plant 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. However, the maximum concentration of use of *H. perforatum* extracts in cosmetics was reported to be 0.07%. This indicates that exposures to hypericin, quercetin and other minor constituents of these ingredients in cosmetics would be below levels of toxicological concern.

Followed by:

{Framework}

However, the Panel also noted that the use of other botanical ingredients that may contain [*constituent(s)*], in combination with [*botanical name*] ingredients in a single formulation, could result in exposures that exceed levels of toxicological concern. Thus, cosmetic products containing multiple botanical ingredients should be formulated to ensure that total exposures to such constituents remain below levels of toxicological concern when used as intended.

2) If no limit is placed on the constituent(s) of concern, and the TTC approach was applied:

{Example Discussion Paragraphs}

Other safety test data of individual chemical components of calendula (e.g., lutein), likewise, did not suggest any adverse effects. There are no dermal reproductive or developmental toxicity data on calendula extracts, but data on coriander oil, high in linalool and other terpenes, demonstrated that adverse effects occurred only at maternally toxic levels and did not occur at levels that were not maternally toxic.

Previous CIR safety assessments of fatty acids, plant sterols, paraffin, p-hydroxybenzoic acid, salicylic acid, and tocopherol, all of which are chemical components of calendula extracts, supported that these chemical components of calendula extracts would be safe at the levels found in the extracts and at the use concentration of the extracts. In previous CIR safety assessments of other listed chemical components of calendula extracts, including pyrogallol, pyrocatechol, and t-butylhydroquinone, adverse effects were identified. These concerns were considered relevant to this safety assessment because, for example, tannins comprise 6% - 10% of material derived from calendula and catechol is a subset of tannins. Analysis of actual calendula extracts, however, demonstrated that catechol and pyrogallol, coumarins (esculetin, scopoletin, and umbelliferon), and α-tocopherolquinone were not present at detectable levels. Given the low use concentrations of the extract, and the concentration of components that are only a small percentage of the total ingredient (below the level of detection in some cases), the Panel concluded that these extracts, as described, did not present a concern as used in cosmetics.

The Panel recognized that every extract would likely be somewhat different and that the characterization of the composition of these plant-derived ingredients presented in this safety assessment is broad. Nonetheless the composition does represent what commonly would be found in these ingredients prepared in the manner described. The conclusion regarding safety, therefore, is valid only for ingredients prepared in a manner that produces a similar chemical profile as that described in this report. Extracts not prepared in a manner that produces a similar chemical profile, could be considered safe only if they have a similar safety test profile.

Followed by:

{Framework}

The Panel also noted that the use of other botanical ingredients that may contain [*constituent(s)*], in combination with [*botanical name*] ingredients in a single formulation, could result in exposures that exceed the threshold of toxicological concern. Thus, cosmetic products containing multiple botanical ingredients should be formulated to ensure that total exposures to such constituents remain below the threshold of toxicological concern.

3) If a limit is placed on the constituent(s) of concern:

{Example Discussion Paragraph}

Because pulegone is toxic, the Panel limited it to ≤1% in cosmetic grade peppermint (mentha piperita) oil, peppermint (mentha piperita) extract, peppermint (mentha piperita) leaves, and peppermint (mentha piperita) water. The Panel was confident that this concentration was achievable both by controlling the time of harvest, and through the patented technique described in this report. Recent data reported that peppermint (mentha piperita) oil is used at a concentration of ≤ 3% in rinse-off formulations and ≤ 0.2% in leave-on formulations. This concentration of use data coupled with the ≤ 1% restriction on pulegone suggested to the Panel that pulegone toxicity would not be seen with cosmetic use.

Or:

{Example Discussion Paragraph}

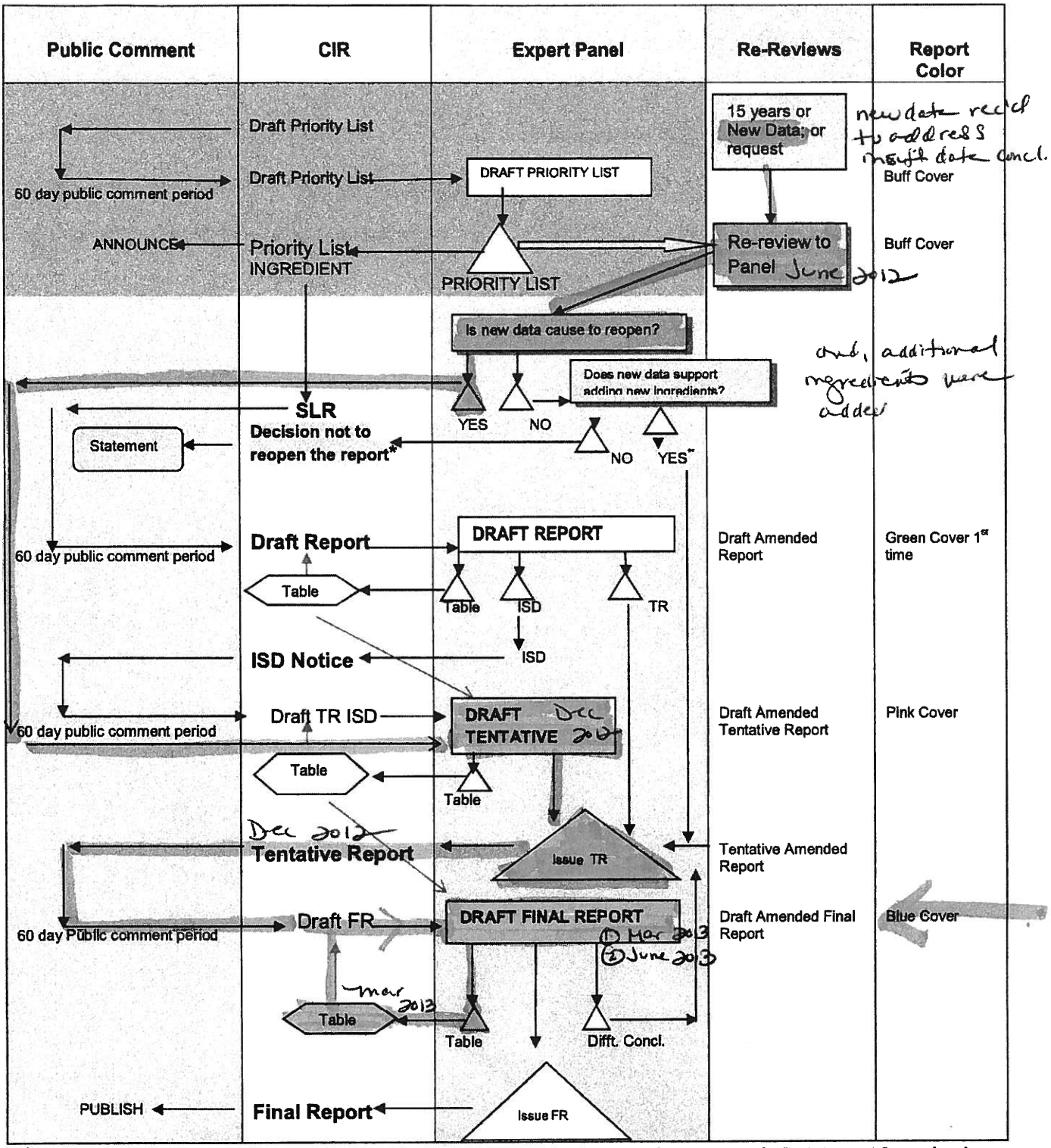
Pulegone is listed as a constituent of *P. quinquefolius*. The Panel recalled that pulegone toxicity was a concern with peppermint oil that required adoption of a concentration limit of ≤ 1% of pulegone. Because of the low use levels of ginseng-derived ingredients, including those derived from *P. quinquefolius*, the Panel was confident that a toxic concentration of pulegone could not be reached in cosmetics. Recent data, for example, reported that *P. quinquefolius* was used at a maximum of 0.002%.

Followed by:

{Framework}

However, the Panel also noted that the use of other botanical ingredients that may contain [*constituent(s)*], in combination with [*botanical name*] ingredients in a single formulation, could result in exposures that exceed levels of toxicological concern. Thus, cosmetic products containing multiple botanical ingredients should be formulated to ensure that total exposures to such constituents do not exceed the limit set by the Panel.

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 examined the Tentative Amended Report and was happy with the safe as used conclusion. Panel did, however, table the report so that new language could be developed in the discussion addressing the possibility of multiple botanical ingredients with the same constituents of concern being used in the same formulation.

June, 2013 – The Panel is to examine the new Discussion/Abstract boilerplate language for multiple botanical ingredients in the same formulation. The Panel should also issue a final report.

Hypericum perforatum (St. John's wort)-derived ingredients Data Profile for June, 2013. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Hypericum perforatum extract							X			X		X			X			X
Hypericum perforatum flower extract															X			X
Hypericum perforatum flower/leaf extract			OX	O			O			O	O		O		O			
Hypericum perforatum flower/leaf/stem extract																		
Hypericum perforatum flower/twig extract																		
Hypericum perforatum leaf extract																		
Hypericum perforatum oil			OX				O			O	O		O					OX
Hypericin and other constituents										X							X	X

X – New data; O – Data from the old (2001) report

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.

TRANSCRIPTS OF HYPERICUM PERFORATUM
MARCH, 2013 PANEL MEETING

DAY 1
Dr. Marks

DR. MARKS: …The next ingredient is hypericum perforatum. In December the panel issued for public comment a tentative amended safety assessment with a safe in the present practices of use conclusion for these plant-derived ingredients also known as St. John's Wort. We're at the point now of issuing a final amended report with a safe conclusion. We heard this morning the issue that Alan brought up a la if we have ingredients in one botanical that may have a toxic effect, how do we deal with multiple botanicals combined and the potential additive effect? The way I thought I could be handled is a botanical boilerplate advising the cosmetic formulators that if the total sum of particular ingredients like in this case hypericum or quercetin reached a potential level of toxicity that they should be aware of that. We might pick out either from botanical to botanical the particular ingredient or we may just have a list of flag ingredients of these botanicals and the combination of these could give a total amount which perhaps could be toxic. That was my idea of how to deal with it. Wilma?

DR. BERGFELD: That was mine too.

DR. MARKS: I guess we could develop that boilerplate. I don't know that we could develop it for this report because it would be delayed I think unless one didn't consider that a significant editorial comment, but it will probably take a few reviews of the boilerplate before we would land on what we're comfortable with.

DR. BERGFELD: May we ask Jay?

DR. ANSELL: We agree that it's likely to take several iterations before we're happy with boilerplate language. We think it's a most interesting issue to bring up and we'd like to have the time to think about it, talk about it more depth and disconnect that discussion from this specific report.

DR. SHANK: This not new for the panel. The toxicologists at least have considered this. We do it not only for botanicals but for all of these. If we review these individually but we realize that chemicals are used in combination, this is a well-recognized situation in toxicology and we'd go on the fact that the use concentration is such that there's a margin of safety which adequately covers the fact that you might be adding two or three other chemicals with the same impurities. There is still not a significant risk. This is not new for the panel.

DR. MARKS: Ron Shank, would your comment then be we don't need a boilerplate or we don't need to do anything, we do this as part of our routine safety assessment of these cosmetic ingredients?

DR. SHANK: I don't object to developing the boilerplate. That would be fine if we have something in print. But conceptually this is done by the panel so I don't think we have a problem in that we need to modify this report or go back to any of the other botanicals.

DR. SHANKS: Ron Hill?

DR. HILL: I agree.

DR. SLAGA: I agree.

DR. MARKS: I'll be presenting a motion and in the discussion of that motion I'll mention that moving forward our team feels that a botanical boilerplate can be developed dealing with this issue but we wouldn't delay the safety assessment of hypernicum based on that and that I would move that we issue a final report with safe in the present practice of use. Is that okay Tom and Rons? Wilma?

DR. BERGFELD: As a reminder, for the same reasons the pesticide boilerplate was developed with botanicals.

DR. SHANK: Yes.

DR. MARKS: Right. Are there any editorial comments, Rons or Tom, on the report? Lillian, you're going to get off easy there.

MS. BURNETT: I'm not done yet.

DR. MARKS: Are there no editorial comments?

Dr. Belsito

DR. BELSITO: Okay. Anything else? Okay. So, hypericum perforatum-derived ingredients. So we issued a tentative safety assessment -- safe in the present practice as used -- for public comment. Submission from industry I think that Tom Ray gave at the panel last year I think was captured very nicely.

Then I guess the question is, do we go with safe in the present practice of use and concentration?

And as Alan pointed out, I was asked at the American Academy of Dermatology this year to give a talk on botanicals because I've been sort of advocating for them among the North American Group. I think I sent you all a copy of the slides which probably made no sense without actually hearing the talk.

But I think the bottom line that got me concerned is -- and I've been patch testing for them -- is that you read some of these ingredients, and it's just botanical after botanical after botanical after botanical, and then when you go into Dr. Duke's phytochemical ethnobiology base you start seeing the same things popping up in these different botanicals.

So you're getting, you know, the sesquiterpene lactone is loaded one on top of another.

So, if you look at a product that contains just, you know, botanical X it may look very nice with botanical X at 0.4 percent. But when you look at a product that has botanical A through Z and they all have a little bit of terpene or carbonol or eugenol or some other ingredient, then they can start becoming an issue.

And you know, with pure defined chemicals it's always been easy for us to say, you know, it's a penetration enhancer, not with things that are concerned with penetration. It's not to be nitrosated, et cetera.

How do we put our handle around largely sensitization issues, I mean?

But then there are times when we say, okay, you know, this ingredient is safe as long as thujone is below the toxicologic threshold.

Or, for this one, hypericin -- you know it's a photosensitizer, but at less than 2 percent it's not in the way this is used and what's present in it. You know.

But then what other botanicals have hypericin? I don't know. You know, and teasing that out. So it just left me as I was putting this talk together and as I've been dealing with, increasingly, patients presenting with what I believe to be plant allergies in clinic and trying to work them out.

I'm just throwing out my concerns that how do we address the fact that when you're mixing botanicals, I mean, you've got to know what's in the botanical.

And there are probably some safety limits that we don't have because we haven't asked, okay, we know photosensitization for hypericin, once safe, where it goes, but do we know what is the concentration limit for sensitization to beta-pinene or alpha-pinene or citronella?

I mean, a lot of those we don't have. We can get some of them from the fragrance industry, but I don't know the fragrance industry has set standards for all of them.

And is it just the essential oils that are concerned? From my standpoint, probably. I mean, that's what the lactones and the oils -- on the lactones, I think we have some idea of where to go.

So do we set limits? You know. Do we go safe when combined with other botanicals not to cause an end-point toxicity, like say, for formulated to be nonsensitizing?

How do we wrap our hands around this issue of products containing 20 different plants?

DR. LIEBLER: So I think in the near term that's probably our best alternative -- is to say safe when formulated to be nonirritating/nonsensitizing because we don't have enough information about the concentrations of the different specific compounds in those different botanicals.

And in many cases we might not even have enough information about the relative amounts of each botanical product, I guess, or each botanical ingredient.

I guess we might have that, but then batch to batch it could be an order of magnitude or more variation for thujone or pinene or something.

Unless we get into the business of saying -- putting percent limits or ppm limits on individual ingredients and saying safe when pinene concentration not to exceed 500 ppm or something, I think our only fallback option is to say when formulated to be nonirritating or nonsensitizing.

DR. BELSITO: You know, I guess I'm okay with that. In a way, it's a little bit of a copout, but we ended up having to do that for cocamidopropyl betaine because of the same issue.

DR. LIEBLER: Well, we just can't get it right. We don't have enough information to do it right.

I hear what you're saying. You know, we would like to be able to be more specific. The problem is we lack the information about the concentration of all the ingredients and all the botanicals.

DR. BRESLAWEC: But you have a concentration on, or a limit on, a certain ingredient, considering (inaudible). Just bear in mind, of course, a lot of these botanical extracts are used at very, very low concentrations.

DR. BELSITO: No, I understand that, and that's been our argument not to be concerned about safety. But, you know, I mean if you look at a couple of the formulation sizes sent around -- boom! I mean, just the list is endless. It's plant after plant after plant after plant after plant. And you start adding 0.04 together, and they start to be 1 and 2 and 3 percent.

Then when you start -- I mean, I hate people who come in with plant-derived products, and I suspect it's a cause of their allergic reactions because, I mean, it takes me hours. Thank God that I have access to that, or maybe it's a curse because I know it's there and then I have to do it.

But Dr. Duke's database -- I mean, you have to look at, okay, here's what all is adding up and do I have that individual plant ingredient or not; how am I going to get around this?

DR. SNYDER: So couldn't we just address that in our conclusion, to say that the conclusion is based upon this as a sole source?

DR. BELSITO: Yes, but in fact --

DR. SNYDER: If there are multiple botanicals, then the safety is not determined or it's insufficient, I mean. Right?

DR. BELSITO: Yes, but the truth of the matter is start reading labels; there are very few cosmetic products that contain only one plant.

DR. BRESLAWEC: But what you're suggesting is if you look at the finished product and you test the finished product and make sure that it's not sensitizing or irritating. It's formulated not to be.

DR. BELSITO: Right.

DR. BRESLAWEC: And that would take into account the total amount, correct?

DR. BELSITO: Right. I mean, again, I think it's probably the only avenue we

have -- is to say that to maybe work on a boilerplate in the discussion, saying that it is not unusual for one botanical product to be used with additional botanicals in a given cosmetic ingredient. This may increase the total exposure to a sensitizer, an irritant or whatever. The formulator should be -- however we said it for cocamidopropyl betaine -- cognizant when doing this and ensure that their product is formulated not to cause sensitization or irritation.

The alternative is we're never going to go safe on any of these because we're going to have to look at all their individual potential sensitizers. We're going to need to know: Okay, where is, as we've saying, the fragrance ingredients lexicon? Where's the nestle -- the level at which you don't expect to see sensitization for all of them? And then say, okay, this is safe when put into a cosmetic ingredient as long as the level of alpha-pinene does not exceed this, the level of this does not exceed that -- boom, boom, boom!

I mean, it's going to be endless.

DR. SNYDER: Well, it becomes a slippery slope because even here in the third paragraph of the discussion of impurities we're saying impurities in this botanical were concluded that the amount of exposure is below the threshold of toxicologic concern. But if you combine it with seven other botanicals which have similar profiles of impurities, all of a sudden you may start to approximate levels of toxicologic concerns.

DR. BELSITO: Well, I mean, that's why I think we need to develop a boilerplate that addresses not only the issues of sensitization but the issues of heavy metal, or pesticide, of all of the impurities -- of things that, for instance, when we talk about hypericin here, you know there are other botanicals that also contain hypericin. We need to be concerned about combining those because of photosensitization.

I mean, I think we need to deal with all of those because -- I mean, it's just -- I read labels all the time, and I can't tell you the last time I saw a product that contained a botanical that only had one. Most of the time, the minute they contain one, they have at least four or five others.

DR. LIEBLER: So the Dr. Duke's -- I've never looked at it, but the Dr. Duke's is just a listing of the components, or does it have some concentration --

DR. BELSITO: You can use it in many different ways. You can put in the plant you're interested in, and it lists the components.

DR. LIEBLER: But if it had, for example, thujone, would it indicate how much --

DR. BELSITO: You could do thujone.

DR. LIEBLER: Would it indicate how much thujone is in a particular botanical, or the range?

DR. BELSITO: It would give you a list of plants that contain thujone. And then you could click on that plant, and it could give you a range for the plant.

DR. LIEBLER: So if you then -- I don't know if this is incorporated then. If you were able to click on and save this botanical to the clipboard and do that with the ingredients in your product, it would come up with a list of ranges of chemical substances of interest?

DR. BELSITO: Right.

DR. LIEBLER: Essentially, that would do the mental calculation you go through when you're dealing with a patient and a product and you're looking at the list of ingredients and you're going through Dr. Duke's and then mentally trying to add it up?

DR. BELSITO: Mm-hmm.

DR. BRESLAWEC: Without knowing exactly what the concentration is in the product.

DR. BELSITO: Right, but just getting a sense of what are the sensitizers in my opinion that are getting added one on top of the other by combining lavender with arnica, with calendula, with whatever.

It won't go on the screen?

MS. BURNETT: It's on my computer.

DR. LIEBLER: Okay, I see.

MS. BURNETT: So that was for the hypericum perforatum.

So I just put in the plant name and asked for it, and it spits out whatever.

DR. LIEBLER: Right, a bunch of biological activities.

MS. BURNETT: For each component.

DR. LIEBLER: Right. Okay. Got it. Cool. Thank you. Subscription service?

MS. BURNETT: No.

DR. BELSITO: No, it's free.

DR. LIEBLER: Okay.

MS. BURNETT: It's a government web site.

DR. SNYDER: Regarding impurities, if we -- on that last sentence of that third paragraph there, because the maximum concentration in cosmetics containing these extracts is reported to be 0.07 percent, the panel concluded that the amount of exposure to these constituents would be below the level of toxicologic concern. However, when combined with other source ingredients that contain these impurities, the potential toxicity may occur.

Would that then be the type of language you're talking about as a kind of boilerplate to capture?

DR. BELSITO: Yes, but then you don't want to say that the toxicity may occur in a cosmetic product. You want to say something to the effect that the manufacturer should be aware of this and prevent that from happening.

DR. LIEBLER: Okay. So this is like what Paul said --

DR. SNYDER: This is in the discussion. This is in the discussion.

DR. BELSITO: No, I understand. I understand, but I think it's very critical that we sort of get this right.

DR. LIEBLER: So instead of saying the additive concentrations where a toxicity may occur, you would say the addition of other botanical ingredients would increase the concentrations of some specific compounds that could produce irritation or sensitization. Manufacturers should formulate these products to be nonsensitizing and nonirritating -- should be aware of this issue and formulate products to be nonsensitizing and nonirritating.

DR. BELSITO: Right. I mean, that should be a boilerplate for all of the plant-derived products.

DR. LIEBLER: Right.

DR. SNYDER: And that's why I changed it. Instead of combined, I said, however, when formulated with other source ingredients that contain these impurities, the potential for toxicity may occur.

DR. BELSITO: Right. And then for this particular one, we go on and talk about the hypericin and quercetin. It says: Because the maximum concentration used in cosmetics that contain these H. perforatum extracts is reported to be 0.07 percent, the panel concluded the amount of exposure to these constituents will be below the level of toxicologic concern. However, manufacturers using other botanicals that may contain hypericin or quercetin should be aware of the possible -- I don't know how to phrase it -- additive effects, or should take care to assure that the finished product -- or, the level of these ingredients in the finished product remains below the level of toxicologic concern, or something to that effect.

DR. SNYDER: I mean, that's easy to do for the impurities. I think it's a little bit harder to do --

DR. BELSITO: And then we have the heavy metals and pesticides, which will need to be a boiler -- so, I mean, I think the sensitization and irritation and the heavy metal and

pesticide needs to be a boilerplate on all of these botanicals.

DR. BRESLAWEC: I think there's a boilerplate on impurities and heavy metals in botanicals, and maybe what CIR needs to do is --

MS. BURNETT: Aflatoxins.

DR. BRESLAWEC: Aflatoxins -- need to look at the overall --

DR. BELSITO: Right.

DR. BRESLAWEC: -- boilerplate and make sure that these unintended constituents are considered as well.

DR. BELSITO: Okay. But this was supposed to go final, and we're asking for a lot of stuff in the discussion. Do we get a chance to look at it before it's submitted to the journal?

MS. BURNETT: Formally or informally? We can email it to you after the edits have been made.

DR. BELSITO: Yes. I mean, I would like -- I mean, I don't -- you know, we can vote on it because I think we're going to keep our conclusion, but I think the crafting of the discussion is critical. And certainly -- particularly now that my name appears on the report, oftentimes immediately after the author -- I would like to know exactly what I said in the discussion.

So, yes, I think informally as an email.

DR. LIEBLER: Don, I tried to capture what you said to put at the end of the third paragraph, and so what I wrote is: However, manufacturers using other botanicals should be aware that these additional botanical ingredients could elevate levels of some specific compounds above the level of toxicologic concern.

Now you want to add to that?

DR. BELSITO: And assure that this does not happen, or something to that effect.

DR. BRESLAWEC: And what is the level of toxicologic concern?

COURT REPORTER: Speak up, please.

DR. SNYDER: That's where it becomes difficult. That's why I think just simple wording. Say: However, when formulated with other source ingredients that contain these constituents and impurities, the potential toxicity may occur.

We don't --

DR. BRESLAWEC: Well, what happens --

DR. SNYDER: Because we can't define it.

DR. BRESLAWEC: Yes.

DR. SNYDER: If we could define it, then we could deal with it.

DR. LIEBLER: I like your language better than mine, actually. So we go with that, but I think you could simply add one more short sentence that says: Therefore, these -- or, in view of this, something like that.

In view of this information, these products should be formulated to be nonsensitizing and nonirritating.

DR. BELSITO: Well, the level of toxicologic concern has typically been defined in the report because there's been -- you don't think so?

I mean, there's been a report that hypericin at 5 percent caused photosensitization; at 2 percent, it didn't. There was a report suggesting that quercetin can be carcinogenic, and there was a level given at which that was observed.

And so, that seems to be the level of toxicologic concern, and we're using it. That was 10 percent, and we're using 0.004 percent.

DR. BRESLAWEC: But you're using that for two ingredients, specifically, and the conclusion applies across the board.

DR. BELSITO: Mm-hmm.

DR. BRESLAWEC: And I think that's what -- I don't like the language that

suggests the potential for toxicologic concern because I really do think these ingredients are used at such low levels that that's not an issue. So it would be nice to develop some kind of --

DR. BELSITO: That's what you usually use the words, below the level of the threshold of toxicologic concern, for -- that the ingredient itself is used at such a low concentration. And then the constituent of concern -- thujone, quercetin or whatever it is -- is a small percentage of that ingredient.

DR. BRESLAWEC: If you limit it to the ingredient -- constituent of concern -- then that's one thing. But I think we were applying the language a little more broadly.

DR. BELSITO: No, I mean in the case of this the two ingredients of concern were hypericin and quercetin.

DR. BRESLAWEC: Could I suggest that on this particular report I think you know exactly where you are, what you're concerned about and what levels you'd be concerned about?

If you wanted to act on this report, kind of using the existing paradigm, I think you could do so and then suggest that the panel work on revising the existing boilerplates for all the unintended constituents.

DR. SNYDER: It could be that we could go into a thing like we have for inhalation for the hair dye epidemiology where we actually have a site and we talk about the botanicals and the evaluation of safety in these assessments is focused as this is a sole source.

However, then with other source ingredients that may contain contaminants identified in safety assessments, we could have some language that could kind of deal with that maybe?

MS. BURNETT: We actually discuss that in-house last week.

DR. SNYDER: I think that might be a way to --

DR. KATZ: I'm going to make a suggestion. It doesn't sound like this report is ready to go final. There are a number of issues that need to be readdressed or at least talked about and reconsidered, and I think doing it informally will not get it done that way. Especially if you're considering adopting a boilerplate language to go for other things, I think there probably needs to be more discussion.

DR. BELSITO: Yes, I was actually just thinking about maybe just tabling it and hearing the discussion from the other group tomorrow and thrashing out some boilerplates that can be used for the botanicals and then seeing it back and having time to think about it.

DR. BRESLAWEC: Yes. I mean, as an industry, we spent a lot of time developing a botanical boilerplate and a path forward for being able to evaluate botanicals. I think it's a good idea to take the time we need to work that through.

DR. BELSITO: Yes, that really is critical.

DR. LIEBLER: While we are on comments, I do have one comment on page 18 of the PDF, which is report page 4, under pharmacokinetic effects. The first paragraph describes essentially something that's sort of pharmacodynamics.

I mean, it's the effect of hypericin on release of mediators of response to (inaudible) esters and so on. It's definitely not pharmacokinetics.

The start of the second paragraph begins with pharmacokinetics.

So this stuff isn't pharmacokinetics. I'm not sure it's really relevant to the report.

MS. BURNETT: Do you want to delete it?

DR. LIEBLER: I would suggest deleting. If the panel felt like we needed to keep it, then it should have another heading, perhaps Other Pharmacological Effects or Anti-Inflammatory Effects. But I'm not sure that the effects studied in these cell models are really relevant to effects that would be produced by use of the product.

DR. SNYDER: This is where Curt mentioned that he wanted that changed to drug effects.

DR. LIEBLER: Yes. So, if you keep it, it needs another heading, either Drug Effects or Anti-Inflammatory Effects, but I would say that you don't really need to keep these.

Or, Drug Interactions. I'm sorry. Drug Interactions.

Did you feel like they should be in there, Don?

DR. BELSITO: I agree with what you're saying.

DR. LIEBLER: Okay. Paul, do you think they could be dropped?

DR. SNYDER: I agree.

DR. LIEBLER: So I guess the three of us here would say delete that paragraph.

MS. BURNETT: Okay.

DR. LIEBLER: And that takes care of it.

MS. BURNETT: That whole, essentially, section of pharmacokinetic effects?

DR. LIEBLER: Yes.

MS. BURNETT: Okay.

DR. LIEBLER: Right.

MS. BURNETT: Okay.

DR. LIEBLER: From here to here.

MS. BURNETT: Oh, just that paragraph?

DR. LIEBLER: Just that. This is okay. This is pharmacokinetics.

MS. BURNETT: Okay.

DR. LIEBLER: But this is what you delete, right here.

DR. EISENMANN: But it's really not pharmacokinetics of the ingredients. It's a drug interaction. So drug interaction would be a better --

DR. SNYDER: Yes, that's why Curt was suggesting Drug Interactions.

DR. LIEBLER: I agree.

DR. BELSITO: So just move it?

DR. LIEBLER: You're still deleting this part. Kevin is making some --

DR. BELSITO: Deleting --

DR. LIEBLER: I'll do it on my copy.

DR. SNYDER: Yes, I have it on my too.

MR. FRIES: I'm just pointing.

MS. BURNETT: Okay.

DR. LIEBLER: Yes, okay.

MS. BURNETT: I was just going to tell Lill to delete that paragraph. And then re-title that section?

DR. LIEBLER: Mm-hmm.

MS. BURNETT: Okay.

DR. BELSITO: All right. Anything else? Okay.

DAY 2

DR. BERGFELD: ...Then moving on to botanical hypericum perforatum, and Dr. Marks presenting.

DR. MARKS: In December, the panel issued a tentative amended safety assessment for hypericum perforatum a.k.a. St. John's wort with a conclusion of safe. We move that a final amended report be issued with that conclusion, safe as used.

Now, move on to a little bit of discussion.

DR. BERGFELD: Okay.

DR. MARKS: There was concern raised that there perhaps could be components of these botanicals that in the individual ingredient are botanical, it would be they wouldn't rise to a level of being toxic, but if you added a number of botanicals together, perhaps there could be

toxicity.

So, our team suggested that a boilerplate be devised which would address that. In fact, the discussion was around the issue of well, we've known this with other ingredients, also; they have potential toxic effects, and perhaps if you added multiple ingredients together, it could rise to a level that caused some toxicity.

So, we would not delay the issuing of the final amended report for this boilerplate, but work on it for the future. And specifically in this, just as an example, hypericin causes phototoxicity and quecetin causes liver toxicity and perhaps if you added it with other botanicals, the level might become significant.

So, longwinded discussion, the motion stands to move forward with a final amended report with safe for this ingredient.

DR. BERGFELD: Paul or a second?

SPEAKER: No second.

DR. BERGFELD: No second. Discussion, Paul?

DR. SNYDER: Yes, so, we raised the exact same concerns. Our philosophy towards this report was to table the report until we could determine how that was going to be handled with complex mixtures of multiple botanicals. We felt that this particular ingredient, having the two impurities that you talked about and having them be at fairly high levels and we know that many other botanicals, particularly quercetin, are within other botanicals and when you start accumulating these and getting these added up, we just wanted to make sure that we sent a loud and clear message to the formulators that when they start to combine these, that they need to take under serious consideration and we weren't comfortable just issuing a final report without a little bit stronger language.

We tried to modify some of the language in the current discussion, but Don wasn't comfortable that that was going to be a message received. And, so, we wanted to propose to table it, have the writers and Alan's staff visit this and come to us with some kind of resolution that we then could move forward or we didn't see any issues with individual ingredients, it was just that when we start to -- knowing that many of these are in complex mixtures containing multiple botanicals, we were concerned.

DR. BERGFELD: Well, a motion to table precedes an original motion which was not seconded.

Is there a second to table?

DR. MARKS: Well, team members, one of the discussants we had was how long was it going to take to get this boilerplate? So, we didn't want it to delay indefinitely awaiting a boilerplate. But any rate, obviously, if it's done with some urgency, certainly tabling is a reasonable alternative than moving forward with a final.

Team members? (No response) So, I'll withdraw my motion.

DR. BERGFELD: And you're seconding the table?

DR. MARKS: Second the table to address --

DR. BERGFELD: All those in favor of the table, please indicate by raising your hands.

(Hands raised)

DR. BERGFELD: Oh, unanimous. Okay, it's tabled for the boilerplate.

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

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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.

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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. Because formulators may use more than one botanical ingredient in a formulation, caution was urged to avoid reaching levels of concern for constituent chemicals and impurities such as pesticides. 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 interactions 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.

Information on the characterization of different commercial *H. perforatum* extracts with regards to hypericins, hyperforin, and flavonoids 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, and 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 has 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% in Beeler base) for 24 h.[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 after 2 weeks.

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 placebo-controlled parallel-group 8-day 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).

Intravenous

HYPERCICIN

Intravenous administration of hypericin (2 mg/kg in 2% benzyl alcohol and saline) to rhesus monkeys (*Maccaca mulatta*; n = 3) resulted in 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.

In Vitro

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.

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.

Drug Interactions

HYPERICIN

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.

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; and 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. Males were not treated. 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 liver, kidney, heart, lungs, brain, and small intestine 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 liver 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 decrease in glomerular size with decrease 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) observed 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

In an in vitro study, 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 concentrations 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, QUERCETIN, 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 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.

In a test of the protective effect of quercetin, a natural antioxidant compound, on hypericin-induced cytotoxicity under light conditions 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.

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 x 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 that were identified because 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 extrapolating the available toxicological data to support the safety of the entire group.

The Expert Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

Formulators must minimize the overall concentrations of impurities and constituents of concern when more than one botanical ingredient is used in a cosmetic formulation. A cosmetic formulation may contain multiple botanical ingredients, each of which can contribute to the total concentration of pesticides, heavy metals, or other substances of concern in the botanical ingredients. As a result, industry must employ the procedures necessary to limit the concentrations of pesticide residues and heavy metals that result from combining botanical ingredients in the entire finished product, NOT just to each of the component ingredients in the formulation.

For example, the Panel noted that one constituent of *Hypericin perforatum*-derived ingredients is hypericin. Hypericin has been shown to be a photosensitizer in visible light and to have possible teratogenic effects in an in vitro 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 threshold of toxicological concern.

The Panel also noted that the use of other botanical ingredients that may contain hypericin and/or quercetin, in combination with *H. perforatum*-derived ingredients in a single formulation, could result in exposures that exceed levels of toxicological concern. Thus, cosmetic products containing multiple botanical ingredients should be formulated to ensure that total exposures to such constituents remain below levels of toxicological concern when used as intended.

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 seven *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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FDA VCRP Use Data 2013 *H. Perforatum*

01B - Baby Lotions, Oils, Powders, and Creams	HYPERICUM PERFORATUM EXTRACT	1
03D - Eye Lotion	HYPERICUM PERFORATUM EXTRACT	1
03F - Mascara	HYPERICUM PERFORATUM EXTRACT	2
03G - Other Eye Makeup Preparations	HYPERICUM PERFORATUM EXTRACT	2
05F - Shampoos (non-coloring)	HYPERICUM PERFORATUM EXTRACT	1
07I - Other Makeup Preparations	HYPERICUM PERFORATUM EXTRACT	1
12A - Cleansing	HYPERICUM PERFORATUM EXTRACT	1
12C - Face and Neck (exc shave)	HYPERICUM PERFORATUM EXTRACT	6
12D - Body and Hand (exc shave)	HYPERICUM PERFORATUM EXTRACT	7
12F - Moisturizing	HYPERICUM PERFORATUM EXTRACT	6
12G - Night	HYPERICUM PERFORATUM EXTRACT	2
12I - Skin Fresheners	HYPERICUM PERFORATUM EXTRACT	3
12J - Other Skin Care Preps	HYPERICUM PERFORATUM EXTRACT	3
		36

07C - Foundations	ST JOHNS WORT (HYPERICUM PERFORATUM)	1
12C - Face and Neck (exc shave)	ST JOHNS WORT (HYPERICUM PERFORATUM)	1
12J - Other Skin Care Preps	ST JOHNS WORT (HYPERICUM PERFORATUM)	1
		3

01B - Baby Lotions, Oils, Powders, and Creams	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
02B - Bubble Baths	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
03D - Eye Lotion	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
05A - Hair Conditioner	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
05F - Shampoos (non-coloring)	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	8
05I - Other Hair Preparations	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	2
07I - Other Makeup Preparations	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
10A - Bath Soaps and Detergents	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
10E - Other Personal Cleanliness Products	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
11A - Aftershave Lotion	HYPERICUM PERFORATUM FLOWER/	3

	LEAF/STEM EXTRACT	
11E - Shaving Cream	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
12A - Cleansing	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	8
12C - Face and Neck (exc shave)	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	7
12D - Body and Hand (exc shave)	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	7
12F - Moisturizing	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	10
12G - Night	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	4
12H - Paste Masks (mud packs)	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	4
12I - Skin Fresheners	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
12J - Other Skin Care Preps	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	10
13B - Indoor Tanning Preparations	HYPERICUM PERFORATUM FLOWER/ LEAF/STEM EXTRACT	1
		73

03D - Eye Lotion	HYPERICUM PERFORATUM OIL	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYPERICUM PERFORATUM OIL	1
11A - Aftershave Lotion	HYPERICUM PERFORATUM OIL	1
11G - Other Shaving Preparation Products	HYPERICUM PERFORATUM OIL	1
12A - Cleansing	HYPERICUM PERFORATUM OIL	2
12C - Face and Neck (exc shave)	HYPERICUM PERFORATUM OIL	3
12D - Body and Hand (exc shave)	HYPERICUM PERFORATUM OIL	4
12F - Moisturizing	HYPERICUM PERFORATUM OIL	1
12H - Paste Masks (mud packs)	HYPERICUM PERFORATUM OIL	1
12J - Other Skin Care Preps	HYPERICUM PERFORATUM OIL	2
13A - Suntan Gels, Creams, and Liquids	HYPERICUM PERFORATUM OIL	1
		18

03D - Eye Lotion	999002190	HYPERICUM PERFORATUM FLOWER EXTRACT	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

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: March 12, 2013

SUBJECT: Comments on the Draft Report on *Hypericum perforatum*-Derived Ingredients Prepared for the March 18-19, 2013 CIR Expert Panel Meeting

Key Issues

This report should also include some basic information about the plant, e.g., what are other genus species names used for this plant? e.g., *Hypericum vulgare*, what type of plant is it? what does it look like? where does it grow?, and the report should include some information on historic uses of this plant. If this information was in the original CIR report, it should be mentioned in the summary of the original safety assessment.

In the Discussion, it is misleading to state that hypericin has been shown "to have possible teratogenic effects in studies using rats." The basis of this statement needs to be included in the Discussion. 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

Additional Comments

p.2 - Although it may have come from the original CIR report, the meaning of "although some undesirable drug effects were observed" is not clear. This statement suggests that *Hypericum perforatum* extract itself had some undesirable drug effects, it is more likely some undesirable drug interactions were observed.

p.3, 10 - In the cosmetic use section and the Discussion section, it is not clear why the 0.07% concentration in a body and hand product is being classified as a possible "loose powder". It could just as easily be a lotion or a pressed powder. For many FDA product categories, the form of the product is not known. No concentrations of use are shown in powder products in Table 4 (p.20). In the text, why is it necessary to artificially identify a specific product as having potential inhalation exposure? If the CIR Expert Panel would like potential inhalation exposure to be discussed in each report, there should be some general language developed that states that it is not know whether or not x ingredients are used in cosmetic sprays or powders. Then the potential exposure sprays and powders should be described.

p.3 - Please include the vehicle and the duration of exposure used in the dermal absorption study of hypericin in mice.

p.3 - The duration of the "short-term" exposure study in humans is not clear. Was this just a 1 day

exposure study in which the subjects were given 3 doses? Or where the subjects dosed for more than 1 day?

p.4 - How long was the repeated dose study described in the paragraph starting: "In a second human double-blind study,..."

p.4 - The study in the last paragraph under the Oral heading appears to be an *in vitro* study. Therefore, it should be moved to a different subsection.

p.4 - Please revise the following phrase: "Intravenous administration of hypericin to rhesus monkeys had a mean peak plasma concentration..." as this sentence is written, the word "administration" is the subject of the sentence.

p.4, Pharmacokinetic Effects - Please revise: "released from the cells by ELISA test kits"

p.4 - The newly added paragraph is about a study that looked at potential phototoxic effects, but there is no description of light exposure. This study needs to be moved to the *in vitro* phototoxicity section (p.8) where there are other studies that suggest that complete extracts of *Hypericum perforatum* are less phototoxic than hypericin alone.

p.5 - Please describe how the male mice were treated in the two-generation study.

p.6 - The study examining the contractility of the vas deferens suggests that rats were exposed. Please include the route of exposure (or it should be stated if this was an *in vitro* study).

p.7 - It would be helpful if the Phototoxicity section also had human and animal subsections.

p.8 - Please revise the following sentence (as it is likely the keratinocytes were exposed to hypericin and the plant extracts): "Hypericin combined with *H. perforatum* extracts (plant parts not specified) or constituents exerted less phototoxicity than pure hypericin when exposed to HaCaT keratinocytes."

p.9 - In the Summary, it is not clear why hypericin is being called "the most active constituent of *H. perforatum*". Where is the study that compares the "activity" of hypericin to other constituents? It is not clear what is meant by "active". What type of activity?

p.10 - In the Summary, please indicate the route of exposure, or if the study on the vas deferens of rats and humans was an *in vitro* exposure study.

p.10 - The following sentence does not make sense as human leukocytes are not viruses or tumors: "Hypericin demonstrated antiviral, anti-inflammatory, and antitumor effects to human leukocytes."

p.10 - Please revise the following sentence (human keratinocyte cells is the subject of the sentence - it is unlikely that they caused effects when exposed to UVA): "Human keratinocyte cells incubated in *H. perforatum* extracts and constituents demonstrated increased cytotoxic and photogenotoxic effects when exposed to UVA."

p.10 - In addition to identifying quercetin as a possible genotoxicant, it would also be helpful to state that it is an antioxidant.

p.10 - As these ingredients are unlikely to be particles, the following sentence in the Discussion does not make sense: "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."

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