PINK

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

CIR EXPERT PANEL MEETING

DECEMBER 10-11, 2012

Cosmetic Ingredient Review
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November 16, 2012

MEMORANDUM

To: CIR Expert Panel and Liaisons

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

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

At the June, 2012 meeting, the CIR Expert Panel agreed to reopen this safety assessment to incorporate the large amount of new data provided for Hypericum perforatum-derived ingredients (the common name for this plant is St. John's wort). The Panel determined that the new data likely addressed the data needs and suggested that this ingredient may be safe for use in cosmetics, so a draft tentative amended report has been prepared.

The Panel also determined to add the following Hypericum perforatum-derived ingredients:

- hypericum perforatum callus culture 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

Attached is a draft tentative amended safety assessment that includes the data submitted by the Personal Care Products Council's CIR Science and Support Committee. In addition, the relevant data from the European Medicines Agency's review of *Hypericum perforatum* (2009) have been added to the report along with other published studies.

Note that since the original report was published, the name of **hypericum perforatum extract** was changed to **hypericum perforatum flower/leaf/stem extract**. 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*.

The Panel should review the draft tentative amended report and confirm that it is appropriate to add the new ingredients. Then the Panel should confirm that the new data satisfy the needs of the Panel and issue a tentative amended report for public comment.

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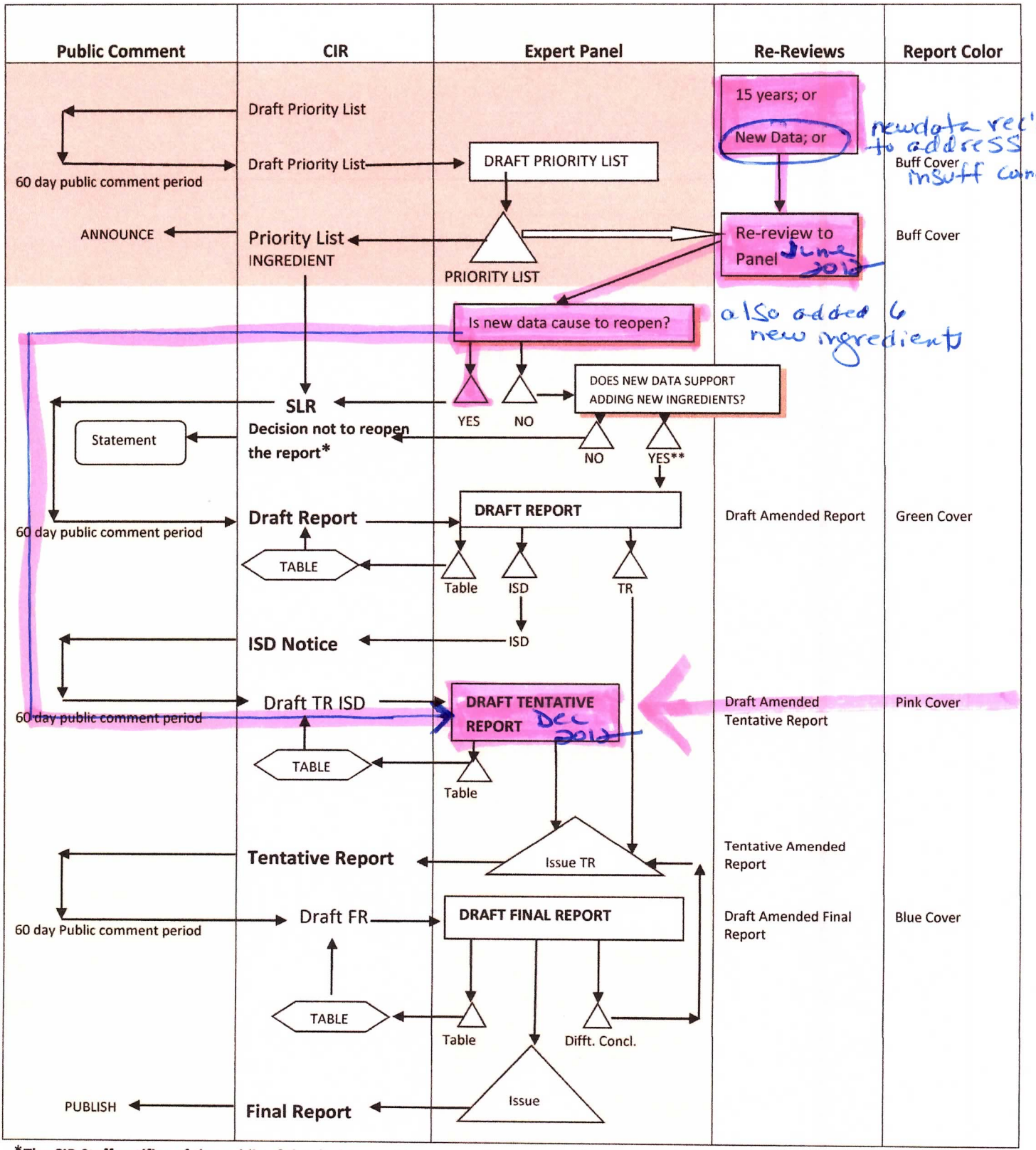
Hypericum Perforatum Ingredients Dec 2012

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 perofratum* (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 examines the Tentative Amended Report with the new data.

Hypericum perforatum (St. John's wort)-derived ingredients Data Profile for December, 2012. 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 callus culture extract																		
Hypericum perforatum extract							X			X		X			X			X
Hypericum perforatum flower extract															X			X
Hypericum perforatum flower/leaf extract			X															
Hypericum perforatum flower/leaf/stem extract																		
Hypericum perforatum flower/twig extract																		
Hypericum perforatum leaf extract																		
Hypericum perforatum oil			X															X
Hypericin and other constituents										X							X	X

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.

Transcript

Hypericum Perforatum-Derived Ingredients
Transcripts from June, 2012

DR. MARKS: Okay, next. Same book, one tab behind, hypericum. And in '98 the Panel found these two ingredients, the extract and the oil, had insufficient data. There were a number of data needs. So now the question is, does it look like we're going to have enough data that we should reopen? And then the second, of course, would be, do we also add on these other things?

DR. SLAGA: Yes.

DR. MARKS: Yes to both?

DR. SLAGA: Yes. Could we also tomorrow have the group's pathology, histopathology in the skin -- it says it's from an abstract that has no details or is short on details, whatever that means.

DR. ANDERSEN: I have heard back from the author, and the response was, "The person that paid me to do this work won't let me give you the details," so go fish. He was more polite than that.

DR. SLAGA: Oh, he was?

DR. ANDERSEN: The data are not going to be available.

DR. MARKS: Okay. So reopen?

DR. SLAGA: We need to reopen..

DR. SHANK: Well, we still have a problem with photosensitivity.

DR. MARKS: Yeah, it's phototoxic.

DR. SHANK: So if we reopen but still find it insufficient, is it worth reopening? Because the one dermal, mouse dermal, study with hypericin -- is that how it's pronounced? -- now that's a chemical from the plant -- was from toxic, and we had asked for phototoxicity data.

DR. MARKS: Right below that it says it's "unpublished guinea pig max." It says "no sensitization or photosensitization noted."

DR. SHANK: And that was a low concentration.

DR. MARKS: It says 10 percent, so the whole plant presumably at a 10 percent dilution for induction.

DR. SHANK: 1.1 percent of the plant diluted 10 percent.

DR. MARKS: And we don't have -- do we have -- we don't have a concentration and use table, right? Or do we?

DR. ANDERSEN: No, not yet.

DR. MARKS: Well, we had that and then the phototoxin. And then I have on the next page where it says "skin irritation/sensitization," it says "one published human irritation study was negative," but it doesn't -- I don't know if that's irritation meaning is that an RIPT or not. It doesn't say sensitization was negative. So we could still reopen and wean down the insufficient needs, or we may feel comfortable that that may come in.

DR. SLAGA: We could also bring in all these additional ones, too.

DR. MARKS: Yes, and bring in the additional ones. There might be something in that that actually would be reassuring.

DR. ANSELL: I think our position is we would like to have this discussion.

DR. MARKS: Yeah.

DR. ANSELL: To put the data on the table, see where you come out. It's quite possible that companies would be willing to go back, and we'd at least have the opportunity -- like to have the opportunity -- to go back to the companies and say here's where we are in 2012.

DR. MARKS: So reopen, yes. Add-ons, yes. Okay. What is this? St. John's wort is the common name? There certainly should be medicinal stuff on that, too.

DR. HILL: There is, lots.

Dr. Belsito's Team

DR. BELSITO: Okay. Staying right in the Yellow Book, I believe --

DR. KLAASSEN: Yes.

DR. BELSITO: I haven't moved my page. But I think we're doing it. The hypericum perforatum extract and oil. Again, '98 we looked at these two ingredients and found them insufficient. We wanted concentration of use. We wanted function in cosmetics. We wanted photosensitization and

phototoxicity. We wanted gross pathology and histopathology, dermal repro, developmental tox, skin irritation and sensitization, ocular irritation and concentration of use if available. We pretty much got everything we asked for except for ocular irritation. I'll ask Paul again about the male repro effects but I assume that's dose-related. I guess from the dermatologic standpoint it's quite clear to me that at least a component hypericum is a significant photosensitizer in the visible wave length and that's well documented throughout. There are a couple of statements that would indicate it has to be at levels of greater than 100 ng/ml but then on Panel Book page 220 there's an incident where it was present at 2.8 ng/ml and induced phototoxicity with visible light.

So it gives me a little bit of a pause as to if I'm going to make Lillian -- this would be Lillian's or -- LG, this would be yours to assign. If I'm going to tell Lillian Gill to assign this to someone, am I already set in my ways that it can't be safely used because of this absorption in the visible? I mean, this isn't even like UVB or UVA. This is, you know, we're talking about 440 nanometers. I don't know. And then obviously we would have the quercetin. We'd have to look back and see how we've regulated that.

So with that as my off the top of my head background, Paul, comment on the repro and other people comment on your thoughts.

DR. SNYDER: Yeah, I have the same comment. I'm going to retract the reopen statement. I think we should proceed to consider reopening. I think that's the correct terminology. That we want to see the rest of the data. The same thing here. I want to see the rest of the data. It appears to be on the surface that we will have data needs met and there are not going to be any major issues to address. And so I think we want to proceed to the next level and get the studies, get the data, and look at it. And then at that time we'll determine whether we're going to reopen. I believe that's the correct thing. Right?

DR. BELSITO: Yeah, I guess. You know, I mean, again, I guess, I just struggle with the idea that I'm always comfortable setting limits and in this case, you know, we could set limits for cosmetic grade in terms of quercetin presumably and I would ask if we do reopen that whoever is doing this go back and look at the data in terms of what we know about quercetin and mutagenicity. But if you read this tome that was put together by EMEA in 2009, and it's their page 46 of 77, but it's Panel Book 200, page 200, I believe, where they're looking -- at least I said it was 200 -- 200, I'm sorry. Panel Book 220, where they're looking at phototoxicity. That's 2.3. It's about six lines up from the bottom. It says, "After steady state administration," -- this is where they're giving it orally -- "mean serum level of total hypericin was 12.5 ng/ml and the mean skin blister fluid level was 2.8 ng/ml. These skin levels are far below hypericin skin levels that are estimated to be phototoxic, greater than 100 ng/ml."

That made no sense to me. First of all, where do they get that 100 ngs. And in the next paragraph they say hypericin extracts always to be lower than the assumed phototoxic hypericin threshold levels of 1000 ng/ml. So now they suddenly went up tenfold. So none of this data -- and I don't know where they're getting this data. This report was written by someone -- is consistent. You know, is it 1,000? Is it 1,000? If the blister fluid contained 2.8 ng/ml, then they're getting a phototoxic reaction because they're getting a blister. So where is the level and where do we set a level for hypericin? Because I think a level needs to be set. Because when you start getting down to 2.8 ng/ml, I don't care where your levels are being used. You know, 0.5 percent, you know, we really need to know more. So, I mean, I'm fine with reopening it. I just want CIR and PCPC to know that Don Belsito is going to be bird-dogging you about information on where hypericin starts causing phototoxicity and what's the amount of hypericin in the cosmetic-grade product.

DR. LIEBLER: Fair enough. I agree with Paul though; we should reopen this.

DR. BELSITO: I'm okay with reopening it. I just want to, you know, just let you know that I have very strong concerns about phototoxicity. And it probably all can be addressed. You know.

DR. EISENMANN: And I don't know why it is, but much of the phototoxicity is oral. I mean, if you take it orally there's a problem and I'm not sure that there has been as much of a problem when you put it on your skin for some reason. I think we need to look at that in more detail, too.

DR. KLAASSEN: Sure.

DR. BELSITO: I'm okay with that. I'm just telling you that as you tease through these studies, pay particular attention and, you know, rouse the manufacturers of hypericum perforatum extract in oil to give you everything they know about hypericin and phototoxicity.

Okay, so open with the add-ons is what we concluded.

DR. KLAASSEN: Actually, as many of you probably know, this has been used as a drug, especially allowed in Europe for depression. And it turns out that it's not valuable for depression but the one thing that it does do is it induces the cytochrome P450 3A-4. So if people take this as well as the drug, they can have drug interactions. And in fact, there were some young ladies on birth control pills that were taking this anti-depressant and it metabolized their birth controls more rapidly and they got pregnant.

DR. BELSITO: And got even more depressed.
DR. KLAASSEN: And they really got depressed.
DR. BELSITO: Okay. Okay. Anything more? Any more pregnant thoughts?
DR. KLAASSEN: How about a pregnant pause?

DAY TWO

DR. BELSITO: Hypericum perforatum extract in oil. In 1998 we wanted to know concentration of use, its function, photosensitization, toxicity in the visible spectrum, gross pathology and histopathology, dermal repro, developmental tox, skin irritation and ocular irritation. We pretty much got all of that data. There are some issues with some malreproductive effects, there are issues with hyperricin and absorption in visible wavelengths, so that will have to be addressed, but we felt that overall we should proceed with reopening this document and seeing the whole magilla. So that's a motion.

DR. MARKS: We second that motion and also would endorse with this opportunity of reopening this report to add the other St. John's Wort ingredients as listed on page 129.

DR. BELSITO: Agree.

DR. BERGFELD: Are there any other suggestions or inclusions? Seeing none, I'll call for the vote. All those in favor of reopening St. John's Wort? Thank you. Unanimous.

Report

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

Status: Tentative Amended Report for Panel Review
Release Date: November 16, 2012
Panel Meeting Date: December 10-11, 2012

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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INTRODUCTION

This is a draft tentative amended safety assessment of hypericum perforatum (St. John's wort)-derived ingredients. These ingredients function in cosmetics as skin-conditioning agents – miscellaneous, skin-conditioning agents – humectants; skin protectants; antioxidants, hair conditioning agents; and antimicrobial agents. The eight ingredients in this safety assessment are:

- Hypericum perforatum callus culture extract
- 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] The CIR Expert Panel concluded that there were insufficient data to determine the safety of these ingredients. The data needs were:

- 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.

Data have been submitted to meet these needs and are summarized below along with new data discovered in the literature. Data on the major constituents of *H. perforatum* are also included in this safety assessment.

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 (now hypericum perforatum flower/leaf/stem extract) is an extract of the capsules, flowers, leaves, and stem heads of *Hypericum perforatum,* commonly called St. John's wort.[1] Hypericum perforatum oil is the fixed oil from *H. perforatum*.

Techniques for preparing hypericum flower/leaf/stem perforatum extract include crushing in stabilized olive oil, gentle maceration over a period of weeks, followed by dehydration and filtration. Propylene glycol and butylene glycol extractions were also reported.

The following components have variously been reported to be found in *H. perforatum:* hypericin, naphtodianthrones, flavonoids, terpene and sesquiterpene oils, phenylpropanes, biflavones, tannins, xanthones, phloroglucinols, and essential oils.

Hypericum perforatum flower/leaf/stem extract is used in over 50 cosmetic formulations and hypericum perforatum oil in just over 10, both across a wide range of product types.

Acute toxicity studies using rats, guinea pigs, and mice indicate that the extract is relatively nontoxic. Animals fed *H. perforatum* flowers for 2 weeks showed signs of toxicity, including erythema, edema of the portion of the body exposed to light, alopecia, and changes in blood chemistry. In a chronic study, rats fed *H. perforatum* gained less weight than control animals.

Mixtures containing the extract and the oil were not irritants or sensitizers in animals. Because of the presence of hypericin, *H. perforatum* is a primary photosensitizer.

In clinical tests, a single oral administration of hypericum extract resulted in hypericin appearing in the blood. With long-term dosing, a steady state level in blood was reached after 14 days. The polyphenol fraction of *H. perforatum* had immunostimulating activity, whereas the lipophilic portion had immunosuppressing properties.

Mixtures of the extract and the oil produced minimal or no ocular irritation in rabbit eyes. Mutagenic activity in an Ames test was attributed to flavonols in one study and to quercitin in another, but other genotoxicity assays were negative. No carcinogenicity or reproductive and developmental toxicity data were available.

A mixture of the extract and the oil was not irritating in clinical studies. Adverse reactions to hypericum extract in the clinical treatment of depression include skin reddening and itching, dizziness, constipation, fatigue, anxiety, and tiredness.

CHEMISTRY

Definition

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

Constituents

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

Hypericum 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;
- Naphtodianthrones: 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 chloregenic acid and other caffeoylquinic and p-coumaroylquinic acids, and also free amino acids.

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

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

Method of Manufacture

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

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 4).[8] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group.[9] The Council survey covered the two ingredients in the original safety assessment (hypericum perforatum flower/leaf/stem extract and hypericum perforatum oil). A new survey is being conducted for all of the ingredients in this safety assessment.

Hypericum perforatum flower/leaf/stem extract is reported to be used in 49 leave-on products with maximum concentrations from 0.003% to < 5%; in 25 rinse-off products with maximum concentrations from 0.03% to < 5%. The VCRP reports that it is also used in 2 products that are diluted for bath.

Hypericum perforatum oil is reported to be used in 13 leave-on products and in 4 rinse-off products, both with maximum concentrations at < 0.5% and in 4 rinse-off products at < 0.5%.

The VCRP reported that:

- Hypericum perforatum extract is used in 32 leave-on products and 3 rinse-off products, including 1 baby product.
- Hypericum perforatum flower is used in 1 leave-on product.

The VCRP reported no uses for:

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

Non-Cosmetic

Oral therapeutic use hypericum perforatum was reported to be safe up to 900 mg/d (~13 mg/kg/d) for humans.[10]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Dermal/Percutaneous

HYPERICIN AND MIQUELIANIN

Hypericin is absorbed through the intestinal epithelium by passive transcellular diffusion.[11]

There was no hypericin detected in the plasma of Balb/c mice after administration to the ear (0.1% - 1%).[12] 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 was 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 hypericum 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.[13] 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 hypericum 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.[14] 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 hypericum 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.

HYPERICUM PERFORATUM EXTRACT

After oral administration of hypericum perforatum extract (dose not provided), maximum hypericin plasma concentrations of 0.21 to 1.33 µg/L were reached at 6 - 12 h. The terminal half-life was 15.1 to 63.1 h. Steady state hypericin plasma concentrations of 2 to 3 µg/L following multiple doses of 250 mg extract were reached in less than 14 days.

Short-term hypericum perforatum extract (300 mg 3 x/d) oral administration resulted in a selective induction of CYP3A activity in the intestinal wall. Hypericum perforatum did not alter the CYP2C9, CYPlA2, or CYP2D6 activities. 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). Blood and urine samples were taken before and during treatment. Subjects continued to take the hypericum 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 hypericum perforatum reduced the therapeutic efficacy of drugs metabolized by CYP3A and this effect should be anticipated during long-term administration.

In 36 samples of breast milk from mothers (n = 5) who were taking hypericum perforatum extract (300 mg 3/d), hyperforin was present in the milk at 0.9% - 2.5%.[15] 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 hypericum perforatum extract pills (3 x 300 mg/d; 0.12% - 0.28% hypericins, ~4.5% hyperforin).[16] 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 hypericum perforatum extract (612 mg) was administered to subjects (n = 18) in one dose or daily for 14 days.[17]

The Cmax of hyperforin was ~ 370 ng/mL (~ 690 nM) at ~3 h after oral administration of an ethanol/water extract of hypericum perforatum (0, 300 mg/kg; 5% hyperforin) to Sprague-Dawley rats (n = 5 for each sampling interval).[18] 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 hypericum perforatum ethanol/water extract.[18] In an open, single-dose, four-way crossover study, the same hypericum 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 study was a double-blind, placebo-controlled parallel-group study of hypericum perforatum extract (300, 600, 1200 mg; in pill form) or a second extract (0.5% hyperforin), the half-life and mean residence time were 9 and 12 h, respectively. Hyperforin pharmacokinetics were linear up to the 600 mg dose. Increasing the doses to 900 or 1200 mg resulted in lower Cmax and AUC values than those expected from linear extrapolation of data from lower doses. Plasma concentration curves in volunteers fitted well in an open two-compartment model. In the repeated dose study, there was no accumulation of hyperforin in the plasma. The estimated steady state of hyperforin in plasma was ~100 ng/ml (~180 nM).

Using human colonic Caco-2 cells as a model for human intestinal absorption, porcine capillary endothelial cells for the blood-brain barrier, and plexus choriodei epithelial cells for the blood-cerebrospinal fluid barrier, it was shown that orally ingested miquelianin (quercetin 3-O-beta-D-glucuronopyranoside; a flavonoid with antidepressant activity) can cross all three barriers and reach the central nervous system.[19] The permeability coefficients of miquelianin were 0.4 +/- 0.19 x 10^{-6} cm/sec), 1.34 +/- 0.05 x 10^{-6} cm/sec, and 2.0 +/- 0.33 x 10^{-6} cm/sec, respectively.

Intravenous

HYPERCICIN

Intravenous administration of hypericin (2 mg/kg in 2% benzyl alcohol and saline) to rhesus monkeys (*Maccaca mulatta*; n = 3) had a mean peak plasma concentration of 142 ± 45 μM; elimination was bi-exponential with an average alpha half-life of 2.8 ± 0.3 h and terminal half-life of 26 ± 14 h.[20] Hypericin was not detected in the CSF of any animal.

Miscellaneous Studies

HYPERICUM PERFORATUM FLOWER EXTRACT

Hypericum 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.[21] 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 edema by 50% (ID_{50}) from 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.

TOXICOLOGICAL STUDIES

Acute Toxicity

No acute toxicity studies were discovered or submitted.

Repeated Dose Toxicity

Dermal

There were no dermal repeated dose toxicity studies discovered or provided.

Oral – Non-Human

HYPERICUM PERFORATUM EXTRACT

Hypericum perforatum extract (900 and 2700 mg/kg) was orally administered to rats and dogs daily for 26 weeks.[10] Reduced body weight; slight changes in the hemography; changes in the clinical-chemical parameters, which indicate a slight load damage to the liver and kidneys were observed in both dose groups. A mild hypertrophy of the zona glomerulosa of the adrenals was observed.

Oral – Human

HYPERICUM PERFORATUM EXTRACT

In a randomized, double-blind crossover study, hypericum 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).[22] 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. Hypericum 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.

Inhalation

No inhalation toxicity studies were discovered or provided.

Intravenous

HYPERICIN

Intravenous administration of hypericin (2 mg/kg in 2% benzyl alcohol and saline) was well tolerated by rhesus monkeys (n = 3).[20] At a dose of 5 mg/kg, a transient severe photosensitivity rash was observed. 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.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Animal

HYPERICUM PERFORATUM EXTRACT

There were no reproductive or developmental effects observed in a two-generational study of hypericum perforatum extract using CD-1 mice (n = 20).[23] The female mice were administered hypericum perforatum (180 mg/kg in feed) for 2 weeks prior to mating through gestation. Body weight, body length, and head circumference (measurements taken from postnatal day 3 through adulthood) increases were similar between the two groups of offspring, regardless of gender. No differences in reaching physical milestones (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 hypericum perforatum extract.

There were no clinical signs of maternal or developmental toxicity when pregnant Wistar rats (n = 15) were administered hypericum perforatum extract (36 mg/kg/d in saline; 0.4% hypericin) during gestation days 9 – 15.[24] Maternal toxicity was evaluated through: water and food intake, body weight gain, piloerection, locomotor activity, diarrhea and mortality. Animals were killed on day 21 of gestation and necropsied. The indices of implantation and resorption were calculated.

Examination of the livers, kidneys, hearts, lungs, brains, and small bowels of the pups of Wistar rats (n = 6) orally treated with hypericum perforatum extract (methanol solvent containing 0.3% hypericin; 0, 100, 1000 mg/kg/d) showed severe damage to the livers and kidneys of animals killed postnatally on days 0 and 21.[25] Three dams were treated starting 2 weeks prior to mating through 21 days of breastfeeding. The other three were treated from delivery through 21 days of breastfeeding. Maternal body weights, gestation time, number of live pups, and weight of pups at birth were similar between groups. The livers of newborn pups of dams in the low dose group treated before and during pregnancy showed focal hepatocyte damage was apparent, with vacuolization of cells. In the high dose group, these lesions were much more evident, with hepatocyte hyaline degeneration, lobular fibrosis, and disorganization of hepatocyte arrays. In the low dose group, the kidneys showed a reduction in glomerular size with disappearance of Bowman's space and hyaline tubular degeneration and in the high dose group, these lesions were more severe. The same lesions, but much more diffuse and serious, were observed in pups killed after 21 days of breastfeeding 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 breastfeeding.

There were no effects on maternal weight gain or gestation length nor any effect on offspring body weights (up to postnatal day 56) behavior, or whole and regional brain weights in Sprague-Dawley rats (n = 35) fed diets containing hypericum 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.[26] 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 hypericum perforatum extract (0.75 mg/g/d in feed; 0.3% hypericin) for 2 weeks before and through gestation.[23] There were also no effects on reproductive behavior or success in the next three generations of offspring. In the male pups, the treatment group weighed less than the controls. The offspring were tested with homing, locomotor activity, exploratory, forced swim, and anxiety tests.

HYPERICUM PERFORATUM FLOWER EXTRACT

The contractility of the vas deferens of Wistar rats exposed to the hydromethanolic extract of the flowering tops of Hypericum perforatum (1 – 300 µg/mL; 0.3% hypericin) and hyperforin (10-8 – 10-4 M was inhibited in a concentration dependent manner.[27] 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.[28] Embryos were explanted at gestational day 9.5 and were examined on day 11.5. The embryos exposed to high concentration of hypericin (71.0 and 142.0 ng/mL) had lower total morphological score and number of somites compared with the control group. There was a negative linear trend in total morphological score, yolk sac diameter, and number of somites, indicating a progressive reduction in these parameters with increasing concentration of hypericin. There were no differences detected in crown-rump length.

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).[29] 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 patients 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 Hypericum 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).[30]

In 36 samples of breast milk from mothers (n = 5) who were taking hypericum perforatum extract (300 mg 3/d), hyperforin was present in the milk at 0.9% - 2.5%.[15] 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).[16] 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 patients (n = 15) who underwent prostatectomy (9 who were 60 to 72 years old) or orchiectomy (3 who were 28 to 35 years old). Hypericum perforatum flower extract and hyperforin inhibited contractions stimulated by phenylephrine (3 x 10-6 M).[27] 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.

CARCINOGENICITY

Studies

HYPERICIN

Hypericin demonstrated antiviral, anti-inflammatory, and antitumor effects on human leukocytes.[31] The authors suggested that this is possibly due to the inhibition of the PKC-mediated signaling pathway, which influences the arachidonic acid metabolism and the interleukin-1-alpha production, which resulted in an immunosuppressive effect.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Human

HYPERICUM PERFORATUM EXTRACT

In an irritation test (n = 18), a bath oil containing hypericum perforatum extract (concentration not provided; 50 μL) did not cause irritation and was similar to the control of distilled water.[32] 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 hypericum perforatum extract (1.1%) was not photosensitizing to the backs of guinea pigs when applied to tape-stripped skin.[33] The backs of the guinea pigs were irradiated (320-400 nm; 10.2 j/cm2) 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 hypericum perforatum (> 50 μg/mL; 0.3% hypericin-like derivatives) was phototoxic to human keratinocyte HaCaT cells in UVA light.[34] 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

Hypericum 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.[35] 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 hypericum 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 & OTHER CONSTITUENTS

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.[12] 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 hypericum 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.[36] 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 MED (minimal erythema dose) values did not differ from controls.[37] Hypericum perforatum extract (3 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 hypericum 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.[38] There was no evidence of a phototoxic effect. Phototesting 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.[39]

In Vitro

HYPERICUM PERFORATUM EXTRACT, HYPERICIN, AND PSEUDOHYPERICIN

Hypericum 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.[40] 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 hypericum perforatum extracts (plant parts not specified) or constituents exerted less phototoxicity than pure hypericin when exposed to HaCaT keratinocytes.[41] The keratinocytes were exposed to two hypericum 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.[42] 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 Hypericum 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.[43] The IC_{50} of irradiated hypericin was 100 ng/mL and 200 ng/mL for pseudohypericin.

Ocular

HYPERICIN

Human lens epithelial cells incubated in hypericin (0.1-10 μM) and irradiated (4 J/cm^2 UVA or 0.9 J/cm^2 visible light) had increased necrosis and apoptosis.[44] 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 hypericum 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).[45] 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.[46] 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.

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 hypericum 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.[47] The authors stated that hypericum perforatum may increase the risk of cataracts but the mechanism is not established.

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.[48] 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 photooxidative 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 hypericum perforatum-derived substances.

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 hypericum 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.[49] One patient developed contact eczema to the vehicle. In the subjects 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 patient developed large blisters that resolved with some hyperpigmentation after laser treatment at 532 nm at 1.5 J/cm^2.[50] She had recieved a previous treatment with no ill effects. It was discovered that the patient 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 hypericin perforatum extract in a suicidal attempt of a 16-year-old girl resulted in seizures and confusion that resolved after 6 days.[51] It has been reported that the girl had taken up to 15 300 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 hypericum perforatum extract (500 mg/d) and exposure to sunlight.[52] 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.[53] The authors stated concern about the use of *Hypericum* instead of an established effective treatment because safety of *Hypericum* in pregnancy and lactation has not been established.

SUMMARY

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

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

Hypericum perforatum-derived ingredients are used in leave-on products up to 5% and in rinse-off products up to 0.5%

Hypericin, the most active constituent of *H. perforatum*, did not penetrate mouse ear skin. Hypericin, pseudohypericin, hyperforin quercetin, and isohamnetin were observed in the plasma after oral administration of hypericum perforatum extract. Hyperforin was detected in human breast milk but not in the feeding infant's plasma in mothers that took hypericum perforatum extract.

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

Orally administered hypericum 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 hypericum 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 hypericum perforatum during pregnancy nor any effects to their infants. No effects were observed in breast feeding infants of mothers who took hypericum perforatum.

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

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

A bath oil with an unknown concentration of hypericum 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%. Hypericum 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 hypericum perforatum extract did not increase photosensitization in humans. Human keratinocyte cells incubated in hypericum perforatum extracts and constituents demonstrated increased cytotoxic and photogenotoxic effects when exposed to UVA.

Human and bovine ocular cells/lenses 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 efficacy clinical trials included: nausea, headache, dizziness abdominal pain, insomnia/sleep disturbance, cold symptoms, and diarrhea.

DISCUSSION

Discussion to be determined based on Panel discussion at the December, 2012 meeting.

DRAFT CONCLUSION

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

- Hypericum perforatum callus culture extract
- 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. *To be confirmed at the December, 2012 Panel meeting*

TABLES AND FIGURES

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

Ingredient CAS #	Definition	Function
Hypericum perforatum callus culture extract	the extract of a culture of the callus of *Hypericum perforatum*	Antioxidants; hair conditioning agents; skin protectants; skin-conditioning agents-humectant
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* L.[54]

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	
Adhyperfolin	Fruit	

Table 2. Constituents found in *Hypericum perforatum* L.[54]

Chemical	Plant part	Concentration (ppm)
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
Cadmium	Root	1-3
Cadmium	Plant	1-5
Caffeic-acid	Plant	1000
Caffeic-acid	Shoot	1000

Table 2. Constituents found in *Hypericum perforatum* L.[54]

Chemical	Plant part	Concentration (ppm)
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
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	

Table 2. Constituents found in *Hypericum perforatum* L.[54]

Chemical	Plant part	Concentration (ppm)
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	
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

Table 2. Constituents found in *Hypericum perforatum* L.[54]

Chemical	Plant part	Concentration (ppm)
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	
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

Table 2. Constituents found in *Hypericum perforatum* L.[54]

Chemical	Plant part	Concentration (ppm)
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	
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

Table 2. Constituents found in *Hypericum perforatum* L.[54]

Chemical	Plant part	Concentration (ppm)
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 of various commercial *H. perforatum* extracts.

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.

Table 3. Parameters of various commercial *H. perforatum* extracts.

Parameter	Value
	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%
	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] A survey of the use concentrations of the other 6 ingredients is being conducted by the Council.

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Hypericum perforatum callus culture extract		**Hypericum perforatum extract**		**Hypericum perforatum flower extract**		**Hypericum perforatum flower/leaf extract**	
Total/range	**NR**	NS	**35**	NS	**1**	NS	NR	NS
Duration of use								
Leave-on	NR	NS	32	NS	1	NS	NR	NS
Rinse-off	NR	NS	3	NS	NR	NS	NR	NS
Diluted for (bath) use	NR	NS	NR	NS	NR	NS	NR	NS
Exposure type								
Eye area	NR	NS	5	NS	1	NS	NR	NS
Incidental ingestion	NR	NS	NR	NS	NR	NS	NR	NS
Incidental Inhalation-sprays	NR	NS	NR	NS	NR	NS	NR	NS
Incidental inhalation-powders	NR	NS	1	NS	NR	NS	NR	NS
Dermal contact	NR	NS	31	NS	1	NS	NR	NS
Deodorant (underarm)	NR	NS	NR	NS	NR	NS	NR	NS
Hair-noncoloring	NR	NS	22	NS	NR	NS	NR	NS
Hair-coloring	NR	NS	1	NS	NR	NS	NR	NS
Nail	NR	NS	NR	NS	NR	NS	NR	NS
Mucous Membrane	NR	NS	NR	NS	NR	NS	NR	NS
Baby	NR	NS	1	NS	NR	NS	NR	NS

	Hypericum perforatum flower/leaf/stem extract		**Hypericum perforatum flower/twig extract**		**Hypericum perforatum leaf extract**		**Hypericum perforatum oil**	
Total/range	**76**	**0.003-<5**	NR	NS	NR	NS	**17**	**0.5**
Duration of use								
Leave-on	49	0.003-<5	NR	NS	NR	NS	13	0.5
Rinse-off	25	0.03-<5	NR	NS	NR	NS	4	0.5
Diluted for (bath) use	2	NR	NR	NS	NR	NS	NR	NR
Exposure type								
Eye area	1	<5	NR	NS	NR	NS	NR	NR
Incidental ingestion	NR	NR	NR	NS	NR	NS	NR	NR
Incidental Inhalation-sprays	1	NR	NR	NS	NR	NS	1	NR
Incidental inhalation-powders	1	NR	NR	NS	NR	NS	NR	NR
Dermal contact	64	0.003-<5	NR	NS	NR	NS	16	0.5
Deodorant (underarm)	NR	NR	NR	NS	NR	NS	NR	NR
Hair-noncoloring	12	NR	NR	NS	NR	NS	1	NR
Hair-coloring	NR	NR	NR	NS	NR	NS	NR	NR
Nail	NR	NR	NR	NS	NR	NS	NR	NR
Mucous Membrane	4	NR	NR	NS	NR	NS	NR	NR
Baby	1	NR	NR	NS	NR	NS	NR	NR

NR = Not reported; NS = Not surveyed. 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 clinical trials.

Extract	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%)	[55]
WS 5572	3 x 300 mg	Sinusitis, bronchitis, Common cold	[56]
Ze 117	2 x 250 mg	N=6 of 81 (7.4%) Abdominal pain (2), moderate diarrhea (1), moderate Melancholia (1), moderate acute deterioration (1), moderate dry mouth (1)	[57]
Ze 117	2 x 250 mg	8% Only GI disturbances (5%) with an incidence greater than 2%	[58]
PM235, (Cederroth International AB, Sweden)	3 x 270 mg	Mild, mainly headache, gastrointestinal symptoms	[59]
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	[60]
Ze 117	2 x 250 mg	62 of 157 (39%) Dry mouth (13) , headache (3), sweating (2), asthenia (2), nausea (1)	[61]
STEI 300	3 x 350 mg	0.5 Events per patient (22%) Most frequently reported adverse event: Nausea	[62]
STW3	612 mg	9.8% Related to study medication Diarrhea (1) Serious adverse events (3): shoulder blade after falling down the stairs, somatic disorder, cerebral hemorrhage	[63]
LI 160	3x 300 mg	Adverse events: 38 Patients 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)	[64]
WS 570	600 mg or 1200 mg (2 x 600 mg)	All adverse events. 49 (39.8%) 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%)	[65]
LI 160	3 x 300 mg	N=90 Most common adverse events: headache (42%), dry mouth (22%), nausea (20%), gastrointestinal upset (20%), sleepiness (18%)	[66]
LI 160	900 mg/d for 4 weeks, after this period no adequate response, new dose 1200 mg/d	Headache (41%), Abdominal pain (≥ 10%)	[67]
LI 160	900 to 1500 mg (3-5 x 300 mg)	Diarrhea (21%), Nausea (19%), Anorgasmia (25%), Forgetfulness (25%), Frequent urination (27%), Sweating (18%), Swelling (19%)	[68]
WS 5570	900 mg (3 x 300 mg) – 1800 mg (3 x 600 mg)	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 patients), Nervous system disorders (35 events in 29 patients), 2 serious adverse events (psychic decompensation attributable to social problems, hypertensive crisis), both not caused by Hypericum	[69]
?	900 to 1800 mg/d	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)	[70]
WS 5573 WS 5572	3 x 300 mg	WS 5573 (28.6% of 49 patients) WS 5572 (28.6% of 49 patients) Bronchitis (3/1), Influenza-like symptoms (2/0), Cough (2/0), Infection (1/0)	[71]

Table 5. Reported adverse events in clinical trials.

Extract	Daily dose	Adverse events	Reference
Ze 117	2 x 250 mg	8 % Hypericum, GI disturbances (5%)	[58]
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)	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)	[72]
LoHyp 57	2 x 400 mg	N=12 (For this reason withdrawn: 6)	[73]
STW3-VI	900 mg	Total AEs. 58 (17.2%); Related: 10 Gastrointestinal disorders (6), Ear and labyrinth disorders (1), Skin and subcutaneous tissue disorders (1)	[74]
LI 160	3 x 300 mg	37 % of the patients Dry mouth (5%), drowsiness (1%), sleepiness (2%), dizziness (1%), lethargy (1%), nausea/vomiting (7%), headache (7%), constipation (5%), pruritus (2%)	[75]
LI 160	3 x 600 mg	23% of the patients N=37 Dry mouth (3); gastric symptoms (5), tiredness/sedation (5), restlessness (6), tremor (2), dizziness (5), allergic skin reaction (1)	[76]
WS 5572	600 mg/1200 mg	17 patients N=21 (13 with relation to hypericum) AEs frequency < 1% Skin irritation, pruritus, allergic exanthema, nervousness, restlessness, gastrointestinal disorders (4), diarrhea, insomnia	[77]

AE = Adverse event

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Data

Cosmetic Ingredient Review
Commitment . . . Credibility
Since 1976

Memorandum

To: CIR Expert Panel

From: Lillian C. Becker
Scientific Analyst/Writer

Subject: Submitted data on *Hypericum perforatum* – derived ingredients

Date November 16, 2012

Attached are the data submitted by the Personal Care Products Council's CIR Science and Support Committee to meet each of the insufficient data needs. The data have been inserted into the safety assessment.

In addition, the relevant data from the European Medicines Agency's review of *Hypericum perforatum* (2009) have been added to the report along with the other published studies.

Data need identified in 2001	**New data provided**
Concentration of Use	Use concentration data are available and are less than 5% for the flower/leaf/stem extract and less than 0.5% for the oil. The Council would survey for the other *Hypericum perforatum* – derived ingredients if this is reopened and expanded.
Function in cosmetics	Functions, while general, are now given.
Photosensitization/phototoxicity in the visible range	Published study with 16 human volunteers given hypericum topical oil (110 µg/ml hypericin) or ointment (30 µg/ml hypericin) and exposed to solar simulator up to 144 J/cm^2 with no phototoxic rxns published human oral study with 48 volunteers in single-dose study arm 24 in repeated dose study arem. Hypericum extract for the single dose was 5.4 and 10.8 mg hypericin and for the repeated dose was 5.4 mg followed by 2.7 mg over 7 days. Four lamp sources were tested: UVB, UVA, visible, solar simulator. No rxns. Published mouse dermal study using hypericin (0.01, 0.1, and 1.0%) and hypericin acetate (0.015, 0.15, and 1.5%) ointments and radiation with sodium vapor lamps (lines at 586 and 589 nm, i.e., yellow). Ear swelling was the measure of phototoxicity. 1.0% hypericin and all hypericin acetate concentrations were phototoxic. unpublished guinea pig maximization study (10 animals) given product at two sites with 1.1% Hypericum Perforatum Extract (presumably whole plant) at a 10% dil for induction and 0.1 or 1.0% dil at challenge. One site at induction and at challenge given UVA at 10.2 J/cm^2. No sensitization or photosensitization noted. one published case report of a positive rxn in a patient receiving dermal Nd:YAG laser treatment on the leg (532 nm) at 1.2 J/cm^2, and probably a + rxn with a tunable dye laser treatment of the face (582 nm) at 6 J/cm^2 who was taking St. John's wort (dose not given) orally.

Gross pathology and histopathology in skin and other major organ systems with repeat dermal exposures	An abstract from 1996 was provided, but it is short on detail. We've emailed the author to see if more may be available.
Dermal reproductive/developmental toxicity	4 published studies (human, mouse, 2 rat) all of which were negative
Skin irritation/sensitization	1 published human irritation study was negative
Ocular irritation at concentration of use, if available	No studies were available.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: February 10, 2012

SUBJECT: *Hypericum perforatum*-Derived Ingredients

The CIR Science and Support Committee (CIR SSC) has identified additional information in the published literature to support the safety of ingredients derived from *Hypericum perforatum* (St. John's wort) as outlined below (studies marked with a letter are published studies provided in separate pdf files). Based on this new information, the CIR SSC requests that the CIR Expert Panel consider opening this report to review the safety of *Hypericum perforatum*-derived ingredients as used in cosmetic products.

The original CIR report (published in 2001) included Hypericum Perforatum Extract and Hypericum Perforatum Oil. Since the report was published, the name of Hypericum Perforatum Extract was changed to Hypericum Perforatum Flower/Leaf/Stem Extract, although more recently an ingredient named Hypericum Perforatum Extract, defined as an extract of the whole plant, has been added to the *International Cosmetic Ingredient Dictionary and Handbook*. The CIR report concluded that data were insufficient to support the safety of Hypericum Perforatum Extract and Hypericum Perforatum Oil. The information requested by the CIR Expert Panel and the information identified is outlined below. Unpublished information is attached to this memo.

1. Current concentration of use data
   A use survey on Hypericum Perforatum Flower/Leaf/Stem Extract and Hypericum Perforatum Oil was completed in 2010. This survey resulted in use concentrations of <5% for the extract and 0.5% for the oil (attached). If the report is opened, an updated concentration of use survey will be completed on all of the ingredients the CIR Expert Panel selects for inclusion in the report. The following *Hypericum perforatum*-derived ingredients are currently included in the *International Cosmetic Ingredient Dictionary and Handbook*:
   Hypericum Perforatum Callus Culture Extract
   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

2. Function in cosmetics

The following table shows the functions for each ingredient as listed in the *International Cosmetic Ingredient Dictionary and Handbook.*

Ingredient	**Function(s)**
Hypericum Perforatum Callus Culture Extract	Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents - Humectant
Hypericum Perforatum Extract	Skin-Conditioning Agents - Miscellaneous
Hypericum Perforatum Flower Extract	Skin-Conditioning Agents - Miscellaneous
Hypericum Perforatum Flower/Leaf Extract	Skin-Conditioning Agents - Miscellaneous
Hypericum Perforatum Flower/Leaf/Stem Extract	Skin-Conditioning Agents - Miscellaneous
Hypericum Perforatum Flower/Twig Extract	Antimicrobial Agents; Skin-Conditioning Agents - Miscellaneous
Hypericum Perforatum Leaf Extract	Skin-Conditioning Agents - Miscellaneous
Hypericum Perforatum Oil	Skin-Conditioning Agents - Miscellaneous

3. Photosensitization and phototoxicity data using visible light (550-610 nm; 5-10J)

a. Schempp CM, Lüdtke R, Winghofer B. 2000. Effect of topical application of Hypericum perforatum extract (St. John's wort) on skin sensitivity to solar simulated radiation. Photodermatol Photoimmunol Photomed 16: 125-128.

Human phototoxicity study, dermal application (n=16)
Materials tested: Hypericum oil (110 μg hypericin/ml), Hypericum ointment (30 μg hypericin/ml)
Light exposure: solar simulator 290-2500 nm with a maximum of 300-800 nm; 24, 48, 96 and 144 J/cm^2
Results: No phototoxic reactions were observed. There was a trend towards increased erythema index for the oil but not the ointment

b. Schempp CM, Winghofer B, Müller K, et al. 2003. Effect of oral administration of Hypericum perforatum Extract (St. John's wort) on skin erythema and pigmentation induced by UVB, UVA, visible light and solar simulated radiation. Phytother Res 17: 141-146.

Human oral study (n=48 single dose study; n=24 steady-state study)
Results: No evidence of a phototoxic effect at typical clinical doses

This study is also summarized in:

c. Schempp CM, Müller K, Winghofer B, et al. 2001. Single-dose and steady-state administration of Hypericum perforatum extract (St. John's wort) does not influence skin sensitivity to UV radiation, visible light and solar-simulated radiation. Arch Dermatol 137: 512-513.

d. Boiy A, Roelandts R, van de Oordt J. 2008. Photosensitizing activity of hypericin and hypericin acetate after topical application on normal mouse skin. British Journal of Dermatology 158: 360-369.

Mouse study (n=5-10/group)
Mice treated with 0.01%, 0.1% or 1% hypericin or 0.015% 0.15 or 1.5% hypericin acetate
Light exposure: 586 and 589 nm 10 J/cm^2 (maximum absorption of hypericin)
Results: no effects at 0.1% hypericin, positive at 1% hypericin and all concentrations of hypericin acetate
This paper also includes some information regarding dermal penetration of hypericin compared to hypericin acetate.

Anonymous. 2011. Safety data of Adipoblock (1.1% of Hypericum Perforatum Extract) Photoallergenicity.

Guinea pig study (n=5)
Induction: 10% of Adipoblock (contains 1.1% Hypericum Perforatum Extract) in distilled water
Challenge: 1, 5, 10 and 20% in distilled water
Light exposure: 320-400 nm; 10.2 joules/cm^2
Results: Under the conditions of the test, Adipoblock was not photosensitizing

Case Report

e. Cotterill JA. 2001. Severe phototoxic reaction to laser treatment in a patient taking St. John's wort. J Cosmetic & Laser Ther 3: 159-160.

4. Gross pathology and histopathology in skin and other major organ systems associated with repeated dermal exposures

f. Leuschner J. 1996. Preclinical toxicology profile of Hypericum extract LI 160. Phytomedicine Supplement 1 (Abstract).

This abstract briefly mentions some oral systemic studies (26 week rat and dog studies at 900 and 2700 mg/kg/day) in which unspecific toxic symptoms were observed.
The author concluded a daily dose of 13 mg/kg body weight/day would be acceptable for humans.

5. Dermal reproductive/developmental toxicity data

g. Moretti ME, Maxon A, Hanna F, et al. 2009. Evaluating the safety of St. John's wort in human pregnancy. Reproductive Toxicology 28: 96-99.

Epidemiology study of 54 St. John's wort exposed pregnancies compared to 108 non-exposed pregnancies
Rates of major malformations, live birth and prematurity were not different between the groups

h. Rayburn, WF Gonzalez CL, Dix Christensen H, et al. 2001. Effect of prenatally administered hypericum (St. John's wort) on growth and physical maturation of mouse offspring. Am J Obstet Gynecol 184: 191-195.

Mice (n=20)
Fed (in diet) 180 mg/kg/day Hypericum (containing 0.3% hypericin) for 2 weeks before conception and throughout gestation
Offspring followed until maturity and a subset was used to product a second generation
No effects observed

I. Borges LV, Corrêa do Carmo Cancino J, Peters VM, et al. 2005. Development of pregnancy in rats treated with *Hypericum perforatum*. Phytother Res 19: 885-887.

Pregnant rats (n=15)
Treated by gavage with 36 mg/kg/day *H. perforatum* containing 0.4% hypericin on days 9-15 of gestation
No clinical signs of maternal toxicity were observed
Evaluation of offspring on gestation day 21 did not reveal any effects

This study also appears to be published in Portugese (with an English abstract):
j. Borges LV, Corrêa do Carmo J, Peters VM, et al. 2005. A toxicidade do *Hypericum perforatum* administrado a ratas prenhes. Rev Assoc Med Bras 51(4): 206-208.

k. Gregoretti B, Stebel M, Candussio L, et al. 2004. Toxicity of *Hypericum perforatum* (St. John's wort) administered during pregnancy and lactation in rats. Toxicol Appl Pharmacol 200: 201-205.

Rats (n=6/group gestation group; 3/group postnatal treatment group)
Treated by gavage with 100 or 1000 mg/kg/day *Hypericum perforatum* containing 0.3% hypericin from 2 weeks before mating to 21 days after delivery or treatment of dams from birth until 21 days after delivery
Microscopic examination of livers, kidneys, hearts, lungs, brains and small bowels of offspring completed
Renal and hepatic damage observed in offspring, effect was more severe at the higher dose. Effects also observed in offspring exposed only during lactation.

6. Skin irritation/sensitization data in humans on Hypericum Perforatum Oil

l. Reuter J, Huyke C, Scheuvens H et al. 2008. Skin tolerance of a new bath oil containing St. John's wort extract. Skin Pharmacol Physiol 21: 306-311.

Human irritation study (n=18) of a bath oil containing a lipophilic extract of *Hypericum perforatum*
The product was not different from the water control

7. Ocular irritation data, if available

No studies were identified

Suppliers have reported the following information regarding Hypericum Perforatum Flower/Leaf/Stem Extract sold to the cosmetics industry:

Extraction solvents: water/propylene glycol; propylene glycol; 86% ethanol; 50% butylene glycol; water; sunflower oil; olive oil; caprylic/capric triglycerides; glycerin
Plant material: may be fresh, but is more frequently dried before extraction
Percent solids: 0.1-5%
Hypericin and Hyperforin content: Not measured in some extracts; extract of fresh plant material with 86% ethanol (3% solids) has a hypericin content of 60-65 μg/ml and a hyperforin content of 240-900 μg/ml

Published papers with additional information

The European Medicines Agency (EMEA) completed a review of *Hypericum perforatum* in 2009. This review can be found at:
http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2010/01/WC500059144.pdf
The final EMA monograph can be found at:
http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2010/01/WC500059144.pdf

m. Booth JN, McGwin G. 2009. The association between cataracts and St. John's wort. Current Eye

Research 34(10): 863-866

n. Butterweck V. 2003. Mechanism of action of St John's wort in depression What is known? CNS Drugs 17(8): 539-562.

o. Greeson JM, Sanford B, Monti DA. 2001. St. John's wort (*Hypericum perforatum*): a review of the current pharmacological, toxicological and clinical literature. Psychopharmacology 153: 402-414.

p. Ondrizek RR, Chan PJ, Patton WC, et al. 1999. An alternative medicine study of herbal effects on the penetration of zona-free hamster oocytes and the integrity of sperm deoxyribonucleic acid. Fertility and Sterility 71(3): 517-522.

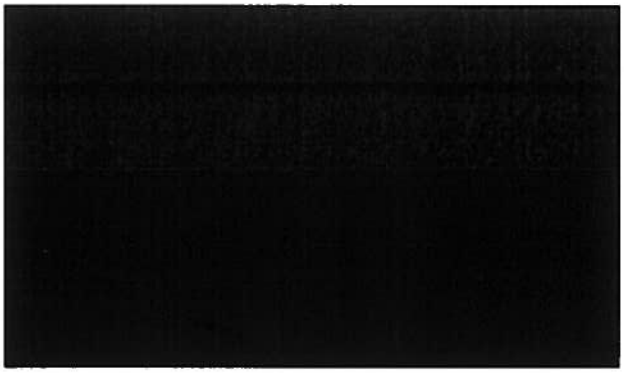
q. Staffeldt B, Kerg R, Brockmöller, et al. 1994. Pharmacokinetics of hypericin and pseudohypericin after oral intake of the Hypericum Perforatum Extract LI 160 in health volunteers. J Geriatr Psychiatry 7(Suppl. 1): S47-S53).

Concentration of Use by FDA Product Category
Hypericum Perforatum Flower/Leaf/Stem Extract and Hypericum Perforatum Oil

Ingredient	Product Category	Concentration of Use
Hypericum Perforatum Flower/Leaf/Stem Extract	Eye lotion	<5%
Hypericum Perforatum Flower/Leaf/Stem Extract	Skin cleansing (cold creams, cleansing lotions liquids and pads)	0.03-<5%
Hypericum Perforatum Flower/Leaf/Stem Extract	Face and neck creams, lotions and powders	<5%
Hypericum Perforatum Flower/Leaf/Stem Extract	Body and hand creams, lotions and powders	0.003%
Hypericum Perforatum Flower/Leaf/Stem Extract	Night creams, lotions and powders	0.02%
Hypericum Perforatum Flower/Leaf/Stem Extract	Skin fresheners	0.1%
Hypericum Perforatum Flower/Leaf/Stem Extract	Other skin care preparations	0.01-<5
Hypericum Perforatum Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.5%
Hypericum Perforatum Oil	Night creams, lotions and powders	0.5%
Hypericum Perforatum Oil	Skin fresheners	0.5%

Information collected in 2010
Table prepared November 2, 2010

SAFETY DATA OF ADIPOBLOCK™
(1.1% of HYPERCUM PERFORATUM EXTRACT)



April 22nd, 2011

Index

ADIPOBLOCK™
(1.1% of HYPERCUM PERFORATUM EXTRACT)

ADIPOBLOCK™
(1.1% of HYPERICUM PERFORATUM EXTRACT)

1. Photoallergenicity

Photoallergenicity of ADIPOBLOCK™ was evaluated by the adjuvant & strip test method*. ADIPOBLOCK™ contains 1.1% of HYPERICUM PERFORATUM EXTRACT. Test method and results are summarized as follows.

*Ichikawa H., et al., J. Invest. Dermatol. 76: 498-501, 1981

Date of the first exposure (induction phase): May 12, 2003
Test laboratory: [redacted]
Animals: Species, and strain: Ten female Hartley strain albino guinea pigs.
Age and body weight at the beginning of the study: 8 weeks of age; 440.0-509.6g
Animal room environment: Each animal was individually housed in stainless steel cage. Room temperature and humidity were maintained at 20-26°C and 40-70%. Light cycle was 12 hr on and 12 hr off per day.

Test materials and test groups:

Groups	Number of animals	Test materials	
		Induction phase	Challenge phase
I: ADIPOBLOCK™	5	ADIPOBLOCK™ 10% in DW	ADIPOBLOCK™; 1, 5, 10 and 20% in D.W.
II: DW (Control)	5	DW	ADIPOBLOCK™; 1, 5, 10 and 20% in DW

Methods:
Test group: Ten animals were divided into two groups, 5 in each group. One group was for the treatment with ADIPOBLOCK™ (Group I) and the other was for the control (Group II).

Induction phase: On the first day (Day 0), 0.1 mL of emulsified FCA* (E-FCA) prepared from equal volumes of FCA and distilled water was injected intradermally at the 4 corners of a shaved 3 x 4 cm nuchal area of all the animals. Injection area was treated by stripping with a tape. To the site of stripping, 0.1 mL of 10% solution of the test

article was applied. After application, the treated site was irradiated with light. Action wavelength was 320 – 400 nm, and the amount of energy was 10.2 joules/cm^2. Light exposure with tape stripping were repeated once daily on 5 consecutive days. Control animals (Group II) were treated with DW.

*: Freund's Complete Adjuvant

Challenge phase: At 2 weeks after the induction, the 1% and 0.1% solutions of the test article in volumes of 0.02 mL were each applied to the symmetric skin areas the size of 1.5 x 1.5 cm^2 on the two sides of midline on the back. With one side covered with aluminum foil, the skin was irradiated after application of the test sample. The conditions of photoirradiation were the same as in the induction.

Assessment: At 24 hours and 48 hours after application of the test sample, the skin response was evaluated according to the following criteria by observation of erythema and scabbing as well as the degree of edematization.

Evaluation of skin reaction (scoring):

(1) Erythema and scabbing

Description	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

(2) Edematization

Description	Score
No edema	0
Slight edema	1
Moderate edema	2
Severe edema	3

The responses at the irradiated and non-irradiated areas were evaluated separately, and difference between the scores for two areas was calculated, and the mean of these differences was worked out. Score was calculated with weight on the time point when photosensitization was most clearly detected.

When the score of skin reaction was 2 or more, the reaction was judged as positive.

Results and conclusion:

Results of photoallergenecity test of ADIPOBLOCK™, which contains 1.1% of HYPERICUM PERFORATUM EXTRACT, by the adjuvant & strip method in guinea pigs are summarized in Table 1.

In photosensitization and control groups, no response was detected at the sites of application of the 1, 5, 10 and 20% in DW of ADIPOBLOCK™ in DW that were irradiated with light or non-irradiated.

It is concluded that ADIPOBLOCK™ does not possess photosensitizing potential under this test conditions.

Table 1 Photoallergenicity of ADIPOBLOCK™

Induction	10% ADIPOBLOCK™	DW
Challenge	ADIPOBLOCK™ 1%-20%	ADIPOBLOCK™ 1%-20%
Number of animal	4[a)]	5
Photosensitization rate[b)]		
Hours after challenge		
Application		
24	0/4	0/5
48	0/4	0/5

a): One animal was excluded because of non-specific response.
b): Number of positive animals/number of animals

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

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

03D - Eye Lotion	999002190	HYPERICUM PERFORATUM FLOWER EXTRACT	1

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

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

07C - Foundations	977009963	ST JOHNS WORT (HYPERICUM PERFORATUM)*	1
12C - Face and Neck (exc shave)	977009963	ST JOHNS WORT (HYPERICUM PERFORATUM)	1
12J - Other Skin Care Preps	977009963	ST JOHNS WORT (HYPERICUM PERFORATUM)	1
			3

*Combined with HYPERICUM PERFORATUM FLOWER/LEAF/STEM EXTRACT