Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 11, 2018
Panel Meeting Date:	June 4-5, 2018

The 2018 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: May 11, 2018
Subject: Draft Final Safety Assessment on *Ginkgo biloba*-Derived Ingredients

Enclosed is the Draft Final Report of the Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics. (It is identified as *ginkgo062018rep* in the pdf document).

In March 2018, the Panel issued a Tentative Report with the conclusion that the data are insufficient to determine the safety of the 10 *Ginkgo biloba*-derived ingredients. The Panel's data needs were:

- Method of manufacturing, composition, and impurities data for each of these ingredients, except Ginkgo Biloba Meristem Cell;
- 28-Day dermal toxicity data for each of these ingredients,
    - Dependent on the results of these studies, additional data on other toxicological endpoints, such as developmental and reproductive toxicity and carcinogenicity, may be needed;
- Dermal irritation and sensitization data at leave-on use concentrations; and
- Ocular irritation data, if available.

Since the March Panel meeting, CIR has received the following data, which have been incorporated into the report and have been designated with highlighting in the text and tables.

- Updated concentration of use for the other *Ginkgo biloba*-Derived Ingredients (maximum use concentration for Ginkgo Biloba Leaf Extract in face and neck products decreased from 1% to 0.1%; the new overall maximum concentration of use for Ginkgo Biloba Leaf Extract in leave-on products is 0.24%) (*ginkgo062018data1* and *ginkgo062018data2*)
- HRIPT on test material containing 0.0005% Ginkgo Biloba Leaf Extract (*ginkgo062018data3*)
- Results of the concentration of use survey for Gingko Leaf Cell Extract (no uses; *ginkgo062018data4*)

CIR has yet to receive the requested data on method of manufacturing, composition and impurities, 28-day dermal toxicity, dermal irritation and sensitization data at the maximum leave-on use concentration (now 0.24%), and ocular irritation. The Panel should note that there is a HRIPT on 0.2% Ginkgo Biloba Leaf Extract in the report.

Comments provided by the Council prior to the March meeting and on the Tentative Report have been addressed (*ginkgo062018pcpc1*and *ginkgo062018pcpc2)*. The CIR Science and Support Committee (SSC) have provided comments on the safety assessment that are included in this report package (*ginkgo062018cirscc*).

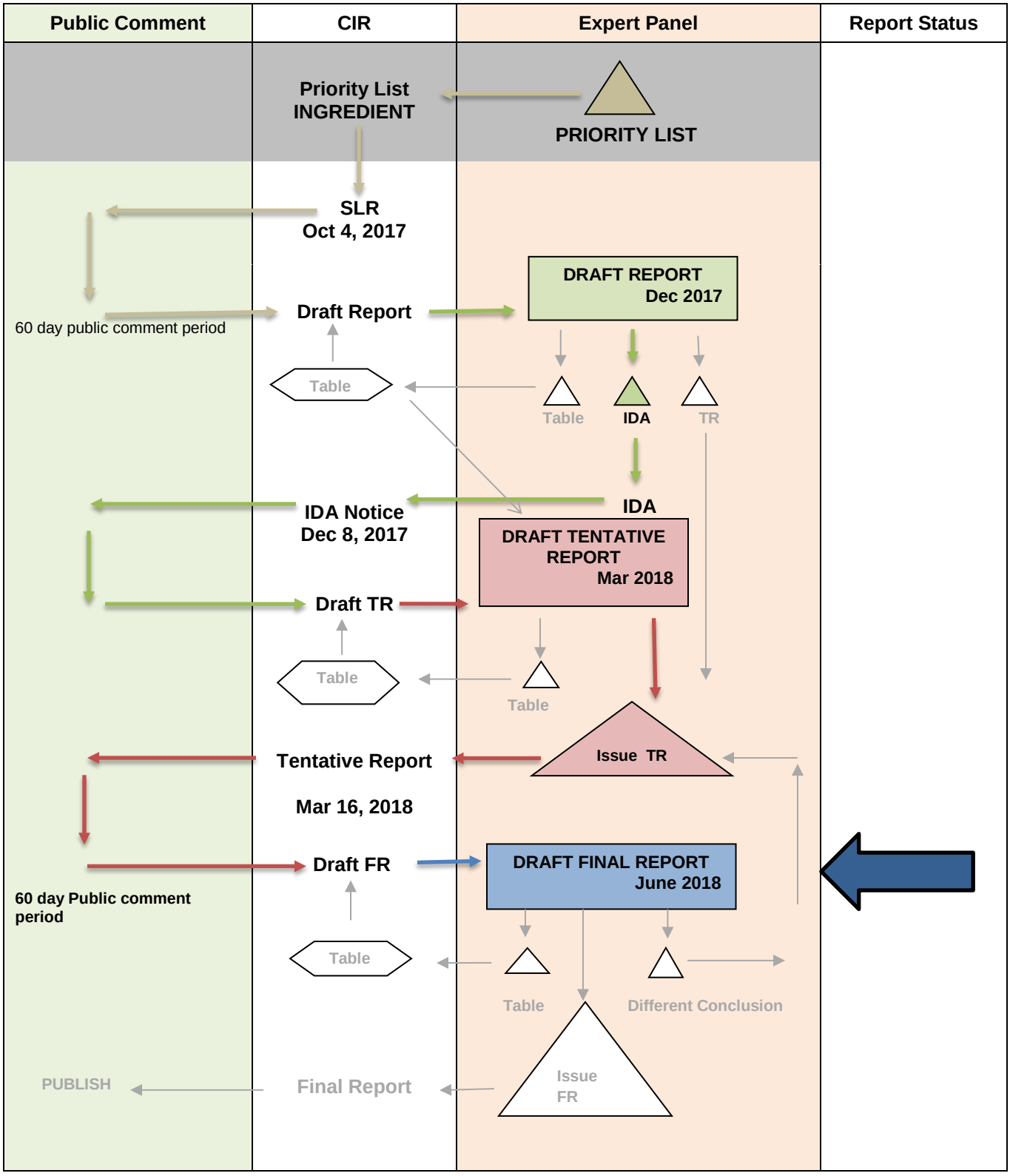
There were no significant changes in the number of uses of these ingredients according to the recently obtained 2018 VCRP data. Ginkgo Biloba Leaf Extract still has the most reported uses in personal care products at 712 (a decrease from 2017 by 14 formulations); the majority of uses are in leave-on products.

The Panel should carefully consider and discuss the available data, the comments from the CIR SCC, and the current Abstract, Discussion, and Conclusion presented in this report, and either issue a Final Report with the current insufficient data conclusion or revise the conclusion and issue a revised Tentative Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Ginkgo biloba*-derived ingredients

MEETING June 2018



***Ginkgo biloba*-Derived Ingredients History**

October 2017 – Scientific Literature Review announced.

December 2017 - The Panel issued an Insufficient Data Announcement for these 10 ingredients. The Panel's data needs were:

- Method of manufacturing for each of these Ginkgo biloba-derived **cosmetic ingredients**
- Composition and impurities data for each of these Ginkgo biloba-derived **cosmetic ingredients**
- 28-Day dermal toxicity data
- Dermal irritation and sensitization data at leave-on use concentrations
- Ocular irritation data, if available
- Genotoxicity data
- Developmental and reproductive toxicity data
- Data on the absorption spectra or phototoxicity of these **cosmetic ingredients**

March 2018 - The Panel issued a Tentative Report for public comment with the conclusion that the data are insufficient to determine the safety of these 10 cosmetic ingredients. The data needed to issue a conclusion of safety for these cosmetic ingredients were:

- Method of manufacturing, composition, and impurities data for each of these ingredients, except Ginkgo Biloba Meristem Cell
- 28-Day dermal toxicity data for each of these ingredients.
    - Dependent on the results of these studies, additional data on other toxicological endpoints, such as developmental and reproductive toxicity and carcinogencity, may be needed
- Dermal irritation and sensitization data at leave-on use concentrations
- Ocular irritation data

The Panel considered the findings of the National Toxicology Program's (NTP) carcinogenicity studies of a *Ginkgo biloba* leaf extract where positive carcinogenic effects were observed in animals, especially in the high dose groups. The *Ginkgo biloba* leaf extract evaluated by the NTP contained unusually high concentrations of certain constituents that are markedly different from those found in the leaf extracts used in dietary supplements. The NTP study administered this specific leaf extract at high doses by gavage, allowing for concentrations in the blood that would not be achieved through cosmetic use. The leaf extract similar to that used in dietary supplements did not produce increased incidences of cancer in a dietary study. This, combined with a long history of use of *Ginkgo biloba* leaf extracts in folk medicine, indicate that the findings of the NTP carcinogenicity study are not relevant to cosmetic use in humans.

***Ginkgo biloba*-Derived Ingredients Data Profile –June 2018 – Writer, Christina Burnett**																
	In-Use	**Physical/Chemical Properties**	**Method of Manufacturing**	**Composition/Impurities**	**UV Absorption**	**Acute Toxicity**	**Repeated Dose Toxicity**	**Genotoxicity**	**Reproductive and Developmental Toxicity**	**Carcinogenicity**	**Toxicokinetics**	**Irritation/Sensitization - Nonhuman**	**Irritation/Sensitization - Human**	**Ocular/Mucosal**	**Phototoxicity**	**Clinical/Case Studies**
Ginkgo Biloba Leaf Extract	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ginkgo Biflavones																
Ginkgo Biloba Leaf																
Ginkgo Biloba Leaf Cell Extract																
Ginkgo Biloba Leaf Powder	X															
Ginkgo Biloba Leaf Water																
Ginkgo Biloba Meristem Cell			X	X		X	X	X								
Ginkgo Biloba Nut Extract	X															X
Ginkgo Biloba Root Extract																
Ginkgo Leaf Terpenoids																

"X" indicates that data were available in the category for that ingredient.

Ginkgo-Derived Ingredients

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Ginkgo Biloba Leaf Extract	90045-36-6	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Biflavones	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Biloba Leaf	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Biloba Leaf Cell Extract	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Biloba Leaf Powder	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Biloba Leaf Water	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Biloba Meristem Cell	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Biloba Nut Extract	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Biloba Root Extract	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Ginkgo Leaf Terpenoids	107438-79-9; 15291-75-5; 15291-76-6; 15291-77-7; 33570-04-6	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	

Botanical and/or Fragrance Websites (if applicable)

Ingredient	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	EMA	AGRICOLA	SSA	IFRA	RIFM
Ginkgo Biloba Leaf Extract	√	√	√	√	√	√	√	√	NA	NA
Ginkgo Biflavones	√	√	√	√	√	√	√	√	NA	NA
Ginkgo Biloba Leaf	√	√	√	√	√	√	√	√	NA	NA
Ginkgo Biloba Leaf Cell Extract	√	√	√	√	√	√	√	√	NA	NA
Ginkgo Biloba Leaf Powder	√	√	√	√	√	√	√	√	NA	NA
Ginkgo Biloba Leaf Water	√	√	√	√	√	√	√	√	√	√
Ginkgo Biloba Meristem Cell	√	√	√	√	√	√	√	√	NA	NA
Ginkgo Biloba Nut Extract	√	√	√	√	√	√	√	√	NA	NA
Ginkgo Biloba Root Extract	√	√	√	√	√	√	√	√	NA	NA
Ginkgo Leaf Terpenoids	√	√	√	√	√	√	√	√	NA	NA

NA = Not applicable

Search Strategy

SciFinder

Search for CAS # and INCI names yielded 14 returns (8 for "Ginkgo Biloba Leaf", 6 for CAS #), reference search was for "adverse effect, including toxicity" (some hits were repeated under the terpenoids CAS #).
Ginkgo Biloba Leaf = 0 hits
107438-79-9 = 3 hits, 2 relevant
15291-75-5 = 14 hits, 5 relevant
15291-76-6 = 4 hits, 3 relevant
15291-77-7 = 123 hits, 10 relevant
33570-04-6 = 23 hits, 15 relevant
90045-36-6 = 1 hit, 1 relevant

PubMed Search: ((((((((((((((ginkgo biloba leaf extract) OR ginkgo biflavones) OR ginkgo biloba leaf) OR ginkgo biloba leaf powder) OR ginkgo biloba leaf water) OR ginkgo biloba leaf cell extract) OR ginkgo biloba meristem cell) OR ginkgo biloba nut extract) OR ginkgo biloba root extract) OR ginkgo leaf terpinoids) OR 90045-36-6) OR 107438-79-9) OR 15291-75-5) OR 15291-76-6) OR 15291-77-7) OR 33570-04-6 AND (tox[sb]) = 605 hits; 53 useful

Search updated April 2018 – no new pertinent references.

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/

- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

Note: ChemPortal can be used to search several of the above databases simultaneously - http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en

Ginkgo biloba-Derived Ingredients
March 5-6, 2018

Dr. Belsito's Team

DR. BELSITO: In December we issued an IDA. We wanted method of manufacturing for each of the ginkgo-derived cosmetics. We wanted composition and impurities for each of them. We wanted a 28-day dermal. We wanted irritation sensitization at leave-on use, which was 1 percent ginkgo biloba leaf extract, ocular irritation, if available, genotox, developmental and repro, and data on absorption.

And we received the following data, an HRIPT on a lotion at .2 percent, but not the 1 percent we asked for. A certificate of analysis on the leaf extract. A composition, method of manufacturing on the meristem. Absorption spectrum on the leaf extract. And summaries for HRIPTs, photo and in vitro ocular on the ginkgo biloba. So, hardly all of the data that we asked for.

MS. BURNETT: And we did receive some more in Wave two. Not a whole lot, but some more.

DR. BELSITO: Yes. We received a whole lot.

I guess I didn't think the Wave two data added much of the information we're asking for; because my conclusion was insufficient for data needs remaining above. And I said irritation for the ginkgo biloba extract was okay. The genotox was okay. The repro needs discussion. There were two negatives and one positive. The photo was okay and the other were not addressed in the new data or Wave two, so it's still insufficient.

We need sensitization at concentration of use, which is 1 percent. The photo is okay. I need comments from my teammates as to what they make of the repro data.

DR. LIEBLER: The Wave two data on the method of manufacture for the nut extract is really inadequate?

DR. BELSITO: Yeah. I didn't think it was.

DR. LIEBLER: And that was one of our major data needs, that and the root, of course. And we also don't have the terpenoids or the biflavones.

DR. BELSITO: I didn't think the Wave two data provided us much in terms of composition at all. I thought method of manufacturing was still really needed.

DR. LIEBLER: The only thing that we got was the meristem cell and that was okay. I think the meristem, at least, method of manufactures is covered now, but the others are not.

DR. BELSITO: Right. The composition and impurities?

DR. LIEBLER: Same.

DR. BELSITO: Meristem is covered or not?

DR. SNYDER: Only the meristem we have data. Only for the meristem.

DR. LIEBLER: Only the meristem. But not the nut root and the biflavones and terpenoids.

DR. BELSITO: Okay, 28-day dermal, we don't have on any of them?

DR. SNYDER: Yeah. And we really don't have absorption data, because that absorption data we have in the report is absorption of quercetin.

DR. BELSITO: Right.

DR. SNYDER: So, that's not adequate.

DR. KLAASSEN: No, just one small ingredient.

DR. BELSITO: Right.

DR. SNYDER: Yeah. That's still a need.

DR. BELSITO: We have irritation for the extract, which is okay, but we don't have sensitization data at concentration of use. And we wanted dermal irritation and sensitization data on leave-on use concentration. So, the sensitization remains insufficient.

Ocular we didn't get, but we always ask if available. The genotox is okay. The DART data, two negative studies, one positive. Paul, what did you make of those?

DR. SNYDER: Well, yeah. I had some questions about this, the material as being standardized, and all this language related to the discussion around the actual material that was tested.

DR. LIEBLER: Could you point to which paragraph in which study you were concerned about?

DR. SNYDER: Well, all these studies say when a standard GBE was administered. And then there's all this language that NTP did not use the specific material that's used as a dietary supplement; industry that did not meet their pharmacopeia, established pharmacopeia standards. That made it really cloudy and difficult to try to interpret what's a cosmetic versus a dietary.

MS. BURNETT: We don't know what the cosmetic is.

DR. SNYDER: That's right.

MS. FIUME: Right. Because the language here was described earlier in the report, right? Identified what standardized --

MS. BURNETT: Right. Standardized is what is generally used in the dietary supplements. The NTP was a special extract that they used for their testing. In terms of actual testing on the cosmetic extract -- DART, there's not.

DR. SNYDER: In lieu of that, we need 28-day dermal study to determine whether there's any systemic issues in my opinion. If we don't have absorption data, then we need to have the 28-day dermal to see whether or not we have anything.

MS. FIUME: Typically, we can't ask for absorption data on a botanical; because of the constituents, we don't know what we're generally looking for.

DR. SNYDER: Right. So, we want a 28-day dermal still? Is it still a data need?

MS. FIUME: 28-day dermal on a specific ingredient?

DR. KLAASSEN: No. The whole.

DR. SNYDER: Well, on the leaf extract and whatever -- the meristem cell and -- that we can get. Yeah. Each of the individual ones. We'll have to see what we can get.

DR. BELSITO: So, you want 28-day dermal on each ingredient?

DR. SNYDER: Correct. At this time. Ask for it.

DR. BELSITO: Still haven't answered my question about the DART.

DR. LIEBLER: Your question is can we use these in NTP data?

DR. BELSITO: No. It's, again, not my area of expertise. We have two negatives and one positive study. Can you explain away the positive study? Do you think the negative studies were poorly done? I mean, which -- or do we say it's two against one and two wins, so it's negative?

DR. LIEBLER: Well, we don't do that with sensitization, so.

DR. BELSITO: I'm just, again, throwing it out.

DR. LIEBLER: The problem is -- I mean, I'm not an expert in repro and developmental toxicity, but I think the major question mark is the nature of the material that was tested.

MS. FIUME: Also, those were oral. In the past it's usually asked for dermal absorption and then positive; then in a response, is it the 28-day dermal study and then if results are seen, additional tests might be needed. Would that be a way to handle it?

DR. BELSITO: Yeah. I'm fine with that.

DR. SNYDER: Again, the issue for me was if the standardized GBE is not related to the cosmetics, we don't really have anything. We need to go back to the original and say, okay 28-day dermal, if we have significant absorption then we're going to ask for repro. Does that make sense?

MS. FIUME: Yes. And knowing what is the cosmetic composition would be helpful.

DR. SNYDER: Yeah.

DR. KLAASSEN: If you do the 28 days, it won't really tell you about absorption, it will tell you about toxicity.

DR. SNYDER: Exposures. Exposures, yeah.

DR. KLAASSEN: But just because you don't get toxicity there, doesn't mean that you won't get reproductive toxicity.

DR. SNYDER: Well, we've always used that as the path.

DR. KLAASSEN: But that's not right. I mean, that's what you're trying to do with the teratogenicity study; is to find the chemical that's more toxic to the fetus than it is to the mother.

DR. SNYDER: No. I think it's a valid strategy. That if you don't see anything that alarms you in a 28-day dermal, then you're not likely going to see anything.

DR. KLAASSEN: In a teratogenicity study?

DR. SNYDER: Yeah.

DR. KLAASSEN: How about thalidomide?

DR. SNYDER: Well.

DR. KLAASSEN: I agree, we've done that, but that's faulty logic.

MS. FIUME: It can be listed separately if it's a concern.

DR. SNYDER: We can ask. Yeah. I guess, we can ask if there's any --

DR. BELSITO: Well, we have two studies -- or three studies. What do you make of the three studies? It's not like we don't have any studies.

We have two studies that are negative, essentially, and one that is positive. Do we have comments on those studies that we do have?

DR. KLAASSEN: That's the problem with all of these plants.

DR. BELSITO: We don't know what we're dealing with. So, that's our comment?

DR. KLAASSEN: We don't know what chemicals, really, they're getting.

DR. BELSITO: Right.

DR. LIEBLER: One question is how different can this standardized ginkgo biloba extract be from a cosmetic ingredient?

DR. SNYDER: Well, the only reason I raised it was because they made big stink that the NTP did not test the standardized material. They tested a very specific, particular material and they felt that that was not valid. And that's one thing that raised my --

MS. BURNETT: If anything to us, it shows that the concentration of the constituents matters. And we don't know what the concentrations are that are in the cosmetic ingredients.

What they had done at the NTP study had, you know, higher concentrations. They're all the same constituents, but showing that those of the constituents make the poison -- well, I don't want to say that, but --

DR. SNYDER: Yeah. Right. Sure. Sure.

MS. BURNETT: -- makes the systemic change.

DR. ANSELL: Our information indicates that the cosmetic grade is mostly similar to the standardized material, which is sold as a dietary supplement. And that's why we felt that the leaf extract data was sufficient for those materials; although -- as pointed out -- not to color --

DR. BELSITO: But do we know that?

DR. SNYDER: Only know it for meristem cell. That's the only thing we have composition on.

DR. BELSITO: Right.

DR. SNYDER: So, we don't know.

DR. LIEBLER: I think we're really stuck here. Without having composition and impurities for the cosmetic ingredient, we're left to infer the equivalency of the data from the standardized extract. And that's where we're stuck. This is a case where we need data.

DR. BELSITO: Yeah. Basically, it's insufficient. And the points I have are method of manufacture and composition impurities for everything except meristem.

DR. SNYDER: Correct.

DR. BELSITO: 28-day dermal tox for all of them.

DR. SNYDER: Yes.

DR. BELSITO: And if positive, then other endpoints may be needed.

DR. SNYDER: Carcinogenicity, et cetera, yes.

DR. BELSITO: Sensitization at leave-on use concentration.

DR. SNYDER: At 1 percent.

DR. BELSITO: Ocular irritation if available. Genotox, we no longer need, correct?

DR. SNYDER: Correct.

DR. BELSITO: Okay. Developmental and repro will be depending upon the 28-day dermal; or, Curt, are you saying we still need it? Ask for it?

DR. SNYDER: The positive study was at the highest level tested, 14.8, so.

DR. BELSITO: Okay.

DR. SNYDER: I'm not very concerned about that. But, again, it's on a material that I don't know how it relates, composition wise, to cosmetic.

DR. BELSITO: Okay. So, we need to know composition. So, this may be needed. Can we say may be needed, depending upon 28-day dermal and information regarding composition?

DR. SNYDER: Right.

DR. BELSITO: And then the photo is no longer needed.

DR. SNYDER: I had on PDF page 83 -- I had a note.

DR. BELSITO: On 83, that's beyond the document. Page 83 is searches.

DR. SNYDER: Just a second here, look that up, ginkgo --

DR. BELSITO: No, wait a minute, 83? I typed in the wrong number, sorry.

MS. BURNETT: The American herbal products comments?

DR. SNYDER: Well, I think -- yeah. I think that was the one that highlighted to me the -- yeah, here. This is it.

These tables here, this alluded to the fact I said about the repro studies and not knowing what was tested. Because if you look here, the ranges of the constituents -- I mean, this highlights how wide the ranges -- the botanicals have with regards to the constituents.

So, unless we see data on what is actually being used, I'm really cautious about using other data. That's why I had this asterisk and wanted to bring that up in defense of --

MS. BURNETT: I don't remember if I included it. I don't think I included any data in the report; but there was like a study where they took standardized off the shelf and tested like 12 different brands. And it was still all over the place when it was supposed to be standardized.

DR. SNYDER: And then I had another thing related to something I read in this document too, to both Curt and Dan. In using corn oil as a vehicle for these complexed mixtures, and whether or not botanical extracts would be -- all the constituents would be solubilized. Because there was some argument in there that some of them --

DR. LIEBLER: Solubility in corn oil?

DR. SNYDER: Yes. And that was on page 95 of this document. And that's another question that I had. So, were they talking about the vehicle for lipophilic chemicals?

DR. LIEBLER: I mean, corn oil would be fine for the lipophilic --

DR. SNYDER: Correct.

DR. LIEBLER: -- it's for the hydrophilic components they might not be soluble.

DR. SNYDER: Yeah. There's an argument here about that. I was curious as to -- not necessarily just for ginkgo, but in general.

DR. LIEBLER: For anything, yeah. The positive DART data are from the NTP, isn't that right?

DR. SNYDER: Yes. One, yeah. The highest.

DR. LIEBLER: One of the two NTP studies.

So, if we had two studies from NTP with negative results, we have no problem. Because we have an NTP test article that's more concentrated with respect to everything. That actually would suggest --

DR. SNYDER: Give it some competency.

DR. LIEBLER: We could definitely treat that in a discussion. But the problem is we have a positive result in one of the NTP studies, with the highest dose.

DR. SNYDER: Correct. Tested.

DR. LIEBLER: And we could say -- I'm not suggesting that we do say this -- but we could say, if the cosmetic ingredient is more typical of the herbal supplements type of material, dietary supplement type of material, it will fall below the levels of the NTP test material, which was only produced in adverse effect at the highest concentration. So, probably higher than we would expect.

However, we have to make the assumption that the cosmetic ingredient is equivalent to the dietary supplement material. And without any data we're --

DR. SNYDER: Just chasing our tail back to the composition. It's all driven by the composition.

DR. LIEBLER: Yes. So, I think we need data.

DR. BELSITO: Okay. Then to go back and reiterate, and then hopefully break for lunch.

We want method of manufacture composition, impurities, everything except meristem. The 28-day dermal on everything. Sensitization at 2 percent. Ocular if available. And developmental and repro will depend upon composition and 28-day dermal results, and the photo goes away.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay.

DR. LIEBLER: See, if we had data that showed that the cosmetic ingredient material is more within the range of these components -- of these other things in this table -- then we could say, well see the lowest dose NTP was negative and has higher concentrations of all of these constituents concerned. Therefore, the panel wasn't really concerned about the finding with the high-dose NTP test article.

But without a number, without some data to confidently place the cosmetic ingredient in the ranges of these other materials for these chemical constituents, we can't do that.

DR. BELSITO: Okay. Any other comments on ginkgo?

MS. BURNETT: So, insufficient is the conclusion. Is there anything else that would go into the discussion at the time, like the other bullet points I have?

DR. BELSITO: Just what's already there. I didn't bring in any other additional points.

MS. BURNETT: Okay.

DR. KLAASSEN: We had some major insufficiencies that I just wonder how consistent the ginkgo is that's used in cosmetics.

DR. SNYDER: According to that report it says that the one that was tested by that Chinese company isn't even sold in the US. It isn't even available in the US. The material.

DR. KLAASSEN: It's not easy.

DR. BELSITO: No. Okay.

DR. KLAASSEN: But it's a natural chemical, it must be okay.

DR. LIEBLER: Must be, yeah.

DR. BELSITO: It's 12:13, but I think we can conclude lunch and be back at 1:00, yes?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay.

Dr. Marks' Team

DR. MARKS: Okay. Next is Ginkgo. We have a draft tentative report on Ginkgo derived ingredients. At the December meeting, last year, the panel issued an insufficient data announcement for these 10 ingredients. And in Christina's memo they are bulleted, including method of manufacture, composition impurities, 28-day dermal tox, dermal irritation and sensitization, ocular irritation, genotox, DART, absorption data, phototoxicity. And we did receive some data, which again is bulleted in Christina's memo.

We're at the point now of can we issue a tentative report. Well, we should be issuing a tentative report. And what is that conclusion going to be? So, Ron, Tom? I had, safe for the leaf extract at 0.2 percent, formulated to be non-sensitizing and the rest insufficient, but I'll let you guide me.

DR. HILL: Say that again.

DR. MARKS: I thought the leaf extract we now had enough data, and it's safe at 0.2 percent. We had sensitization data on that, formulated to be non-sensitizing.

DR. SLAGA: I had the same thing.

DR. MARKS: And then the rest, we didn't get enough to move pass the insufficient. But I want, Tom, your and Ron's input. And then I'll let you know what Ron Shank thought.

DR. BERGFELD: Was the geno and the carcinogenicity studies okay?

DR. SLAGA: Yeah.

DR. BERGFELD: They were okay? They weren't?

DR. SLAGA: I looked at that very carefully. The genotox, once again, was very mixed, positive/negative. But the weight of evidence is towards negativity. The carcinogenicity study that was positive was by high-dose gavage, which in another study, by diet, which would be even much less would get into the blood, it was negative. The dermal relationship would be, obviously, no concern.

DR. BERGFELD: So, that's a discussion piece?

DR. SLAGA: Yeah. All that should be in the discussion.

DR. MARKS: Other comments or do you want me to -- Ron?

DR. HILL: Let me just read and then we'll see if the other Ron flagged any of this.

In wave two, we've got the fresh, dry leaf is extracted with the specified eluent, under appropriate temperature and conditions to produce a concentrate.

That tells me exactly nothing. Because the whole point of the method of manufacture is to sort of get the sense of what compounds might be in there. And while I appreciate that they might want to keep it proprietary, that doesn't work for me here. Or, alternatively, provide me a detail of characterization of the amounts of constituents in that extract.

Because the problem is -- it's the same thing we face, always, with botanicals, what's the extract? What's in there, how is it made? You're going to get a big difference if it's boiling in ethanol and water -- depending on the percentage -- for some hours, if you're steam distilling to extract, or if you're a super critical fluid. The witch hazel, that I didn't bring up earlier, they were cooking it up in D5, cyclopentasiloxane, for some unspecified period of time and some unspecified temperature.

You don't know what you're getting in these things, and then you're trying to read across safety data. And so, my comment about the genotox was something to the effect that they seem to be varying around -- their equivocal, but perhaps varying around based on what's in the extract that's being actually tested.

So, give me something to have some idea of what's actually in these extracts; so that you have some idea that whatever safety testing has been done is something similar to what's being marketed. And since we aren't getting anything real, in the method of manufacture, that tells us anything to get some sense of, well, it's going to give me very oil-soluble things and not much of the water soluble or vice versa, how would we know.

And while we've got typical product specifications info, and it's not completely used, and it provides almost nothing of much value with respect to toxicological safety assessment, maybe accepting PH and water solubility info.

Let's see. I had a couple of other comments scattered. What is the nature of the meristem cell substance tested? But you already said insufficient for that, right now, anyway, right?

DR. MARKS: That's correct.

DR. HILL: But I did have the question, what's the nature of the -- in terms of saying why we don't know. There's nothing about -- are these whole cells, are these shredded cells? I'm not clear from what they provide. They give us a lot of the process and then nothing at the end to know exactly what's coming out that's being given to animals and patients -- or formulated, I should better say, not patients.

And then on the UV absorption spectrum, yes, there are no peaks, but there is significant absorption down in the range where phototoxicity could potentially be a concern. I'm not particularly worried about it, because these things have been out there for a while, and I think we would be seeing that.

I don't want to use the word rouse, but it seems like -- just because there's no peak, doesn't mean there's no absorptivity. And the problem is we don't know what concentration is being test there; so, you have no opportunity to calculate something analogues to a molar absorptivity constant that you would calculate if you had a pure substance.

It's just bothersome. I sort of sense that we would land on -- say, for the leaf extract -- exactly what you said; but the problem is an extract is not an extract, is not an extract. If we have no idea whether or not they're all prepared heating in ethanol water, 40 percent ethanol for 10 hours and then filtering, like that -- we don't know.

The substances in it could vary all over the place. And if this stuff seems to be entirely innocuous, with no biological activity at all, no evidence in the literature for biological activity, I wouldn't worry so much. But people use this for the pharmacology, even if it may not work.

DR. MARKS: Okay. We'll get back for you to summarize that, Ron Hill. I'll read Ron Shank's comments.

Page 42 discussion, first paragraph. The leaf extract did not induce sensitization in animal or human tests. Also, on 42, discussion, at the bottom of that page; genotox studies gave mixed results -- just what you said, Tom. Carcinogenicity study used on an extract of ginkgo, not typical of extracts used in cosmetics and used at high doses, by gavage, capable of producing extract concentrations, in blood, that could not be achieved in cosmetic use.

When the extract was incorporated in the diet of test animals, which would produce lower blood concentrations, increase incidence of cancers were not seen. This all elaborates on what Tom said as part of the discussant points. This combined with a long history of use of extracts and folk medicine, indicates that animal carcinogenicity data are not relevant to cosmetic use by humans.

Page 43 discussion, top, apply the usual cavate for botanicals when formulated to be non-sensitizing. For 43, end of discussion, no more outstanding data needs for the leaf formulation. Still insufficient for the nut and root extracts by flavons and possibly leaf terpenoids. Make clear that this safety assessment is based on the extracts defined in this report, does not necessarily apply to other sources of the ingredients.

Page 43, conclusion, split. Leaf-derived ingredient, safe when formulated to be non-sensitizing. Other ingredients insufficient, as stated in the December 2017. I kind of limited it to the leaf extract. Do you think we can expand it to the other leaf; the leaf alone, the leaf cell extract, the leaf powder, the leaf water? I didn't know whether we could expand. I think Ron Shank -- although he doesn't say it here --

DR. SLAGA: I think you can.

DR. MARKS: -- indicates that the leaf extract represents -- now the one thing is we have the extract at 0.2 percent; that was Wave two. In terms of being a non-sensitizer. Can we say that for the other leaf ingredients? How do we deal -- I guess, if you say -- except we've already said --

DR. SLAGA: For all the leaf products.

DR. MARKS: -- formulated to be non-sensitizing doesn't apply directly to the ingredient, but the combination.

DR. SLAGA: Yeah.

DR. MARKS: I don't know how to quite get past that. We have it specifically -- do we say none of the others can be greater than 0.2 percent?

DR. SLAGA: Well, what you said that Ron said. He said everything was okay with all leaf parts.

DR. MARKS: With all leaf, yeah. Conclusion.

DR. SLAGA: Except for the nut and the root -- didn't you say there was something?

DR. MARKS: Right. Right.

DR. SLAGA: Dry terpenoids and terpenoids or something.

DR. MARKS: The nut and the root, and then terpenoids and the meristem would all be insufficient.

MS. BURNETT: We did have data on meristem. Did that not fill the needs?

DR. MARKS: Yeah. As far as I'm concerned, I didn't know sensitization and irritation. There was a lot more data. When we get into data needs, everything is the same, other than with the meristem cell, I'd want to see sensitization and irritation for that. We had the method of manufacturer, impurities.

I was focused on the leaf extract and I didn't know whether we could read across and use that as an example. And then we set a concentration limit, and is that applicable to the other?

MS. BURNETT: Okay.

DR. MARKS: Let me see. What's the leaf extract? It was 0.2 percent was Wave two, that was okay. I don't have written here a use concentration.

MS. BURNETT: That's used up to 1 percent.

DR. HILL: In leave on.

MS. BURNETT: In leave ons.

DR. HILL: And do we know what that leave on is? That was the question I had written here to ask.

MS. BURNETT: Let me see.

DR. MARKS: Yeah, there I it, 1 percent. So, this would be 1/5 of that. So, the other is setting a limit on it based on the sensitization data we have.

MS. BURNETT: I want to say it's a skincare preparation, but I can't remember exactly. I'll look for it.

MS. FIUME: Face and neck skin preparations.

DR. EISENMANN: Dr. Marks?

DR. MARKS: Um hmm?

DR. EISENMANN: What about the guinea pig sensitization study that's in the sensitization section?

DR. MARKS: The guinea pig for?

DR. EISENMANN: Well, primarily it's on ginkgolic acid and a leaf extract. They determined that the ginkgolic acid is the problematic compound. And as long as you were at a 1000 or less, you were okay. It was when the ginkgolic acid got high, that was when there was an issue.

DR. MARKS: This is what page?

DR. EISENMANN: It's in the sensitization section.

MS. BURNETT: PDF page 40.

DR. MARKS: 40?

DR. HILL: There's a whole section that was added since last time.

DR. EISENMANN: So, they also looked at an extract. They used 10 percent of an extract, and that's the guinea pig study.

DR. MARKS: That's the GBE?

DR. EISENMANN: Yes.

DR. MARKS: That's the extract? So, the highest concentration of the extract that they used was 1 percent, you said?

DR. EISENMANN: It was 10 percent.

DR. MARKS: It was 10 percent. Then there would not need to be a restriction. Okay. So, it would be just say thank you.

DR. BERGFELD: But that was in the animal model, is that okay?

DR. MARKS: Yeah, I think so. There were 10 guinea pigs used, it was with modified Freund's complete adjuvant. I think as long as there's a good sensitization testing, either with animal or human, that's fine. That would mean that we wouldn't need to restrict the concentration since 1 percent would be safe. And that's the use concentration.

DR. HILL: Safe provided that the ginkgolic acid levels were sufficiently low?

DR. BERGFELD: Would be non-sensitizing.

DR. HILL: Which, if they follow the production procedure where they do the heptane wash, which is what they gave us, it would be because that's what removes most of it. Let's see, 1000 ppm, that's .1 percent. All right. And then if you use the extract --

DR. EISENMANN: Which is an exceedingly high level, because that was even higher than what was in the NTP.

DR. HILL: Okay. So, if you use 10 percent and then .1 percent of that was -- I was trying to think -- .1 percent of that would be the ginkgolic acid. So, ten times. Yeah. That's still a pretty small amount. The question is how much can you get away with of ginkgolic acid? Do we have to set a threshold since we know that's a sensitizer, basically?

Or if we have discussion that -- I just think in some way we need to flag if sensitization is the concern. And actually, probably for immunotox, same deal. Because looking at that, they did heptane fractionation versus not, and then looked at the one that's right above it. Almost everything tracks with the presence or absence of the ginkgolic acid.

And we're using it at 1 percent or less, so it's a low use concentration, which is my comfort level. How do we capture, either in the discussion or in the conclusion -- probably in the discussion, I guess -- the need to minimize the ginkgolic acid below some level, it could be 1000 ppm. The good news is, in contrast to other botanicals, I don't think they're going to get ginkgolic acid from any other thing that they might add into the cosmetic.

DR. MARKS: Based on that -- thank you, Carol -- we don't have to set a limit. How about expanding it, going back to all the leaf ingredients are safe. Sounds reasonable.

DR. HILL: I don't know because we don't have any information about how they're made. We don't know what they are.

MS. BURNETT: Does extraction concentrate or remove constituents?

DR. MARKS: You feel uncomfortable because we don't have --

DR. HILL: Well, if they're using it at 1 percent or less, I doubt that there's a problem. But we don't know what they are, so for me, that's bothersome.

DR. MARKS: Tom?

DR. SLAGA: I think the leaf extract covers.

DR. MARKS: Yeah, I think that's the key.

DR. HILL: As long as you do a heptane wash in the production process. Then what happens if you introduce the leaf in some other way? That's what I'm getting at.

DR. BERGFELD: Can you put that in the discussion?

DR. HILL: Probably so. Yeah. If you said the other leaf components are all right, provided that the ginkgolic acid -- I don't know, is there any other -- there are a couple other constituents, but I wasn't as concerned about them as they were -- what was it, quercetin and kaempferol -- at the use levels, so it shouldn't be causing any problem at all.

But it was, in fact, striking in comparing these extracts. It seemed like they came in two flavors; one, where the concentrations of the constituents were fairly high, tens of percent, and the others were much smaller. I went through and highlighted, yellow, gray, yellow, gray, to see that. And then I scratched my head, and puzzled, and went on to the studies to try to get a sense of what they were studying when they did some of these studies.

But, it seems like it's covered if we could find a way in the discussion for all the leaf, like Ron Shank says.

DR. MARKS: So, tomorrow presumably, I will be seconding a tentative report with a conclusion that the leaf ingredients are safe when formulated to be non-sensitizing. The rest of the ingredients are insufficient. And we need, basically, the data that was elicited before. Other than the meristem cell, we have quite a bit we still need the irritation and sensitization on that.

DR. HILL: And what is it? I would like to still know what is it?

DR. MARKS: What meristem cell, yeah.

DR. HILL: No. I mean, they give us the process all the way down to the last step, what's the substance at the end?

DR. EISENMANN: Well, they said it's mostly catechin, gallocatechin, epigallocatechin. In other words, you've reviewed tea that contained very similar -- it's completely different composition than the ginkgo leaf extract.

DR. HILL: That told me about the constituents, but what I was wondering is what else is there in their finished product, because it sounds like they just did a cold press at the end. So, all the juice inside the cells that have passed through that filter, that they're pressing through, I mean, that's what I -- there ought to be a little more information, right there at the end, as to what's actually going in the cosmetic product. The nature of it.

DR. MARKS: Yeah. Since that'll be in the insufficient, let's -- you would like to know more about the composition? Okay.

MS. BURNETT: The meristem?

DR. MARKS: The meristem. Yep.

MS. BURNETT: Just for clarification, on the list of ingredients, when you're saying leaf, you're including the leaf --

DR. MARKS: Everything that has leaf in it.

MS. BURNETT: The leaf cell extract, the leaf powder, the leaf water and the leaf terpenoids?

DR. HILL: Oh, what about the terpenoids?

DR. MARKS: Oh. Thank you.

DR. SLAGA: I don't think we should include them.

MS. BURNETT: Okay. And bioflaviones are insufficient too?

DR. MARKS: Yes.

MS. BURNETT: Okay.

MS. FIUME: Christina, are you good with the rationale as to why the composition and impurities data and method of manufacturer aren't needed for the leaf, other than this sensitization test that we've gotten?

MS. BURNETT: On the other leaf ingredients, or any?

MS. FIUME: Right, any of the leaf ingredients? Because we didn't receive any information on that, right? The only thing we received was sensitization data?

DR. MARKS: No. We already had the leaf extract. And we're using that as the read across, so we had method of manufacturer, composition, et cetera, on the leaf extract.

MS. FIUME: But do we know it for what's used in cosmetic? What the method of manufacturer, and impurities, and constituent data of the ginkgo as used in cosmetic? We know dietary and what was used in the NTP, right? Do we know what's being used in cosmetics, or are we assuming that it's the same as the dietary?

MS. BURNETT: In terms of the constituents?

MS. FIUME: Yes. I'm looking at the list and it wanted method of manufacturer, composition and impurities for all ginkgo biloba-derived cosmetic ingredients.

DR. HILL: This is running together.

MS. FIUME: And I just wanted to make sure that those needs were answered. Or, that you know why it's not needed for the leaf.

MS. BURNETT: We did receive some method of manufacture for the leaf extracts, not for any of the other leaf.

MS. FIUME: Okay.

DR. HILL: That's what I'm trying to remember is, was that supposed to be characteristic of cosmetic ingredient production? Yes? Where did we get that flow scheme that showed -- that was in Wave two -- sorry.

MS. BURNETT: The general manufacturing process flow is for generic leaf extract, not for cosmetic.

DR. HILL: Okay.

MS. BURNETT: I have a manufacture that did report that the cosmetic product of -- ingredient is -- that one ginkgo biloba leaf extract product is produced through extraction with an ethanol water solution. While another product is produced through extraction with ethanol water solution before being evaporated and resolved in 50 percent butylene glycol.

DR. HILL: Yeah, we're looking at page 32, right?

MS. BURNETT: And then there's something in Wave two, I believe.

DR. HILL: Wave two was not informative.

MS. BURNETT: That was not? Okay. That's what we have specifically for the cosmetic ingredient.

DR. HILL: This scheme one is actually relating to the standardize extract, such as EGb761, that's what I thought.

MS. BURNETT: Yes. Correct.

DR. HILL: We really never did get -- and that was my problem, because that heptane wash there is critical, that's what removed the ginkgolic acid.

DR. EISENMANN: But you have some composition information that says .1 ppm ginkgolic acid -- and this is a cosmetic ingredient. And another one that said 2.3 ppm ginkgolic acid.

DR. HILL: Okay. If we can assume that that's what we're looking for --

MS. BURNETT: That would be about middle of the page on PDF, 33.

DR. HILL: 33?

MS. BURNETT: Um hmm. It's in the highlighted --

DR. HILL: Yeah. Okay. Right, I have it highlighted, actually. Well, we actually had at least one of those specification sheets as I remember, but. Because the point is that this molecule is closely related to urushiol, which is found in poison ivy, and is an allergen.

DR. MARKS: Correct.

DR. HILL: Where is the information about the specification sheet? I'm still not seeing it, I'm sorry.

MS. BURNETT: There is a specification sheet in Wave two.

DR. HILL: All right. But where you were just at on page 33 --

DR. EISENMANN: A certificate of analysis -- it's the last paragraph, just before ginkgo biloba meristem cell.

DR. HILL: Okay. I see it.

DR. EISENMANN: It's the one that says 2.3 and the paragraph above it is the .1 ppm ginkgolic acid.

DR. HILL: All right. And this is coming from reference 15.

DR. EISENMANN: From suppliers that responded to me when I requested data on cosmetic ingredients.

DR. HILL: All right. All right. So, we need the discussion to capture that we're making the assumption that this is reasonably representative for leaf extract.

DR. MARKS: Okay. Any other comments? Tom, Ron, anybody else?

MS. BURNETT: I just want to make sure -- I have a little bullet list in the back of discussions and see if everything's been addressed.

DR. MARKS: Okay.

MS. BURNETT: We were going to say that this findings of the genotox and carcinogenicity studies were based using that gavage.

DR. SLAGA: Yeah. Well, and there was a negative one for a diet. I mean, really eating it, not shoving it down their throats.

DR. MARKS: And Ron Shank has that, also, in his notes, which you'll be able to look at, along with what Tom has said.

MS. BURNETT: Okay. I think just generically, staff is looking in -- I know this is something that we're pondering for all our botanical ingredient reports; is some kind of -- I don't know if we want a statement. But to note how the composition of the botanical ingredient, it really is important to know it. Because as we've seen, with this ingredient, the NTP extract -- I mean, it was all the same constituents, but they are higher concentrations than the stuff that's in the dietary; and just how important it is to know what we're looking at.

And they all have the same constituents, but if it's a higher concentration, it can cause adverse effects. Just maybe something to ponder and discuss at some point, with any of these botanical ingredients.

DR. BERGFELD: Are you meaning to say we need to put together a paragraph that can be inserted? Because I think the discussion sort of supports what you've said.

MS. BURNETT: I think something that will need to go broadly in all of our botanical reports. I mean, this group of ingredients, obviously, has this kind of issue. The next botanical, maybe it doesn't have such a thing, but it should possibly still go into either a discussion of introduction, something like that.

DR. MARKS: Are you saying that -- again, like with the sensitization, if you had several botanicals and you put them together, you may have a constituent that alone is safe in reviewing it in that particular botanical; but when you mix botanicals together, you might get above a threshold?

MS. BURNETT: A little different, I think. Not necessarily in terms of formulation, just I would just -- Monice, I'm like floundering, sorry.

MS. FIUME: I think what Christina is trying to point out is that the information in this report emphasizes the importance of knowing the amounts of constituents in the cosmetic ingredients versus a generic plant. Because as we have seen, as we've gone through the botanicals, the amounts of the constituents can vary based on a number of factors. And, two different extracts that were tested, had very different outcomes.

We always ask for the information in the cosmetic ingredients, and we don't have it, but we may know something about the plant. This is just highlighting the importance of knowing the constituents as these ingredients are used in cosmetics -- in whatever is being used in cosmetics. Because it could have different effects on the safety.

DR. EISENMANN: But how's it always been is what's safe is the material that's been tested. If you don't get the information on the cosmetic ingredient, if you have the information on, say, what's being used as the dietary supplement, then the material that's been tested -- the dietary supplement -- as long as you have some skin data. The dietary supplement material is safe. It's up to the cosmetics industry to be using a material that's the same or similar to what's been tested.

MS. BURNETT: Correct. In this case, but we still have the data on NTP, and without --

DR. EISENMANN: Right. So, you need to be clear that the material that the cosmetics industry should be using, is the material -- not the NTP material, but the one -- the lower ginkgolic acid material; that's the one that should be used in cosmetics. I don't think the material that NTP tested is on the market at all anyway.

MS. FIUME: I think what Christina was referring to is not necessarily just in this report, but just in botanicals in general; the importance of knowing the levels of the constituents because the difference in the levels could have different effects.

DR. EISENMANN: We try and try, but it's very difficult information to get out of the companies. So, you have to assess the safety of the material that's tested. And then push the other way and say, the conclusion is for the material that was tested.

DR. DEWAN: Isn't it that we just said that we need to know what's being as the cosmetic ingredients? Until we know the constituents, we would not know what's going in the formulation? That's the discussion that was going on right now.

DR. EISENMANN: Correct.

MS. FIUME: And we understand that you're trying to get the information all the time, Carol. But we also emphasize, in our reports, that we're reviewing the cosmetic ingredients. If we don't have information to even give us an indication what's in the cosmetic ingredient, it makes the panel's job very difficult in trying to guess at the safety.

Yes. This is sort of our plea to industry, like yes, we do need to have an idea of what is in the cosmetic ingredient. Because we now see how it can vary based on the constituents. Hopefully, maybe they'll hear that and answer your questions when you ask for the information.

DR. MARKS: Okay. Christina, anything else?

DR. BERGFELD: Well, I don't think they've missed it, we've been talking about it for years.

MS. BURNETT: Right. I just know I have at least two more botanical ingredients this year, so, yeah.

DR. MARKS: I hate to prolong the discussion, but how do you deal with different growing conditions, different soils in which it's grown, besides the processes alone? I mean, there's a lot of variables.

MS. BURNETT: I think -- I don't remember. I know I saw a study -- but I'm not sure I included it -- that talked about how when they collect the ginkgo leaves, they actually have studied the different levels of the constituents during the different times of the year.

DR. HILL: Yes, it's in there. Spring/fall versus fall/spring.

MS. BURNETT: The green leaves versus yellow leaves and the constituent profiles flipflop. It all depends on whether you're using green leaves or yellow leaves, spring, summer, fall.

DR. HILL: That's the importance of finding data that covers those parameters. And it's even more complicated than that -- I hate to point out -- because you can have competing effects of the same molecules. I mean, if you look at some of these flavones, at this concentration they're anticancer; ramp it up a factor of 100 and now they're tumor promoting or something like that. The complexities are huge.

Then we look and say, okay, but the use concentration is .05 percent, so who cares. If you have something like urushiol in there, then we still care. I can see poison ivy down the street and I'm going to break out. My wife can pull it with her bare hands and no problem.

DR. MARKS: Christina, I don't know whether we helped you at all. But it was a robust discussion.

MS. BURNETT: It was just that when we're in the office, these continuing discussions, and just -- I don't know if we're looking for guidance or some kind of statement, but we just want to note, especially, with this example of how you have an extract and you had the same constituents and you're seeing different effects.

DR. SLAGA: Would it be worthwhile to have kind of a statement on --

DR. BERGFELD: Boilerplate.

DR. SLAGA: A boilerplate on -- whatever we want to call it. Where we give all the problems that occur with growing it different places in the world, and different times of the year. And give a couple of examples. Maybe ginkgo would be one good one. That may be worthwhile.

MS. BURNETT: I think we note that there can be -- maybe not this report. In the past, I have noted that there can be various growth conditions and things that might yield --

DR. SLAGA: Right. Influence.

MS. BURNETT: Yeah.

DR. HILL: You know, and I think the industry has been mostly well aware of this. If it's pharmaceutical use for these things, of course, then they tend to try to go for standardization. Of course, in the United States we have almost no things approved that are herbals. But Europe's a little further ahead, they have a few. And we've talked about that.

I don't know, it seems like some sort of guidance to industry document to help us with these reviews would be of value, but it might not be that easy to put together.

MS. FIUME: We have talked about that. What we'll do is, we'll try and draft some language for you to look at the next time we have a botanical, at the next meeting, and see if it helps at all. And then that way you can look at it and we can go from there to see what kind of guidance it provides.

DR. MARKS: Okay.

DR. BERGFELD: Are we now -- we have three or four -- three maybe -- botanical boilerplates? We have one about pesticides and metals. We have another about mixtures and formulating to be non-sensitizing; it includes various other botanicals that could be present. There's another one we have, manufacturing good practice to avoid things, that's one.

MS. BURNETT: Yes. And then the pesticides, heavy metals and other plant species.

DR. BERGFELD: It might be nice to put them in one sheet and let's see what we have, and then develop around that.

DR. MARKS: Okay. Good, any other comments? Again, I'll repeat, tomorrow expect our team will be seconding a motion to issue a tentative report with a conclusion that five leaf ingredients are safe, the leaf terpenoids are not, and -- as long as they're formulated to be non-sensitizing, and the rest are insufficient. Okay.

Full Panel Meeting

DR. BELSITO: Okay. The third of the botanicals we're looking at, at this meeting.

In December, we issued an insufficient data announcement for the ten ingredients. We asked for method of manufacture for each of the ginkgo biloba derived cosmetic ingredients, composition impurities for each of these, 28-day dermal tox, dermal irritation and sensitization data, leave on use concentration, up to 1 percent ginkgo biloba leaf extract, ocular irritation for available genotox, developmental and repro tox, and data on the absorption spectrum or phototoxicity of these materials.

Since that meeting, we have received some information. We did get an HRIPT, but it was only at .2 percent, not at the 1 percent. We got a certificate of analysis on ginkgo biloba extract, we got some information on composition manufacturing toxicity on the meristem cell, but none of the other plant parts. We got absorption spectrum on the leaf extract, and we got the summary of some HRIPTs, phototox/photoallergy, in vitro ocular test on gingko biloba extract.

However, this still really did not meet all of our needs, so we felt the data were still insufficient. What we needed was method of manufacture and composition and impurities on everything, but the meristem, which is now okay. We needed 28-day dermal toxicity on each of the ingredients. And depending upon what we saw from that, we may need developmental and reproductive toxicity.

We continue to need dermal sensitization at concentration of use, which is 2 percent. We dropped the genotox requirement. The developmental repro will depend upon the 28-dermal, and we thought the photo was okay.

So, to capture, method of manufacture for everything, but the meristem cell extract, composition impurities for everything but the meristem, 28-day dermal for all of them, and sensitization at 2 percent, and depending upon the 28-day dermal, potentially other tox endpoints may be needed.

DR. BERGFELD: Dr. Marks, comments?

DR. MARKS: Yeah. Our team came to a different conclusion, not surprising with this botanical. Obviously, I think we're going to defer to your needs. But we felt we could move forward with a tentative report; that we could say that it was safe for the five leaf ingredients with a left extract being the lead.

We thought we had enough tox data to say the leaf extract was safe. And then we'd read across from the leaf extract to the other leaf ingredients, other than the terpenoids. We didn't feel we could include that.

DR. SLAGA: And the flavonoids.

DR. MARKS: Yeah. The flavonoids, that's -- but that -- was that a leaf flavonoid?

MS. BURNETT: No.

DR. MARKS: No, it's not a leaf. And then the rest -- those would be formulated to be nonsensitizing, and the rest insufficient.

DR. BERGFELD: Don, comment?

DR. BELSITO: I mean, I really didn't think we got a lot on the ginkgo leaf extract. I mean, we basically got heavy metals, which we regulate, so, that's not such an issue. We got a list of which of the 26 fragrance materials that are defined in EU to be labeled, that were contained in ginkgo biloba.

And then we got some information upon appearance and color. But we really don't know what's in it. And so, I thought we still were insufficient for how it was made and what was in it. I will turn that over, any other comments, to Dan and Paul. We weren't convinced that we got the true composition.

DR. BERGFELD: Paul, Dan, Curt, any comments?

DR. LIEBLER: The thing that really hung me up the most was the NTP study data with the positive findings and carcinogenicity. The Wave two data that we got in comparison, with some of the NTP material in terms of some chemical composition categories with some of the apparently nutrient supplement gingko products, indicated that this NTP material was relatively enriched in many of these ingredients, compared to these others.

If we had data that would confidentially place the cosmetic ingredient in that group with the nutrient supplements, I would be able to explain away the NTP results, saying it was a highly enriched extract and the carcinogenic effects were at the top dose. But we don't have anything to peg the cosmetic ginkgo to. That was the thing that made it really hard for me to try -- you know, I'm pretty flexible with read across, but that's a bridge I couldn't cross.

DR. SLAGA: First of all, I agree that the NTP study was actually a different type of an extract. The genotox was mixed, but really the weight of evidence still was from negative genotoxicity. The carcinogenicity studies were done by gavage, and that's just cramming a large amount down -- and that's the only way I can define it.

It's really not relevant to a dermal. That was positive, but if you look at in the diet, where they actually eat it, it was negative. So, we accepted that that -- really even though it wasn't exact extract, we felt that any dermal exposure would not lead to cancer.

DR. BERGFELD: Paul?

DR. SNYDER: Yes. I was comfortable with the NTP data largely. But what I was most concerned about was -- and I think it highlights something to be aware of across all botanicals -- is that table on PDF page 83, where they show the constituents of four different extracts. And there was a large range of differences. The NTP one stood out in particular.

I think it's due diligence that we need to know a little bit more about what's in these ingredients that are used. We don't know anything about the cosmetic one, and that's the problem. I think that's where the hurdle is for us.

DR. KLAASSEN: That's basically the problem that we have on a lot of these botanicals, is actually to know what was tested. And from one test to another test -- it's not when you use a pure chemical. It's hard to be scientifically confident.

DR. BERGFELD: Ron Hill, comment?

DR. HILL: I don't disagree with everything they said. The UV absorption spectrum doesn't, for me, completely rule out phototoxicity either; because even though we see no peaks, there is UV absorption. And if you have a number of substances in there, you don't tend to see discrete peaks in this, there's one prominent one.

Also, we weren't given the concentration to be able to calculate something like the molar absorptivity. That was the other issue I had with that. I didn't highlight that to the extent yesterday, other than what will be captured in the transcript of my concern, but I wanted to at least point out that there is UV absorption.

The fact that there's no big prominent peak doesn't necessarily rule that completely out. Because we have a lot of substances in there, it's a mixture.

DR. BERGFELD: Don, you want to state your motion, or restate it?

DR. BELSITO: Yeah. Method of manufacture for each, except meristem, composition and impurities for each, except meristem, 28-day dermal toxicity; depending upon that, other toxicologic endpoints. We still need sensitization and concentration of use at 2 percent, we don't have that. And that was it, essentially.

DR. BERGFELD: Jim?

DR. MARKS: I want to talk about the sensitization. For the leaf extract, at least, I thought it was being used at 1 percent; we have an animal study that points to the safety of 1 percent for sensitization and 100 percent was nonirritating. And there's a human study whereas this is significantly less, but at 0.2 percent was safe.

Am I wrong that the use concentration of leave on is -- 1 percent is the highest? It's 1 percent, so that should be corrected.

That's where I felt sensitization of the leaf, and -- I'll just -- yesterday I read all of Ron Shank's notes he sent us. Basically, the conclusion of our team reflects Ron Shank's feelings, both about the carcinogenicity, the sensitization and irritation.

He gives some discussant points, but he also supports the safe when formulated to be nonsensitizing for the five leaf ingredients, with the exception of the terpenoids. The rest insufficient as you have recommended.

DR. BERGFELD: Ron Hill?

MS. BURNETT: Dr. Belsito, that animal study is on PDF page 40.

DR. BELSITO: PDF 40.

DR. HILL: And I think one of the things we discussed, in that particular segment, was 1 percent of what? But then there was that pair of studies that showed that, in particular, if the ginkgolic acid concentrations were reduced below a particular level, then -- and I think this was human studies -- that people didn't react.

That was our discussion, is that we -- just why I went along with the relative lack of information, is that we did have further information as to what was the key player in terms of sensitization, and information to suggest that the review would purvey the idea of that. As long as the cosmetic ingredients were manufactured in the finished formulation, such that we'd reduce the levels of that constituent sufficiently, we wouldn't see a sensitization problem.

That doesn't mean there aren't other loose ends on the genotoxicity and carcinogenicity, but that, again, underscores our question marks with regards to what's out there in the field, so to speak, in the cosmetic ingredients; and how do we read that across to safety.

We talked about what's implicit in our report; if we get it right in the discussion, that it would become clear what the people that make the ingredients and what the formulators needed to do, to make sure they averted sensitization. But I don't dispute everything that they said as far as loose ends.

DR. BERGFELD: Don? Do you want to make a comment about your motion?

DR. BELSITO: I did see that animal study. I wasn't overwhelmed with it. Primarily, it was 10 animals, 10 female albino guinea pigs. It was, I presume, some type of guinea pig maximization test, although it doesn't give the details about the use complete Freund's adjuvant.

They played around, they did an enhanced ginkgolic acid containing leaf extract. And then they did a ginkgo biloba extract. And the ginkgolic extract did induce the expected sensitization. None were sensitized with the extract that

contained 1000 ppm of the ginkgolic acid. And it's ten animals. I'm used to looking at HRIPTs, so I guess that's why I discounted it.

DR. BERGFELD: So, is your motion standing? You're not amending it?

DR. BELSITO: I'm just pointing out, you know, yes, you have something here that clears -- the concentration was 10 percent. It was 10 percent, in acetone, on a shaved flank. I'm presuming it was a guinea pig maximization test; it's hard to tell from the details. I could probably drop the sensitization there. I'm still not sure I could drop the other tox endpoints.

DR. BERGFELD: Is there a second to Don's motion?

DR. SNYDER: Yes.

DR. BERGFELD: You're seconding?

DR. MARKS: I think what our team will do again, if we're going to -- we want to be as cautious and conservative as possible. We'll second the motion, drop the sensitivity; we'll have another look at this, and I'm sure we'll have another robust discussion. We'll see what more data we receive. You've heard our reasoning with our team, and then we'll have another look at it.

Because this would go out as a tentative report now, with insufficient data.

DR. BELSITO: I think what you're hearing from my team is that if we could get better clarification on what the cosmetic composition of ginkgo biloba is, it would really help us understand the other tox studies that were done. At this point, I think that's what we're concerned about. We're still not sure what the cosmetic ingredient is vis-a-vis what people are consuming as herbal supplements.

DR. MARKS: Yeah. We had that discussion also yesterday.

DR. LIEBLER: I'd like to just point out my main concern now is the composition. I appreciate Tom's perspective on the carcinogenicity studies, and I think you've relieved my concern about those data and how to interpret them. And I would feel that much more confident if we had composition.

DR. BERGFELD: Ron Hill, did you want to say something?

DR. HILL: Yeah, two things. I'll come back to that in just a second. I do want to say since we're not asking for more about the meristem cell, I'm still not clear -- we got all that process information, and then at the end they cold pressed through a filter, size unspecified. What is the substance that's actually being formulated into the cosmetic products? What's the nature of it?

Is it juice? Is it shreds of cell? I'm totally unclear on what we end up with after all that process description that's actually going into the product. For me, I didn't feel like we got sufficient information about the meristem cell preparation.

The other thing I was going to say in terms of composition, just to reiterate, we got -- and this is one of two that I saw in this meeting -- the fresh, dry leaf is extracted with specified eluent, under appropriate temperature and condition to produce a concentrate.

It doesn't tell us anything about what temperature. That specified eluent could be anything from a cyclopentasiloxane to ethanol water, to butylene glycol. And temperature could make a huge difference when

you're making an extract. Do you cook it up, are we steam distilling, are we soaking it at room temperature for 24 hours or three days?

And the only reason we really need that information -- because I understand industry wants to protect proprietary processes -- just to get some sense of, well, here are the constituents in this plant, what sorts of things end up in the extract.

And then finally, at the end, how much do you concentrate; because if we put it in a rotovap and drive off most of the solvent, we could have something that's 100 or even 1000 time more concentrated than something else.

It jumped out on me here, we had sets of extracts. This said percentages were in the .5 percent, .1 percent, and then others where we had tens of percents. There were these two flavors of extracts, which really added to the confusion in terms of what's been tested in every endpoint versus what we're trying to assess.

And ultimately, we ride around that as much as we possibly can. But without that information, we don't know what to do. Read across from the test to the cosmetic finished products is very difficult.

DR. BERGFELD: Any other discussion before we go to a vote?

DR. LIEBLER: Just one other note on composition. When I was looking at the ginkgo biloba meristem cell, also, I was -- because of the nature of the other ingredients, I was looking for some kind of an extract or a filtrate or something. And then I read this description, and I kind of just stopped after, cells are harvested with a filter. And I said, well, that's what the name of the ingredient is.

Now I don't know if they're dried further or anything else, but I don't think it's an extract, or I'm not looking for anything else on this, honestly. I'm okay with the meristem. The meristem is always the mystery ingredient in our reports. I'm okay with where we are on the meristem, just in terms of the insufficiencies.

DR. HILL: If you cold press through a filter, then you have two fractions. I don't even know which fraction they're using. Are they using what passed through the filter, the juice, or whatever left of the cells or whole cells that are on the --

DR. LIEBLER: No, it's the cell.

DR. HILL: So, they're putting the cells?

DR. LIEBLER: Yeah. They're just filtering it, basically, and they're keeping the cells. And the cells are the product.

DR. HILL: All right. I guess that's what I wasn't even clear on, are we putting these whole plant cells. And then what are the safety issues that are associated with having these whole plant cells? Grant you they're sterile, pure and a culture.

DR. LIEBLER: That's another issue, obviously, from safety. But basically, it is what it is, and it is what it says.

DR. BERGFELD: Any other discussion? Seeing none, I'll call for the question? All those in favor of the conclusion, please indicate by raising your hands. Unanimous.

Yes, Christina?

MS. BURNETT: Can I just check to make sure that the want list is just method of manufacture, except for the meristem, and composition and impurities, except for the meristem? The sensitization is no longer an issue; and the 28-day dermal is not a need?

DR. BELSITO: The 28-day dermal is a need.

MS. BURNETT: It's still a need?

DR. BELSITO: Yes.

MS. BURNETT: Okay. So, just the three needs?

DR. BELSITO: And depending upon 28-dermal, other tox endpoints may be needed.

MS. BURNETT: Okay. So, those three needs.

MS. FIUME: Can I clarify further?

DR. BELSITO: And clarification is to when we're looking at that, you know, specifically, we want the cosmetic extracts.

MS. FIUME: Is sensitization dropped for all ingredients or just the leaf?

MS. BURNETT: Just the leaf.

DR. MARKS: The leaf.

DR. BELSITO: All.

DR. MARKS: Because we don't have it on the meristem cell.

DR. BERGFELD: Have we clarified everything? And we voted? And it was unanimous?

DR. BELSITO: Yes.

DR. MARKS: Insufficient data conclusion. Tentative report at this point.

Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics

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The 2018 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 10 *Ginkgo biloba*-derived ingredients, which are most frequently reported to function in cosmetics as skin conditioning agents or antioxidants. The Panel reviewed the available data to determine the safety of these ingredients. Because final product formulations may contain multiple botanicals, each containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. With *Ginkgo biloba*-derived ingredients, the Panel was concerned about the presence of ginkgolic acid in cosmetics. Industry should use good manufacturing practices to limit impurities. The Panel concluded that the data are insufficient to determine the safety of these ingredients.

INTRODUCTION

Most of the *Ginkgo biloba*-derived ingredients detailed in this safety assessment are reported to function as skin conditioning agents, while some are reported to function as antioxidants in cosmetics, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*; see Table 1).[1] Reported functions of Ginkgo Leaf Terpenoids include antiacne agent, antifungal agent, and external analgesic. These functions are not considered cosmetic functions in the United States and, therefore, do not fall under the purview of CIR. This assessment of the safety of the following 10 *Ginkgo biloba*-derived ingredients is based on the data contained in this report:

Ginkgo Biloba Leaf Extract
Ginkgo Biflavones
Ginkgo Biloba Leaf
Ginkgo Biloba Leaf Cell Extract
Ginkgo Biloba Leaf Powder
Ginkgo Biloba Leaf Water
Ginkgo Biloba Meristem Cell
Ginkgo Biloba Nut Extract
Ginkgo Biloba Root Extract
Ginkgo Leaf Terpenoids

Ginkgo biloba leaves and nuts (also called seeds) have been used as a source of traditional Chinese medicines.[2] More recently, extracts of the leaves of *Ginkgo biloba* have been used as herbal medicines or dietary supplements in the treatment of heart disease, eye ailments, tinnitus, cerebral and peripheral vascular insufficiency, injuries involving brain trauma, dementias, short-term memory improvement, cognitive disorders secondary to depression, vertigo, and various other cognitive disorders.[2,3] Investigations into the efficacy of the leaf extract for these uses are numerous and are mainly based on oral administration of supplements. However, there are no publically available toxicity data that corresponds to specific use of these ingredients as cosmetics. The focus of this safety assessment will be on data relevant to the use of *Ginkgo biloba*-derived ingredients in cosmetics, with specific focus on dermal application when available.

Because often in the published literature the information provided is not sufficient to determine how well the tested substance represents the cosmetic ingredient, the taxonomic name is used unless it is clear that the test substance is similar to a cosmetic ingredient. However, in the case of data on the extract of *Ginkgo biloba* leaves, the abbreviation GBE will be used, unless the data specifically are related to the cosmetic use of Ginkgo Biloba Leaf Extract.

Botanicals, such as *Ginkgo biloba*-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, CIR is reviewing the potential toxicity of each of the *Ginkgo biloba*-derived ingredients as a whole, complex mixture. CIR is not reviewing the potential toxicity of the individual constituents, except wherein such constituents are also ingredients under review.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

CHEMISTRY

Definition and Plant Identification

The definitions and functions of the *Ginkgo biloba*-derived ingredients included in this report are provided in Table 1. The raw materials for the ingredients in this report are obtained from the deciduous tree, *Ginkgo biloba*, which has fan-shaped leaves that turn golden yellow in autumn and which can grow to 40 m (~131 ft) tall.[2] The female trees bear offensive-smelling, inedible fruit that contain a single thin-shelled semi-edible nut. Ginkgo trees are planted widely as ornamental trees via cultivation. Few naturally-occurring specimens grow in Zhejiang province China. Trees grown commercially for the leaves are found in China, France, and in the United States.

Physical Properties

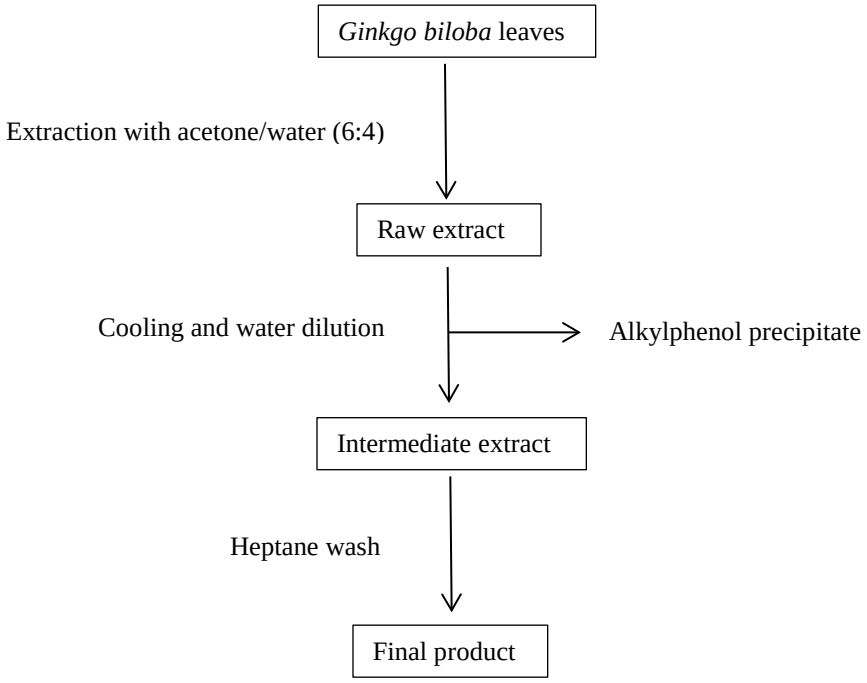
Product specifications for Ginkgo Biloba Leaf Extract (prepared in water) and Ginkgo Biloba Nut Extract (prepared in glycerin) reported by a supplier are described in Table 2.

Methods of Manufacturing

Gingko Biloba Leaf Extract

A general description of manufacturing for "medicinal" GBE reported that the leaves of the *Ginkgo biloba* tree are harvested either mechanically or by hand from plantations or in the wild.[3] The leaves are then dried and pressed into balls. A dry extract from the dried leaf of *Ginkgo biloba* can be manufactured using acetone/water and subsequent purification steps without addition of concentrates or isolated ingredients.

GBEs may be full extracts or standardized extracts.[4] Full extracts are prepared with alcohol and contain all constituents soluble in alcohol. Standardized extracts (one of which is referred to as EGb 761® in published literature) are more common, especially in herbal supplements, and are prepared in manufacturer-dependent multi-step processes (Scheme 1). These processes may include additional steps in which some compounds, such as flavonoids and lactones, are enriched while others, such as ginkgolic acids, are removed.



Scheme 1. General manufacturing process of a standardized *Ginkgo biloba* leaf extract (EGb 761®)[5]

A manufacturer has reported that one Ginkgo Biloba Leaf Extract product is produced through extraction with an ethanol-water solution, while another product is produced through extraction with an ethanol-water solution before being evaporated and resolved in 50% butylene glycol.[6]

Ginkgo Biloba Meristem Cell

Ginkgo Biloba Meristem Cell is produced by sterilizing cambium-containing tissue from the *Ginkgo biloba* plant, isolating the cambial meristem cells from the tissue, and then culturing the cells for proliferation.[7] The cultured cambial meristem cells are then subjected to specific culture conditions (details not provided) in order to produce various secondary metabolites. Finally the cultured cambial meristem cells are harvested with a filter-press.

Composition/Impurities

Ginkgo Biloba Leaf Extract

Table 3 summarizes the composition ranges of the major constituents of various extracts (standardized and non-standardized) of *Ginkgo biloba* leaves. This table does not include constituents of extracts that may have been provided by suppliers of the cosmetic ingredient Ginkgo Biloba Leaf Extract.

The target levels of the major constituents of the standardized GBE EGb 761® are reported to be: not less than 6% total terpene trilactone content, not less than 24% total flavonol glycosides, and not more than 5 ppm (0.0005%) ginkgolic acids.[4] This extract is reported to be a brown powder with characteristic smell containing not more than 20 ppm heavy metals and not more than 2 ppm arsenic. The standardized extract used in National Toxicology Program (NTP) studies is reported to contain 15.4% terpene trilactones, 31.2% flavonol glycosides, and 10.45 ppm (0.001%) ginkgolic acids.[8]

According to an analysis of crude extracts of *Ginkgo biloba* leaves, there are seasonal differences in the levels of certain constituents, with concentrations of flavonol glycosides higher in the spring than in the autumn (136.3 mg/100 g versus 46.0 mg/100g) and biflavones higher in the autumn than in the spring (194.8 mg/100 g versus 44.28 mg/100 g)[9]

General *Ginkgo biloba* composition was reported in the *Physician's Desk Reference for Herbal Medicines* to be the following: flavonoids (0.5% to 1.8%) including monosides, biosides and triosides of quercetin, isorhamnetins, 3-*O*-methylmyristicins, and kaempferol (may be esterified with *p*-coumaric acid); biflavonoids (0.4% to 1.9%) including amentoflavone, bilobetin, 5-methoxybilobetin, ginkgetin, and isoginkgetin; proanthocyanidins (8% to 12%); trilactonic diterpenes (0.06% to 0.23%) including ginkgolide A, B, and C; and trilactonic sesquiterpene bilobalide (0.04% to 0.2%).[3]

The *United States Pharmacopeia* states that "ginkgo" consists of the dried leaf of *Ginkgo biloba* Linne (Fam. Ginkgoacaeae).[10] It contains not less than 0.5% of flavonoids, calculated as flavonol glycosides, with a mean molecular mass of 756.7; and not less than 0.1% of terpene lactones, calculated as the sum of bilobalide, ginkgolide A, ginkgolide B, and ginkgolide C, both on the dried basis. This reference also states that "powdered ginkgo extract" is prepared from dried and comminuted leaves of Ginkgo extracted with an acetone-water mixture or other suitable solvents. It contains not less than 22.0% and not more than 27.0% of flavonoids, calculated as flavonol glycosides, with a mean molecular mass of 756.7; and not less than 5.4% and not more than 12.0% of terpene lactones, consisting of between 2.6% and 5.8% of bilobalide and between 2.8% and 6.2% of ginkgolide A, ginkgolide B, and ginkgolide C.

The *British Pharmacopoeia* states that "ginkgo leaf" content should be not less than 0.5% of flavonoids, calculated as flavone glycosides (dried drug).[11]

An extraction with 60% w/w ethanol of dried green *Ginkgo biloba* leaves yielded an extract comprised of 3.4% flavone glycosides, 0.7% terpene lactones, and 5.5% ginkgolic acids.[12] Further fractionation by liquid-liquid partition between water and heptane yielded a fraction containing 0.3% flavone glycosides, 0.1% terpene lactones, and 24.6% ginkgolic acids.

For use as an herbal medicine in Germany, GBE must be extracted with acetone/water and contain 22% - 27% flavone glycosides (quercetin and kaempferol) with a molar mass of 756.7 (quercetin glycoside) and 740.7 (kaempferol glycoside); 5% - 7% terpene lactones of which 2.8% - 3.4% consists of ginkgolides A, B, and C and 2.6% - 3.2% bilobalide; and less than 5 ppm (0.0005%) ginkgolic acids.[13]

Ginkgolic acid is a salicylic acid derivative with a C_{15} side chain that is related to the pentadecylcatechols (i.e. urushiol) found in poison ivy.[14] One analysis found crude aqueous extracts of *Ginkgo biloba* leaf contained up to a total of 30 ppm urushiols, while the process described in Scheme 1 (i.e., production of a particular standardized GBE) removed long chain alkylphenols to below detection levels.[5] Other extraction processes have been seen to result in a specific standardized extract material containing 10.45 ppm (0.001%) urushiols.[8]

A cosmetic ingredient supplier reported that a Ginkgo Biloba Leaf Extract produced with ethanol/water and sold in a tradename mixture with butylene glycol contains 0.51% flavonol glycosides, 0.16% terpene lactones (0.08% bilobalide, 0.04% ginkgolide A, 0.02% ginkgolide B, and 0.02% ginkgolide C), 0.21% quercetin, and less than 0.1 ppm ginkgolic acid.[6]

A certificate of analysis from a cosmetic ingredient supplier on a Ginkgo Biloba Leaf Extract (solvent not specified) described the sample as a light tan powder that contained 25.3% ginkgo flavonol, 6.4% ginkgolides (bilobalide, ginkgolide A, ginkgolide B, ginkgolide C), 2.3 ppm ginkgolic acid, 0.1 mg free quercetin, 0.2 mg free kaempferol, and less than 20 ppm heavy metals.[15]

A cosmetic ingredient supplier for a tradename mixture of Ginkgo Biloba Leaf Extract in an alcohol base reported that heavy metals were below reporting limits and no residual pesticides were detected.[16] This supplier also reported the 26 allergens defined by the 7th amendment to the EU Cosmetic Directive were below testing thresholds.

Ginkgo Biloba Meristem Cell

A supplier has reported that Ginkgo Biloba Meristem Cell is distinctly different from general GBEs, with major constituents being catechin, gallocatechin, epigallocatechin, and bilobalide.[17,18]

UV Absorption

Ginkgo Biloba Leaf Extract

In a spectral analysis provided by a supplier of a Ginkgo Biloba Leaf Extract (ethanol: water:butylene glycol extract), no maximum UV absorption peaks were observed in the 280 to 450 nm range.[19]

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by

the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2018 VCRP survey data, Ginkgo Biloba Leaf Extract has the most reported uses in cosmetic products, with a total of 712; the majority of the uses are in leave-on eye makeup preparations and skin care products (Table 4).[20] Two other *Ginkgo*-derived ingredients are reported to be in use, with 27 or fewer uses reported in the VCRP. However, the results of the concentration of use survey on these 10 ingredients by the Council in 2018 indicate use for only Ginkgo Biloba Leaf Extract, at a maximum rinse-off concentration of 0.25%, as reported in skin cleansing products, and at a maximum leave-on concentration of 0.24%, as reported in manicuring preparations.[21,22] Ingredients with no reported uses in the VCRP or by the Council are listed in Table 5.

Ginkgo Biloba Leaf Extract may be used in products that can be incidentally ingested or come into contact with mucous membranes; for example, use is reported in a lipstick at up to 0.2%.[20,22] Additionally, Ginkgo Biloba Leaf Extract has been reported to be used in products that may come into contact with the eyes, such as eye shadows and eye lotions at up to 0.01%.[20,22] Moreover, Ginkgo Biloba Leaf Extract was reported to be used in spray products that could possibly be inhaled, like pump spray suntan products at a maximum concentration of 0.05%.[22] In practice, 95% to 99% of the droplets/ particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump spray.[23-26] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[23,25] Ginkgo Biloba Leaf Extract is also used in powders, and these products could possibly be inhaled; for example, it is used in face powders at a maximum concentration of 0.05%. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[27-29]

The *Ginkgo biloba*-derived ingredients described in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[30]

Non-Cosmetic

GBE is used extensively as an herbal supplement for anti-inflammatory, cognitive-promoting, antioxidant, and vascular effects at daily doses of 120 to 240 mg.[2,3,31] In Germany, GBE is an approved herbal medicine for use for treatment of memory deficits, dementia, and other organic brain syndromes when extracted with acetone/water.[13] It is not approved when extracted with other solvents due to lack of supporting safety data.

Standardized GBEs and/or constituents of the extracts, such as bilobalide, kaempferol and ginkgetin, have also been studied for potential neuroprotective effects against Huntington's disease, and for anti-inflammatory and analgesic effects on post-surgical incisions. Additionally, these extracts have been researched for their effects on diseases such as osteoarthritis and atopic dermatitis, for protective effects (antioxidant) against radiation and chemotherapy-induced toxicity, for anticancer effects, and for therapy for vitiligo.[32-40]

GBE as an herbal supplement may interact with pharmaceutical drugs and act as or enhance anticoagulants, anti-inflammatory agents, antihypertensives, and/or anesthetics which may lead to hemorrhage, apraxia, hematoma, hyphema, permanent neurological deficit, and death.[41,42] The *Physician's Desk Reference for Herbal Medicines* reports major drug interaction risks with anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), and trazodone and moderate drug interaction risks with low molecular weight heparins and thrombolytic agents.[3] GBE may also interact with anticonvulsants, buspirone, insulin, monoamine oxidase (MAO) inhibitors, nicardipine, nifedipine, omeprazole, papaverine, St. John's wort, selective serotonin reuptake inhibitors, and thiazide diuretics.

The nuts of *Ginkgo biloba* are a delicacy in Japan and China, but must be removed completely from the pulp, boiled or roasted, and eaten sparingly (limit 8 - 10 per day).[2] In traditional Chinese medicine, the nut is dried and used to treat such ailments as asthma, cough, bronchitis, scabies, and sores.

TOXICOKINETICS

In general, toxicokinetics data are not expected to be found on botanical ingredient because each botanical ingredient is a complex mixture of hundreds of constituents. However, there have been many pharmacokinetics studies on GBEs, specifically on some of the key constituents, which indicate GBE may be well absorbed after oral administration.[8]

Dermal Penetration

The ability of the GBE constituent, quercetin, to penetrate the skin while in a cosmetic formulation was studied in vitro with human dermatomed skin.[43] The cosmetic formulation used in the study was an emulsion containing trilaureth-4 phosphate, ammonium acryloyldimethyltaurate/VP copolymer and emollients, sclerotium gum, humectants, preservatives, and water that was prepared and supplemented with 6.0% (w/w) tritiated *Ginkgo biloba* glycolic leaf extract. An analysis of the GBE used in this study showed it contained 0.12% quercetin. The test formulation (10 mg/cm^2) was applied to the skin samples (n = 6) that were mounted on Franz diffusion cells for 24 h. Samples of the receptor fluid (citrate buffer with 0.5% polysorbate 20; pH 5.5) were taken after 6 h and 24 h exposures and quantified with high performance liquid chromatography

(HPLC). The skin cells were washed at the end of the exposure time and the stratum corneum was removed by tape stripping. The stratum corneum and viable epidermis contained 0.17 ± 0.002 µg/cm^2 (24% of the applied dose) and 0.23 ± 0.04 µg/cm^2 (33% of the applied dose) quercetin, respectively. Quercetin in the dermis and the receptor fluid was below limits of quantification or below limits of detection. Approximately 40% quercetin was measured in the washing solution. The total recovery of quercetin was approximately 97%.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

The absorption, distribution, and elimination of a radiolabeled GBE were studied in male and female Sprague-Dawley rats.[8,44] The rats received a single oral suspended dose (20 µCi; 380 mg/kg) of a radiolabeled GBE. The test material was obtained from *Ginkgo biloba* grown under a supply of [^{14}C]-acetate. Analysis showed that the flavonol glycosides and proanthocyanidins bore the radiolabel; no radioactivity was detected in the terpenes or the main sugars after the hydrolysis of glycosides. The pharmacokinetic results, based on blood specific activity data versus time course, were characteristic of a two-compartment model with an apparent first order phase and a half-life of approximately 4.5 h. Expired [^{14}C]-CO_2 represented 16% of the administered dose 3 h post-treatment. After 72 h, 38% of the radioactivity was excreted via exhalation, while 21% was determined to be excreted in the urine and 29% was excreted in the feces. The researchers of this study concluded that at least 60% of the radiolabeled GBE was absorbed. The site of absorption was likely the upper gastrointestinal tract.

Human

The bioavailability and pharmacokinetics of *Ginkgo biloba* L. in a human plasma study was investigated using 3 different preparations.[45] The preparations were a tincture of fresh *Ginkgo biloba* leaves (extracted with 65% v/v ethanol; 1 ml contains 920 mg *Ginkgo biloba* leaves as active ingredient), *Ginkgo biloba* fresh plant extract tablets (extracted with 67% v/v ethanol; one 250 mg tablet contains 90 mg fresh plant extract), and *Ginkgo biloba* extract EGb 761® tablets (extracted with 60% m/m acetone; one tablet contains 40 mg purified dried extract). The study was performed on 24 healthy volunteers (6 males and 18 females): each volunteer received a single oral dose of the maximum registered daily dosage of either the tincture (90 drops or 2.73 ml), the fresh plant extract (4 tablets), or EGb 761® (3 tablets) with 100 ml. Prior to dosing, each preparation was analyzed for concentrations of bilobalide (646.93 µg, 1974.96 µg, and 3672.39 µg for the tincture, fresh plant extract, and EGb 761®, respectively), ginkgolide A (298.14 µg, 881.52 µg, and 1571.37 µg for the tincture, fresh plant extract, and EGb 761®, respectively), and ginkgolide B (147.45 µg, 524.56 µg, and 836.46 µg for the tincture, fresh plant extract, and EGb 761®, respectively) prior to the plasma study with liquid chromatography-mass spectrometry (LC-MS).

Blood samples (36 ml) were taken 30 min prior to administration and 15, 30, 45, 60, and 360 min after administration. The samples were centrifuged to separate the plasma and plasma was analyzed by LC-MS. The resulting maximum concentrations (median) of bilobalide, ginkgolide A and ginkgolide B in plasma after administration of the maximum daily dose of the different *Ginkgo biloba* products were as follows: 3.53, 3.62, and 1.38 ng/ml, respectively, after administration of the tincture; 11.68, 7.36, and 4.18 ng/mL, respectively, after administration of the fresh plant extract tablets; and 26.85, 16.44, 9.99 ng/mL, respectively, after administration of EGb 761® tablets. The authors of study concluded that ginkgolide A and B and bilobalide are bioavailable after oral dosing of 3 different *Ginkgo biloba* preparations.[45]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Ginkgo Biloba Leaf Extract

Oral

The LD_{50} of a standardized GBE (EGb 761®) administered orally to mice was reported to be 7730 mg/kg.[46]

Intravenous

The LD_{50} after intravenous administration of a standardized GBE (EGb 761®) was 1100 mg/kg for both rats and mice.[8]

Ginkgo Biloba Meristem Cell

Oral

In a toxicity test to determine lethal dose, a single oral dose of 0 or 2000 mg/kg Ginkgo Biloba Meristem Cell was administered to 5 male and female Sprague-Dawley rats in each group (written as provided, no further details).[47] After a 14 day observation period, the animals were killed and underwent necropsy. No unscheduled deaths or treatment-related effects were observed during the observation period or at necropsy. The lethal dose for Ginkgo Biloba Meristem Cell was greater than 2000 mg/kg in this rat study.

In a single dose oral volume increase toxicity test, 2 male and female Beagle dogs (written as provided, no further details) received Ginkgo Biloba Meristem Cell at 250, 500, and 1000 mg/kg, respectively, for 4 days.[47] No unscheduled deaths were observed. All animals vomited after receiving 500 and 1000 mg/kg of the test material. Only 1 animal vomited after receiving the 250 mg/kg dose, but the effects were determined to be too slight a symptom to confirm treatment-related effects. No adverse effects were observed in body weights or at necropsy. The maximum tolerated dose for Ginkgo Biloba Meristem Cell was determined to be greater than 1000 mg/kg in this dog study.

Short-Term Studies

Ginkgo Biloba Leaf Extract

Oral

The results of a combined liver comet assay (see Genotoxicity section) using male and female C3H-derived constitutive androstane receptor knockout (CARKO) and wild-type mice found no abnormal clinical signs and no treatment-related effects on body weight following oral exposure of up to 2000 mg/kg body weight/day of a GBE used by the NTP for 3 days in either mouse genotype.[48] Relative liver weights were significantly increased in male and female wild-type mice at all doses of a GBE in a dose-dependent manner. The liver weights in the CARKO mice were similar to the negative control group. The wild-type mice in all GBE-treated groups had dose-dependent slight-to-moderate hepatocellular hypertrophy in the centrilobular area: this effect was only observed in a single CARKO mouse in the highest dose group. No histopathological findings suggesting cytotoxicity in the liver was observed in any GBE-treated groups.

Ginkgo Biloba Meristem Cell

Oral

In a dose-range finding study for a 13-week oral repeated dose toxicity test (see below), groups of male and female Sprague-Dawley rats received 500, 1000, or 2000 mg/kg Ginkgo Biloba Meristem Cell for 4 weeks (number of rats/group and method of administration not described).[47] No unscheduled deaths or clinical signs of toxicity were observed during the treatment period. Additionally, no treatment-related changes in body weight gains, feed intake, hematological/biochemical measurements, or organ weights were observed. No adverse effects were noted at necropsy in any dose group.

Subchronic Toxicity Studies

Ginkgo Biloba Leaf Extract

Oral

The toxicity of a particular GBE was investigated in a 3-month mouse study performed by the NTP.[8] Groups of 10 male and 10 female B6C3F1/N mice received 0, 125, 250, 500, 1000, or 2000 mg/kg body weight of the GBE in corn oil via gavage, 5 days per week for 14 weeks. Control groups received corn oil (5 ml/kg). Clinical findings and body weights were recorded initially, then weekly, and at the end of the study. Blood was collected at the end of the study from all animals for hematology analyses. Sperm motility and vaginal cytology evaluations were made on the mice in the 0, 500, 1000, and 2000 mg/kg dose groups. At the end of the study period, tissues from over 40 sites were examined for every animal, including ovaries and uteri in females and prostate gland and testes with epididymis and seminal vesicles in males.

One female mouse in the 1000 mg/kg group died of a dosing accident during week 11. Mean body weights of 2000 mg/kg females were significantly less than those of the vehicle control group. Ruffled fur was observed in two 1000 mg/kg males between weeks 7 and 8 and all 2000 mg/kg males between weeks 5 and 9. No treatment-related differences were observed in sperm parameters in males administered 500, 1000, or 2000 mg/kg or in the estrous cycle of females administered 500 or 1000 mg/kg when compared to controls. Female mice in the 2000 mg/kg group had a significantly higher probability of extended estrous than did the vehicle control females. Liver weights of males of the 250 mg/kg or greater dose groups and females of all dose groups were significantly greater than those of the vehicle control groups. Kidney weights of males of the 2000 mg/kg group were significantly less than those of the vehicle control group. Incidences of hepatocytic hypertrophy were significantly increased in males and females dosed with 250 mg/kg or greater. Significantly increased incidences of focal hepatocytic necrosis occurred in males of the 1000 and 2000 mg/kg dose groups. The incidences of hyaline droplet accumulation in the respiratory epithelium of the nose were significantly increased in males of the 500 mg/kg and females of the 1000 and 2000 mg/kg dose groups. In the olfactory epithelium of the nose, the incidences of hyaline droplet accumulation were significantly increased in the 125 (female only), 500, and 1000 mg/kg groups. Incidences of atrophy of the olfactory epithelium were significantly increased in the 1000 mg/kg groups. The incidences of pigment accumulation in macrophages in the olfactory epithelium were significantly increased in males in the 500 mg/kg or greater groups and in females in the 1000 and 2000 mg/kg dose groups.[8]

The NTP also performed a 3-month study of the same GBE used above in rats.[8] Groups of 10 male and 10 female F344/N rats received 0, 62.5, 125, 250, 500, or 1000 mg/kg body weight of the GBE in corn oil via gavage, 5 days per week for 14 weeks. Additional groups of 10 male and 10 female rats received the same doses for a clinical pathology study, 5 days per week for 23 days. Control groups received corn oil (2.5 ml/kg). The same methods that were followed in the mouse

study described above were used in the main study animals, while animals in the clinical pathology study had blood samples collected on days 4 and 23.

All rats survived to the end of the study. Mean body weights of all dosed groups were similar to those of the vehicle control groups. No treatment-related clinical findings were observed. Liver weights of all dosed groups of males and females were significantly greater than those of the vehicle control groups. Incidences of hepatocyte hypertrophy in all dosed groups of males and in 500 and 1000 mg/kg females were significantly greater than those in the vehicle control groups; there was a dose-related increase in severity of this lesion in males. "Hepatocyte fatty change" occurred in all dosed males. The incidences of thyroid gland follicular cell hypertrophy were significantly increased in 500 and 1000 mg/kg males and in 1000 mg/kg females. The incidences of pigmentation in the olfactory epithelium of the nose were significantly increased in 500 and 1000 mg/kg males and in females administered 125 mg/kg or greater.[8]

Ginkgo Biloba Meristem Cell

Oral

In a 13-week oral study, groups of 10 male and female Sprague-Dawley rats received 250, 500, or 1000 mg/kg Ginkgo Biloba Meristem Cell (further dosing details were not provided).[47] Observations made during the treatment period included clinical signs of toxicity, body weight and feed measurements, ophthalmology assessment, and urinalysis. At study end, necropsy, hematological/biochemical examinations of blood, organ weight measurement, microscopic examination, and histopathological examination were performed. No unscheduled deaths or adverse clinical signs of toxicity were observed during the treatment period in any dose group. No treatment-related adverse changes were reported in any of the measured parameters before or after necropsy. Based on the results of this study, the no-observed-adverse-effect-level (NOAEL) in rats for Ginkgo Biloba Meristem Cell was determined to exceed 1000 mg/kg.

Chronic Toxicity Studies

Oral

There was no evidence of organ damage or impairment of hepatic or renal function when a standardized GBE (EGb 761®) was administered orally over 27 weeks to rats and mice at doses ranging from 100 to 1600 mg/kg.[46] No further details were provided.

The results of the NTP chronic toxicity bioassays are summarized in the Carcinogenicity section below.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

The reproductive and developmental toxicity of a standardized GBE (EGb 761®) was studied in mice. In one study, groups of 25 mated female CD-1 mice received 0, 100, 350, or 1225 mg/kg/day GBE in tap water via gavage (20 ml/kg) on days 6 through 15 of gestation.[49] The dams were observed daily for clinical signs of toxicity. Feed and water consumption were monitored during the study. Body weight was measured daily. On day 17 of gestation, the dams were killed and the ovaries, uteri, and the fetuses were removed. The internal organs and the placentae of the dams were examined macroscopically. The fetuses were examined for several parameters, including external and internal damages (malformations), sex, viability, and weight. The skeletal systems and soft tissues of the fetuses were also examined.

No clinical signs of toxicity were observed in the dams and there were no unscheduled deaths. No treatment related effects were observed in body weight gains or feed and water consumption. There were no pathological findings observed during necropsy. No embryotoxic effects were observed during external and internal examinations of the fetuses nor were any observed in skeletal or soft tissues. There were no increased incidences of malformation, variations, or retardations. The authors concluded the no-observed-effect-level (NOEL) was greater than 1225 mg/kg/day for both the dams and the fetuses in this study of a standardized GBE.[49]

Another study examined the effects of oral administration of a standardized GBE (EGb 761®) in saline on the mouse reproductive and developmental toxicity.[50] Female Swiss albino mice received 0, 3.7, 7.4, or 14.8 mg/kg body weight/day for 28 days prior to mating, from day 1 to day 7 of gestation, or from day 10 to day 18 of gestation. There were 10 animals per dose group to study the anti-implantation and abortifacient activities for this GBE, while there were 10 mice per dose group to study the reproductive cycle and 20 mice per dose group to study the developmental cycle (12 test groups total). Blood hormones were measured in the pre-mating group on day 28. Vaginal smears were performed daily. The mice were observed daily for clinical signs of toxicity and premature deaths. Body weights were recorded weekly. On day 20 of gestation, the remaining mice were killed and their kidneys, liver, brain, placenta, spleen and ovaries were removed and weighed. The ovaries were prepared for histological examinations, and then ovarian follicles were counted. Maternal toxicity, estrous cycle, reproductive hormones, ovarian follicle counts, resorption index, implantation index, fetal viability and fetuses, and placenta mean weights were evaluated.

No symptoms of clinical toxicity such as depressed activities, respiratory distress, salivation, tremor, fasciculation, dull eyes, diarrhea, or change in fur appearance were observed in the dams during treatment, and there were no unscheduled deaths. Statistically significant decreases in body weight gains were observed in the 14.8 mg/kg/day dose group for 28 days

when compared to the controls. There were no treatment-related differences in the relative weights of the liver, kidney, brain, spleen, ovary, and placenta, but there was a significant dose-dependent decrease in the relative weight of the gravid uterus in the 14.8 mg/kg/day dose group for 28 days when compared to controls. Ovarian follicle counts, resorption index, implantation index, and fetal viability were significantly reduced in 14.8 mg/kg/day dose group for gestation days 1 to day 7. Treatment with 14.8 mg/kg bw/day of this particular GBE induced disruption of estrous cycle and caused maternal toxicity, in addition to fetal toxicity. No adverse effects were observed in the 3.7 or 7.4 mg/kg bodyweight/day dose groups. The authors concluded that 14.8 mg/kg body weight/day of this GBE produced adverse effects on the estrous cycle, fertility, abortifacient, reproductive performance, and hormone levels of female mice and may cause adverse effects on ovarian function as an antifertility agent.[50]

The effects of an aqueous GBE (similar to EGb 761®) on embryo-fetal development were investigated in pregnant Wistar rats.[51] Groups of 17 rats received 0, 3.5, 7, or 14 mg/kg/day of the test material during the tubal transit and implantation period of pregnancy. The dams were then killed on the 15th day of pregnancy. The following parameters were evaluated during the study: clinical symptoms of maternal toxicity; maternal body weight; feed and water intake; maternal liver, kidney, and ovary weights; number of corpora lutea; implants per group ratio; pre- and post-implantation loss per group ratio; live fetuses mean; dead fetuses percentage; fetus and placenta weight per offspring ratio; and fetal external malformation. No significant adverse effects were observed for any of the parameters in the dams or the embryos. The authors of this study concluded that the studied GBE did not produce adverse effects in maternal or embryonic rats.

GENOTOXICITY

In Vitro

Ginkgo Biloba Leaf Extract

The NTP tested a specific GBE at up to 10,000 µg/plate was mutagenic in an Ames test using *Salmonella typhimurium* strains TA98 and TA100 and *Escherichia coli* strain WP2 *uvrA*/pKM101, with and without metabolic activation.[8]

The genotoxicity of the same GBE and eight of its constituents (quercetin; quercetin-3-β-D-glucoside; kaempferol; isorhamnetin; ginkgolide A; ginkgolide B; ginkgolide C; and bilobalide) were evaluated in mouse L5178Y cells using a lymphoma assay and a Comet assay.[52] The GBE (0.2-1.2 mg/ml) and the eight constituents were tested in a dimethyl sulfoxide (DMSO) solution. A dose-dependent increase in mutant frequency was observed in the studied GBE, quercetin (10-100 µM), quercetin-3-β-D-glucoside (200-1000 µM), and kaempferol (10-200 µM) without metabolic activation. DNA double-strand breaks were also observed in dose-dependent increases in the studied GBE, quercetin, and kaempferol. Negative results were observed in the other constituents. A Western blot analysis confirmed that GBE, quercetin, and kaempferol activated the DNA damage signaling pathway. Additionally, GBE produced reactive oxygen species and decreased glutathione levels in L5178Y cells. An analysis of loss of heterozygosity in *Tk* mutants indicated that GBE, quercetin, and kaempferol resulted in extensive chromosomal damage. The authors concluded that the studied GBE, quercetin, and kaempferol are mutagenic in mouse L5178Y cells.

In a comparative review and analysis of published and unpublished data on the GBE herbal supplement EGb761®, the authors of the review concluded that the positive findings in some in vitro genotoxicity tests are associated with cytotoxic effects of the *Ginkgo biloba* extract and the use of very high test concentrations, as compared to therapeutic use concentrations.[53]

Gingko Biloba Meristem Cell

Ginkgo Biloba Meristem Cell at up to 5000 µg/plate was not mutagenic in an Ames test in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 or in *E. coli* strain WP2 uvrA/pKM101, with and without metabolic activation.[47]

Ginkgo Biloba Meristem Cell did not induce chromosomal aberrations in Chinese hamster lung cultured cells, with and without metabolic activation.[47] The cells were treated with 210.0 µg/ml without metabolic activation (short-time treatment), 333.6 µg/ml with metabolic activation (short-time treatment), and 202.2 µg/ml without metabolic activation (24 h continuous treatment). Short-time treatment was not defined.

In Vivo

Ginkgo Biloba Leaf Extract

In a micronucleus test in male and female B6C3F1/N mice performed by the NTP, no increase in the frequency of micronucleated erythrocytes was observed in peripheral blood of male mice administered 125 to 2000 mg/kg/day of a GBE orally for 3 months.[8] Female mice that received the same doses had results that were deemed equivocal based on a significant trend test and due to no individual dose group being significantly elevated over the vehicle control group. A significant ($P < 0.001$) dose-related decreased in the percentage of circulating polychromatic erythrocytes (PCEs) was observed in male mice, which may indicate the studied GBE induced bone marrow toxicity. In the female mice, a significant ($P = 0.001$) decrease in the percentage of circulating PCEs was also observed, but the response was not as correlated with dose as it was in the males.

In a reporter gene mutation assay using male B6C3F1 *gpt* delta mice, oral dosing of the GBE used in the NTP studies at up to 2000 mg/kg body weight/day (in corn oi) for 90 days did not produce remarkable increases in *gpt* or Spi$^-$ mutation frequencies in DNA extracted from the liver.[48] No treatment-related clinical signs or deaths were observed during the treatment period. Relative liver weights were significantly increased in the 2000 mg/kg group. Hepatocellular hypertrophy in the centrilobular area and slight focal necrosis were observed in the 2000 mg/kg group.

This assay was performed in conjunction with a combined liver comet assay and bone marrow micronucleus assay using male and female CARKO and wild-type mice. The short-term toxicity effects were described in the Toxicological Studies section. In the micronucleus study, no significant alterations in the percentages of PCEs were observed in females of either genotype; however, a significant decrease in the percentage of PCEs were observed in both genotypes in males, indicating the studied GBE induced bone marrow toxicity in male mice. In the comet assay, there was no significant difference in the percent tail DNA in any of the GBE-treated groups in either mouse genotype. Heavily damaged cells called "hedgehogs" indicating cytotoxic effects were not detected in any animals. The researchers performing these 3 assays concluded that the studied GBE is not genotoxic.[48]

Ginkgo Biloba Meristem Cell

In a micronucleus test, no increase in the frequency of micronucleated polychromatophilic erythrocytes in bone marrow was observed in male mice administered 500 to 2000 mg/kg/day Ginkgo Biloba Meristem Cell.[47] There was no significant difference in the ratio of polychromatophilic erythrocytes in total red blood cells when compared to the negative control. The positive control yielded expected results. No further details were provided.

CARCINOGENICITY

Oral

The carcinogenic potential of a GBE administered orally was studied by the NTP in male and female rats and mice.[8] In the study on mice, groups of 50 male and 50 female B6C3F1/N mice received 200, 600, or 2000 mg/kg of this GBE in corn oil 5 day per week for 104 weeks via gavage. In the study on rats, groups of 50 F344/N male and 50 female rats received 100, 300, or 1000 mg/kg body weight of this GBE for 104 (males) or 105 (females) weeks via gavage. Control groups received corn oil (5 ml/kg in mice and 2.5 ml/kg in rats). In rats involved in what was deemed a "special study," groups of 10 male and female rats received the same doses as in the main study; blood was collected from these rats on day 22 and at week 14 for thyroid hormone analyses and other analyses of the liver and thyroid gland. All animals were observed twice daily. Body weights were evaluated at study beginning and ending and at different intervals during the course of the study. At the end of the study period, tissues from over 40 sites were examined for every animal, including ovaries and uteri in females and prostate gland and testes with epididymis and seminal vesicles in males.

In mice, mortality was significantly higher in the 600 and 2000 mg/kg males than in the vehicle controls, with the most frequent cause of death being liver tumors. Survival in the 600 mg/kg females was significantly greater than that of the vehicle controls. Mean body weights in the mid- and high-dose group male mice were less than (10% or more) those of the vehicle controls after weeks 85 and 77, respectively. The mean body weights of the high-dose females were generally less than the vehicle controls between weeks 17 and 69 and after week 93.

In rats, mortality in the 1000 mg/kg males was significantly higher than that of the vehicle controls, with the most frequent cause of death being mononuclear cell leukemia. The survival of the treated groups of female rats was comparable to the vehicle control. In week 14, all dose group males and females of the 1000 mg/kg group in the special study had increased levels of thyroid stimulating hormone compared to the vehicle controls; the increase was dose-related in the male rats. Mean body weights in the mid- and high-dose male and female rats were less than (10% or more) those of the vehicle controls after weeks 93 and 89, respectively.

Lesions in the liver, thyroid gland, and nose were observed in all the studied GBE dose groups in mice and rats. These lesions included hypertrophy in the liver and thyroid gland in rats and mice, liver hyperplasia in male and female rats, and hyperplasia and atrophy of the epithelium in the nose of male and female rats. Inflammation, hyperplasia, hyperkeratosis, and ulcers were also observed in the forestomach of male and female mice. Additionally, increased incidences of cancers of the thyroid gland were observed in male and female rats and male mice and of liver cancers in male and female mice. The study concluded that the studied GBE caused cancers of the thyroid gland in male and female rats and male mice, and cancers of the liver in male and female mice.[8]

In dietary carcinogenicity studies of a standardized GBE (EGb 761®) in mice (at up to 200 mg/kg/day) or rats (at up to 100 mg/kg/day), no neoplastic or pre-neoplastic effects were observed.[53] The rodents received the test material for up to 85 weeks. No changes in body weight gain were reported. No further details are available.

The International Agency for Research on Cancer (IARC) has determined that GBEs are possibly carcinogenic to humans (group 2B) based on inadequate human carcinogenicity evidence and sufficient evidence in experimental animals.[54] The animal data used to reach this determination were from the NTP studies that are described above that used a specific GBE. IARC reviewed the findings of a few randomized and case-control epidemiological studies researching the potential effects of the use of GBE dietary supplements in elderly patients and ovarian cancer patients. IARC suggested that the

mechanisms for carcinogenicity associated with GBEs may be genotoxicity and/or topoisomerase inhibition that could be related to the constituents quercetin, kaempferol, and/or rutin.

OTHER RELEVANT STUDIES

Immunotoxicity

In a popliteal lymph node assay (PLNA), the sensitization potential of a GBE was evaluated.[12] Groups of male C57BL/6 mice received subplantar injections of 10 µl DMSO (induction) followed by another injection of DMSO (negative control group), a crude ethanolic-aqueous GBE, heptane fraction of the crude GBE, or diphenylhydantoin (positive control group) at doses of 2 mg each. The negative control yielded small enlargement of the lymph nodes, while the crude ethanolic-aqueous GBE resulted in statistically significant lymphoproliferative reaction (LPR) in the ipsilateral popliteal lymph node. A massive lymph node hyperplasia that was almost comparable to the positive control was observed in the heptane solution fraction of the crude GBE. Chemical analyses of the crude extract and the heptane fraction found ginkgolic acid at 5.5% and 24.6%, respectively, which were theorized to be responsible for the LPR observed in this study.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Human

No irritation was observed in a 24-h human patch test of a Ginkgo Biloba Leaf Extract (100%; ethanol:water: butylene glycol extract) in 20 subjects.[6] No further details were provided.

Sensitization

Animal

The sensitizing potential of ginkgolic acid and a GBE was studied in 10 female albino guinea pigs using a modified Freund's complete adjuvant (FCA) technique.[55] The pure ginkgolic acid was extracted from *Ginkgo biloba* fruit and the GBE was a prepared through water:acetone extraction and contained 24% flavone glycosides and ~1000 ppm (~0.1%) ginkgolic acid. The animals received intradermal injections (up to 0.15 ml) of an emulsion containing 4 ml physiological saline, 4 ml FCA, 15 mg of the pure ginkgolic acid, and 30 mg ginkgolic acid-containing leaf extract on to the clipped and shaved shoulder area on days 1, 5, and 9 of the study. After an 11 day rest period, the animals were challenged with 0.1% and 1% ginkgolic acid and 10% GBE in acetone on the clipped and shaved right flank. All animals exhibited sensitization to pure ginkgolic acid, while none were sensitized to the GBE that contained 1000 ppm ginkgolic acid.

Human

Human dermal sensitization studies are summarized in Table 6. No dermal irritation or sensitization was observed in human repeat insult patch tests (HRIPTs) of products containing up to 0.2% Ginkgo Biloba Leaf Extract.[56-59]

Cross-Reactivity

Guinea pig sensitization studies of crude *Ginkgo biloba* fruit extract, the main aromatic components of the fruit, and urushiol found no cross-reactions among the compounds. [60] It was also determined that ginkgolic acid was the main allergen in *Ginkgo biloba*.

Phototoxicity/Photosensitization

No phototoxicity or photosensitization was reported to a lip product containing 0.0072% Ginkgo Biloba Leaf Extract in a study of 29 subjects.[58] The test material was applied neat under semi-occlusive patches. No further details were provided.

OCULAR IRRITATION STUDIES

In an EpiOcular in vitro assay of an eye product containing 0.013% Gingko Biloba Leaf Extract, it was predicted that the test substance had no potential for eye irritation.[58] No further details were provided.

CLINICAL STUDIES

Case Studies

The fruit pulp of the *Ginkgo biloba* tree has been reported to cause contact dermatitis, with several cases reported after patients handled the fruit pulp during extraction of the edible nut center.[3,14,61] Symptoms include intense itching, edema, papules, and pustules that usually resolve in 7-10 days.

A 66-year-old woman presented with progressive erythematous eruption over the face, neck, trunk, and extremities that started approximately one week after the patient had ingested two 60 mg doses of a GBE supplement.[62] No other new

medications or changes in behavior were reported. A physical examination, complete blood cell count, and chemistry panel were unremarkable. The authors of the report did not disclose if patch or skin prick tests were performed.

A 45-year-old man developed acute generalized exanthematous pustulosis on his limbs and face 48 h after starting an oral GBE treatment for tinnitus.[63] The patient had not previously taken any GBEs before and was not taking any other medication. The patient had no history of adverse drug reactions or psoriasis. The rash cleared within 10 days of stopping the GBE treatment. The patient refused a follow-up cutaneous patch test.

In anecdotal accounts from Chinese medicine, consumption of fresh *Ginkgo biloba* nuts may cause stomachache, nausea, diarrhea, convulsions, weak pulse, restlessness, difficulty breathing, and shock.[2] Death has been reported in children following consumption of fresh nuts.

Other Clinical Reports

No adverse effects were reported in a clinical study of two cosmetic formulations containing 1.5% GBE (glycolic extract standardized by quercetin concentrations) and other antioxidants in 45 volunteers. [64] One formulation contained sunscreen and was applied during the day, while the other formulation was without sunscreen and was applied at night. These formulations were applied daily for 90 days.

In another clinical study, no adverse effects were reported in 20 volunteers following use of a cosmetic formulation containing 0.30% GBE twice daily for 28 days.[65] No further details regarding the GBE used were provided.

Numerous studies have investigated the efficacy and safety of GBEs in humans in the treatment of various afflictions. In a cross-matching review of much of this published toxicological and clinical data on GBEs (mainly the herbal supplement EGb 761®), the authors of the review evaluated the findings of 75 clinical studies with a total of 7115 patients treated orally with GBEs and found no specific or serious undesired reactions to GBEs.[53] Any adverse events observed frequently occurred at the same frequency as placebo treatments. Based on cross-matching data on the historic use by humans, large intake, toxicological and clinical studies, the authors concluded that GBEs are well tolerated and safe.

SUMMARY

According to the *Dictionary*, most of the *Ginkgo biloba*-derived ingredients detailed in this safety assessment are reported to function as skin conditioning agents, while some are reported to function as antioxidants in cosmetics. Investigations into the efficacy of the leaf extract for these uses are numerous and are mainly based on oral administration of supplements. There are no publically available toxicity data that correspond to specific use of these ingredients as cosmetics. This safety assessment focuses on data relevant to the use of *Ginkgo biloba*-derived ingredients in cosmetics, with specific attention on dermal application when available.

According to 2018 VCRP survey data, Ginkgo Biloba Leaf Extract has the most reported uses in cosmetic products, with a total of 712; the majority of the uses are in leave-on eye makeup preparations and skin care products. Two other *Ginkgo*-derived ingredients are reported to be in use, with 27 or fewer uses reported in the VCRP. However, the results of the concentration of use survey on these 10 ingredients conducted in 2018 by the Council indicate use for only Ginkgo Biloba Leaf Extract, at a maximum rinse-off concentration of 0.25%, as reported in skin cleansing products, and at a maximum leave-on concentration of 0.24%, as reported in manicuring preparations.

GBEs are used extensively as an herbal supplement for anti-inflammatory, cognitive-promoting, antioxidant, and vascular effects and are approved herbal medicine in Germany for use for treatment of memory deficits, dementia, and other organic brain syndromes when extracted with acetone/water. GBEs may interact with pharmaceutical drugs. Nuts from *Ginkgo biloba* are consumed as a delicacy in Japan and China and are used in traditional Chinese medicine. Anecdotal accounts report that consumption of the nuts may have acute adverse effects.

In general, toxicokinetics data are not expected to be found on botanical ingredient because each botanical ingredient is a complex mixture of hundreds of constituents. However, there have been many pharmacokinetics studies on GBEs, specifically on some of the key constituents, which indicate GBEs may be well absorbed after oral administration. The GBE constituent, quercetin, was found to penetrate human dermatomed skin; however, quercetin was not present in the dermis or receptor fluid of this dermal penetration study. In an oral ADME study in rats, at least 60% of a radiolabeled GBE (flavonol glycosides and proanthocyanidins) were absorbed, with the main site of absorption likely in the upper gastrointestinal tract. Radioactivity was measured in exhalation and elimination products. In a human plasma study ginkgolide A, ginkgolide B, and bilobalide were found to be bioavailable after single oral dosing of 3 different *Ginkgo biloba* preparations.

The LD_{50} of a standardized GBE (EGb 761®) administered orally to mice was reported to be 7730 mg/kg, and the LD_{50} after intravenous administration with this standardized GBE was 1100 mg/kg for both rats and mice. The lethal dose for Ginkgo Biloba Meristem Cell was greater than 2000 mg/kg in rats and the maximum tolerated dose for this ingredient was greater than 1000 mg/kg in dogs.

In 3-month studies by the NTP of a specific GBE at up to 2000 mg/kg/day, increased liver weights, decreased kidney weights, increased incidences of hepatocytic hypertrophy and focal hepatocytic necrosis, and increased incidences hyaline droplet accumulation, atrophy and pigment accumulation in macrophages in the olfactory epithelium were observed in mice. In a similar NTP study of the same GBE test material in rats, increased liver weights, increased incidences of

hepatocyte hypertrophy, increased incidences of thyroid gland follicular cell hypertrophy, and increased incidences of pigmentation in the olfactory epithelium of the nose were observed. There was no evidence of organ damage or impairment of hepatic or renal function when a GBE (EGb 761®) was administered orally over 27 weeks to rats and mice at doses ranging from 100 to 1600 mg/kg. In a 4-week oral repeated dose study, no adverse effects were observed in rats that received up to 2000 mg/kg Ginkgo Biloba Meristem Cell. In the follow-up 13-week oral study, the NOAEL in rats for Ginkgo Biloba Meristem Cell was greater than 1000 mg/kg.

In an oral DART study of a standardized GBE (EGb 761®) in mice on gestation days 6 through 15, the NOEL for dams and fetuses was greater than 1225 mg/kg/day. No clinical signs of toxicity were observed in the dams and no embryotoxic effects were observed in the fetuses. In another oral DART study in mice during a 28 day period before mating, gestation days 1 through 7, and gestation days 10 through 18, a standardized GBE (EGb 761®) at 14.8 mg/kg/day produced adverse effects on the estrous cycle, fertility, abortifacient, reproductive performance, and hormone level in female mice and may cause adverse effects on ovarian function as an antifertility agent. No adverse effects in maternal or embryonic rats were observed in an embryo-fetal development study in rats on gestation days 1 through 14 at doses up to 14 mg/kg/day of an aqueous GBE similar to EGb 761®.

The authors of a comparative review of the GBE herbal supplement EGb761® concluded that the positive findings in some in vitro genotoxicity tests are linked to cytotoxic effects of *Ginkgo biloba* extract and the use of very high test concentrations compared to therapeutic use concentrations. The GBE specific to NTP studies was mutagenic in an Ames test at up to 10,000 µg/plate, and the same GBE (0.2 - 1.2 mg/ml) was mutagenic in mouse L5178Y cells. In a mouse micronucleus test of the GBE used by the NTP at up to 2000 mg/kg/day, no increase in the frequency of micronucleated erythrocytes was observed in male mice, but the results were deemed equivocal in female mice. The same GBE at up to 2000 mg/kg/day was not genotoxic in a reporter gene mutation assay, a combined liver comet assay, and bone marrow micronucleus assay in mice. Ginkgo Biloba Meristem Cell was not mutagenic in an Ames test at up to 5000 µg/plate, nor did it induce chromosomal aberrations in Chinese hamster lung cultured cells, with and without metabolic activation. Ginkgo Biloba Meristem Cell did not increase the frequency of micronucleated erythrocytes in male mice at up to 2000 mg/kg/day.

In oral carcinogenicity studies of rats and mice conducted by the NTP, lesions in the liver, thyroid gland and nose were observed in all GBE dose groups (200 - 2000 mg/kg/day, by gavage). Lesions included hypertrophy in the liver and thyroid gland in rats and mice, liver hyperplasia in male and female rats, and hyperplasia and atrophy of the epithelium in the nose of male and female rats. Inflammation, hyperplasia, hyperkeratosis, and ulcer were also observed in the forestomach of male and female mice. Additionally, increased incidences of cancers of the thyroid gland were observed in male and female rats and male mice, as were liver cancers in male and female mice. In dietary carcinogenicity studies of a standardized GBE (EGb 761®) in mice (at up to 200 mg/kg/day) or rats (at up to 100 mg/kg/day) for up to 85 weeks, no neoplastic or pre-neoplastic effects were observed. IARC has determined that GBEs are possibly carcinogenic to humans (group 2B).

In a PLNA validation study, a GBE exposure yielded statistically significant lymphoproliferative reactions in the ipsilateral popliteal lymph node, which was may have been caused by ginkgolic acid.

No irritation was observed in a 24-h human patch test of Ginkgo Biloba Leaf Extract (100%; ethanol:water:butylene glycol extract).

In a guinea pig study, sensitization was observed to ginkgolic acid at concentrations of 0.1% and 1%, but no sensitization was observed to a GBE that contained ~1000 ppm (~0.1%) ginkgolic acid. No dermal sensitization was reported in HRIPTs of products containing up to 0.2% Ginkgo Biloba Leaf Extract.

Guinea pig sensitization studies of crude Ginkgo biloba fruit extract, the main aromatic components of the fruit, and urushiol found no cross-reactions among the compounds. It was also determined that ginkgolic acid was the main allergen in *Ginkgo biloba*.

No phototoxicity or photosensitization was reported to a lip product containing 0.0072% Ginkgo Biloba Leaf Extract.

No ocular irritation was predicted in an in vitro assay using an eye product containing 0.013% Ginkgo Biloba Leaf Extract.

Reports of contact dermatitis have been reported following exposure to the fruit pulp of *Ginkgo biloba*. Patients have reported erythematous reactions and generalized exanthematous pustulosis following ingestion of certain GBE supplements. No adverse effects were reported in clinical studies of cosmetic formulations containing up to 1.5% GBEs. In anecdotal accounts from Chinese medicine, consumption of fresh *Ginkgo biloba* nuts may cause stomachache, nausea, diarrhea, convulsions, weak pulse, restlessness, difficulty breathing, and shock. Death has been reported in children following consumption of fresh nuts. A cross-matching review of multiple clinical studies found no specific or serious undesired reactions to GBEs (mainly EGb 761®).

DISCUSSION

The ingredients in this report are each a mixture of botanical constituents derived from the plant *Ginkgo biloba*. Because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For *Ginkgo biloba*-derived ingredients, the Panel was concerned about the presence of ginkgolic acid, which is a

known dermal sensitizer. The Panel determined that the current data regarding the concentration levels of ginkgolic acid and data on dermal sensitization in *Ginkgo biloba*-derived cosmetic ingredients at use concentrations are insufficient.

The Panel considered the findings of the carcinogenicity studies performed by the National Toxicology Program (NTP) on a *Ginkgo biloba* leaf extract where positive carcinogenic effects were observed in animals, especially in the high dose groups. The *Ginkgo biloba* leaf extract evaluated by the NTP contained unusually high concentrations of certain constituents that are markedly different from those found in the leaf extracts used in dietary supplements. The NTP study administered this specific leaf extract at high doses by gavage, allowing for concentrations in the blood that would not be achieved through cosmetic use. The leaf extract used in dietary supplements did not produce increased incidences of cancer in a dietary study. This, combined with a long history of use of *Ginkgo biloba* leaf extracts in folk medicine, indicate that the findings of the NTP carcinogenicity study are not relevant to cosmetic use in humans.

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

Ginkgo Biloba Leaf Extract was reported to be used in spray and powder products that could possibly be inhaled, such as pump spray suntan products at a maximum concentration of 0.05%, and face powders at a maximum concentration of 0.05%. There were no inhalation toxicity data available. Although the Panel noted that droplets/particles from spray and loose-powder cosmetic products would not be respirable to any appreciable amount, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

After reviewing this safety assessment, the Panel found that the data are insufficient to determine the safety of the *Ginkgo biloba*-derived ingredients detailed in this report. The data needed to issue a conclusion of safety for these cosmetic ingredients are:

- Method of manufacturing, composition, and impurities data for each of these ingredients, except Ginkgo Biloba Meristem Cell;
- 28-Day dermal toxicity data for each of these ingredients,
    - Dependent on the results of these studies, additional data on other toxicological endpoints, such as developmental and reproductive toxicity and carcinogenicity, may be needed;
- Dermal irritation and sensitization data at leave-on use concentrations; and
- Ocular irritation data, if available.

CONCLUSION

The CIR Expert Panel concluded that the data are insufficient to determine the safety of the following 10 *Ginkgo biloba*-derived ingredients.

Ginkgo Biloba Leaf Extract
Ginkgo Biflavones*
Ginkgo Biloba Leaf*
Ginkgo Biloba Leaf Cell Extract*
Ginkgo Biloba Leaf Powder
Ginkgo Biloba Leaf Water*
Ginkgo Biloba Meristem Cell*
Ginkgo Biloba Nut Extract
Ginkgo Biloba Root Extract*
Ginkgo Leaf Terpenoids*

*Not reported to be in current use.

TABLES

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

Ingredient/CAS No.	Definition & Structure	Function
Ginkgo Biloba Leaf Extract 90045-36-6	Ginkgo biloba leaf extract is the extract of the leaf of *Ginkgo biloba*.	skin-conditioning agent – misc.
Ginkgo Biflavones	Ginkgo biflavones is a mixture of biflavones derived from the leaves of *Ginkgo biloba.* It consists predominantly of sciadopitysin, bilobetin, ginkgetin, and isoginkgetin.	antioxidant
Ginkgo Biloba Leaf 90045-36-6	Ginkgo biloba leaf is the leaf of *Ginkgo biloba.*	skin-conditioning agent – misc.
Ginkgo Biloba Leaf Cell Extract 90045-36-6	Ginkgo biloba leaf cell extract is the extract of a culture of the leaf cells of *Ginkgo biloba.*	flavoring agents; skin protectant
Ginkgo Biloba Leaf Powder 90045-36-6	Ginkgo biloba leaf powder is the powder obtained from the dried, ground leaves of *Ginkgo biloba*.	skin-conditioning agent – misc.
Ginkgo Biloba Leaf Water 90045-36-6	Ginkgo biloba leaf water is the aqueous solution of the steam distillate obtained from the leaves of *Ginkgo biloba*.	fragrance ingredient; skin-conditioning agent – misc.
Ginkgo Biloba Meristem Cell	Ginkgo biloba meristem cell are the cultured meristem cells isolated from *Ginkgo biloba.*	antimicrobial agent; antioxidant; skin-conditioning agent – misc.
Ginkgo Biloba Nut Extract 90045-36-6	Ginkgo biloba nut extract is the extract of the seeds of *Ginkgo biloba*.	cosmetic astringent; hair conditioning agent; nail conditioning agent; skin-conditioning agent – misc.
Ginkgo Biloba Root Extract 90045-36-6	Ginkgo biloba root extract is the extract of the roots of *Ginkgo biloba*.	skin-conditioning agent – misc.
Ginkgo Leaf Terpenoids 107438-79-9 15291-75-5 15291-76-6 15291-77-7 33570-04-6	Ginkgo leaf terpenoids is a mixture of terpenoids isolated from the leaves of *Ginkgo biloba* consisting chiefly of ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J, and bilobalide.	antiacne agent; antifungal agent; antimicrobial agent; antioxidant; external analgesics; hair conditioning agent

Table 2. Supplier product specifications for Ginkgo Biloba Leaf Extract and Ginkgo Biloba Nut Extract [16]

Specification	Ginkgo Biloba Leaf Extract (prepared in water)	Ginkgo Biloba Nut Extract (prepared in glycerin)
Appearance	Clear to slightly hazy liquid; light to medium yellow	Colorless to light amber liquid
Microbial Plate Count	Less than 100 organisms/g	Less than 100 organisms/g
Odor	Characteristic	Characteristic
pH	4.8 at 25º C (range 4.0-6.5)	4.7 at 25º C (range 4.0-6.5)
Refractive Index	1.3332 at 25º C (range 1.3295-1.3395)	1.3982 25º C (range 1.3920-1.5000)
Solubility	Soluble in any proportion in water	Soluble in any proportion in water
Specific Gravity	1.00 at 25º C (range 0.99-1.02)	1.12 at 25º C (range 1.05-1.15)

Table 3. Major constituents of GBEs (%). †

Class	Identified	Standardized Extract (EGb 761®) Specification[4‡]	Standardized and Non-Standardized GBEs*[13,66-68]	NTP Study Extract[8]
Terpene trilactones	Total	6	0.07-14.23	15.4
	Bilobalide		0.03-8.64	6.94
	Ginkgolide A		0.01-2.90	3.74
	Ginkgolide B		< 0.005-1.75	1.62
	Ginkgolide C		< 0.005-1.75	3.06
	Ginkgolide J		0.03-0.78	Not measured
Flavonol glycosides	Total	24	0.18-35.54	31.2
	Quercetin		< 0.01-8.34	16.71
	Kaempferol		0.02-5.57	12.20
	Isorhamnetin		0.04-1.13	2.37
Alkylphenols	Ginkgolic acids, cardanols	≤ 0.0005	< 0.0005-9.0	0.001

† Adapted from the NTP 2013 report.

‡ Van Beek 2009 also reports EGb761® contains 13% carboxylic acids, 7% proanthocyanidins, 2% catechins, 20% non-flavonol glycosides, 4% high molecular weight compounds, 5% inorganic constituents, 3% water (solvent), and 3% various and 13% unknown compounds.

*Constituent ranges are not specific to the cosmetic ingredient Ginkgo Biloba Leaf Extract but to constituent ranges of standardized and non-standardized GBEs found in the published literature.

Table 4. 2018 frequency and concentration of use according to duration and type of exposure for *Ginkgo biloba*-derived ingredients[20-22]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Ginkgo Biloba Leaf Powder		**Ginkgo Biloba Leaf Extract***		**Ginkgo Biloba Nut Extract**	
Totals†	**5**	**NR**	**712**	**0.000002-0.25**	**27**	**NR**
Duration of Use						
Leave-On	3	NR	626	0.000002-0.24	17	NR
Rinse Off	2	NR	86	0.00002-0.25	10	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	NR	215	0.00001-0.01	NR	NR
Incidental Ingestion	NR	NR	5	0.00002-0.2	NR	NR
Incidental Inhalation-Spray	1[a]; 1[b]	NR	4; 163[a]; 116[b]	0.05; 0.00005-0.0041[a]	3[a]; 7[b]	NR
Incidental Inhalation-Powder	1[b]	NR	44; 116[b]	0.00001-0.05; 0.00038-0.1[c]	7[b]	NR
Dermal Contact	3	NR	651	0.00001-0.25	26	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	48	0.00005-0.001	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	5	0.000002-0.24	NR	NR
Mucous Membrane	NR	NR	19	0.00002-0.2	1	NR
Baby Products	NR	NR	NR	0.005	NR	NR

NR = Not reported.

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

*Combined with the generic entry "Ginkgo Biloba (Ginkgo) Extract" in the VCRP database, which is not an INCI name.

[a.] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

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

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 5. Ingredients not reported in use.[20-22]

Ginkgo Biflavones
Ginkgo Biloba Leaf
Ginkgo Biloba Leaf Water
Ginkgo Biloba Meristem Cell
Ginkgo Biloba Root Extract
Ginkgo Leaf Terpenoids
Ginkgo Biloba Leaf Cell Extract

Table 6. Human dermal sensitization studies on Ginkgo Biloba Leaf Extract

Concentration	Number of Subjects	Method	Results	References
0.0005% in a test article	52	HRIPT, approximately 0.05 ml/cm^2 applied to the back of subjects with occlusive patch	No dermal irritation or sensitization	[59]
0.0085% in a cream	48	HRIPT, tested neat under occlusive patch	No dermal irritation or sensitization	[58]
0.0072% in a lip product	109	HRIPT, tested neat under occlusive patch	No dermal irritation or sensitization	[58]
0.1% in a leave-on product	201	HRIPT, 4 cm^2 semi-occlusive patches; dose density = 0.05 mg/cm^2	No sensitization	[57]
0.2% in a lotion	208	HRIPT, 0.2 ml applied with a 2 cm^2 Webril pad and semi-occluded	No sensitization	[56]

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2018 FDA VCRP RAW DATA

03D - Eye Lotion	GINKGO BILOBA (GINKGO) EXTRACT	2
03G - Other Eye Makeup Preparations	GINKGO BILOBA (GINKGO) EXTRACT	2
05F - Shampoos (non-coloring)	GINKGO BILOBA (GINKGO) EXTRACT	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	GINKGO BILOBA (GINKGO) EXTRACT	2
05I - Other Hair Preparations	GINKGO BILOBA (GINKGO) EXTRACT	1
07A - Blushers (all types)	GINKGO BILOBA (GINKGO) EXTRACT	1
07I - Other Makeup Preparations	GINKGO BILOBA (GINKGO) EXTRACT	1
12A - Cleansing	GINKGO BILOBA (GINKGO) EXTRACT	4
12C - Face and Neck (exc shave)	GINKGO BILOBA (GINKGO) EXTRACT	5
12D - Body and Hand (exc shave)	GINKGO BILOBA (GINKGO) EXTRACT	3
12F - Moisturizing	GINKGO BILOBA (GINKGO) EXTRACT	6
12G - Night	GINKGO BILOBA (GINKGO) EXTRACT	1
12H - Paste Masks (mud packs)	GINKGO BILOBA (GINKGO) EXTRACT	4
12J - Other Skin Care Preps	GINKGO BILOBA (GINKGO) EXTRACT	2
03B - Eyeliner	GINKGO BILOBA (GINKGO) LEAF EXTRACT	1
03C - Eye Shadow	GINKGO BILOBA (GINKGO) LEAF EXTRACT	170
03D - Eye Lotion	GINKGO BILOBA (GINKGO) LEAF EXTRACT	22
03F - Mascara	GINKGO BILOBA (GINKGO) LEAF EXTRACT	2
03G - Other Eye Makeup Preparations	GINKGO BILOBA (GINKGO) LEAF EXTRACT	16
04E - Other Fragrance Preparation	GINKGO BILOBA (GINKGO) LEAF EXTRACT	2
05A - Hair Conditioner	GINKGO BILOBA (GINKGO) LEAF EXTRACT	12
05B - Hair Spray (aerosol fixatives)	GINKGO BILOBA (GINKGO) LEAF EXTRACT	2
05F - Shampoos (non-coloring)	GINKGO BILOBA (GINKGO) LEAF EXTRACT	18
05G - Tonics, Dressings, and Other Hair Grooming Aids	GINKGO BILOBA (GINKGO) LEAF EXTRACT	2
05I - Other Hair Preparations	GINKGO BILOBA (GINKGO) LEAF EXTRACT	10
07A - Blushers (all types)	GINKGO BILOBA (GINKGO) LEAF EXTRACT	21
07B - Face Powders	GINKGO BILOBA (GINKGO) LEAF EXTRACT	44
07C - Foundations	GINKGO BILOBA (GINKGO) LEAF EXTRACT	11
07E - Lipstick	GINKGO BILOBA (GINKGO) LEAF EXTRACT	5
07F - Makeup Bases	GINKGO BILOBA (GINKGO) LEAF EXTRACT	1
07I - Other Makeup Preparations	GINKGO BILOBA (GINKGO) LEAF EXTRACT	9
08B - Cuticle Softeners	GINKGO BILOBA (GINKGO) LEAF EXTRACT	1
08E - Nail Polish and Enamel	GINKGO BILOBA (GINKGO) LEAF EXTRACT	2
08G - Other Manicuring Preparations	GINKGO BILOBA (GINKGO) LEAF EXTRACT	2
10A - Bath Soaps and Detergents	GINKGO BILOBA (GINKGO) LEAF EXTRACT	4
10C - Douches	GINKGO BILOBA (GINKGO) LEAF EXTRACT	1
10E - Other Personal Cleanliness Products	GINKGO BILOBA (GINKGO) LEAF EXTRACT	9

11E - Shaving Cream	GINKGO BILOBA (GINKGO) LEAF EXTRACT	2
12A - Cleansing	GINKGO BILOBA (GINKGO) LEAF EXTRACT	20
12C - Face and Neck (exc shave)	GINKGO BILOBA (GINKGO) LEAF EXTRACT	81
12D - Body and Hand (exc shave)	GINKGO BILOBA (GINKGO) LEAF EXTRACT	27
12F - Moisturizing	GINKGO BILOBA (GINKGO) LEAF EXTRACT	71
12G - Night	GINKGO BILOBA (GINKGO) LEAF EXTRACT	13
12H - Paste Masks (mud packs)	GINKGO BILOBA (GINKGO) LEAF EXTRACT	11
12I - Skin Fresheners	GINKGO BILOBA (GINKGO) LEAF EXTRACT	7
12J - Other Skin Care Preps	GINKGO BILOBA (GINKGO) LEAF EXTRACT	17
13A - Suntan Gels, Creams, and Liquids	GINKGO BILOBA (GINKGO) LEAF EXTRACT	2
13B - Indoor Tanning Preparations	GINKGO BILOBA (GINKGO) LEAF EXTRACT	54
13C - Other Suntan Preparations	GINKGO BILOBA (GINKGO) LEAF EXTRACT	5
03D - Eye Lotion	GINKGO BILOBA (GINKGO) LEAF POWDER	1
05C - Hair Straighteners	GINKGO BILOBA (GINKGO) LEAF POWDER	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	GINKGO BILOBA (GINKGO) LEAF POWDER	1
12A - Cleansing	GINKGO BILOBA (GINKGO) LEAF POWDER	1
12D - Body and Hand (exc shave)	GINKGO BILOBA (GINKGO) LEAF POWDER	1
05A - Hair Conditioner	GINKGO BILOBA (GINKGO) NUT EXTRACT	1
10E - Other Personal Cleanliness Products	GINKGO BILOBA (GINKGO) NUT EXTRACT	1
12A - Cleansing	GINKGO BILOBA (GINKGO) NUT EXTRACT	5
12C - Face and Neck (exc shave)	GINKGO BILOBA (GINKGO) NUT EXTRACT	4
12D - Body and Hand (exc shave)	GINKGO BILOBA (GINKGO) NUT EXTRACT	3
12F - Moisturizing	GINKGO BILOBA (GINKGO) NUT EXTRACT	1
12H - Paste Masks (mud packs)	GINKGO BILOBA (GINKGO) NUT EXTRACT	3
12I - Skin Fresheners	GINKGO BILOBA (GINKGO) NUT EXTRACT	2
12J - Other Skin Care Preps	GINKGO BILOBA (GINKGO) NUT EXTRACT	7

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: March 20, 2018

SUBJECT: Updated Concentration of Use by FDA Product Category: *Ginkgo Biloba*-Derived Ingredients

Concentration by FDA Product Category – *Ginkgo biloba*-Derived Ingredients*

Ginkgo Biloba Leaf Extract
Ginkgo Biflavones
Ginkgo Biloba Leaf
Ginkgo Biloba Leaf Powder
Ginkgo Biloba Leaf Water
Ginkgo Biloba Meristem Cell
Ginkgo Biloba Nut Extract
Ginkgo Biloba Root Extract
Ginkgo Leaf Terpenoids

Ingredient	Product Category	Maximum Concentration of Use
Ginkgo Biloba Leaf Extract	Baby lotions, oils and creams not powder	 0.005%
Ginkgo Biloba Leaf Extract	Eye shadow	0.00001-0.01%
Ginkgo Biloba Leaf Extract	Eye lotion	0.00038-0.01%
Ginkgo Biloba Leaf Extract	Hair conditioner	0.001%
Ginkgo Biloba Leaf Extract	Shampoos (noncoloring)	0.0008-0.001%
Ginkgo Biloba Leaf Extract	Tonics, dressings and other hair grooming aids	0.00005-0.001%
Ginkgo Biloba Leaf Extract	Blushers (all types)	0.001%
Ginkgo Biloba Leaf Extract	Face powders	0.00001-0.05%
Ginkgo Biloba Leaf Extract	Foundation	0.002-0.1%
Ginkgo Biloba Leaf Extract	Lipstick	0.00002-0.2%
Ginkgo Biloba Leaf Extract	Makeup bases	0.1%
Ginkgo Biloba Leaf Extract	Makeup fixatives	0.0001%
Ginkgo Biloba Leaf Extract	Other makeup preparations	0.01%
Ginkgo Biloba Leaf Extract	Basecoats and undercoats (manicuring preparations)	0.000002%
Ginkgo Biloba Leaf Extract	Nail polish and enamel	0.000002%
Ginkgo Biloba Leaf Extract	Other manicuring preparations	0.24%
Ginkgo Biloba Leaf Extract	Bath soaps and detergents	0.00029%
Ginkgo Biloba Leaf Extract	Other shaving preparations	0.013-0.025%
Ginkgo Biloba Leaf Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0001-0.25%
Ginkgo Biloba Leaf Extract	Face and neck products not spray	 0.00038-0.1%
Ginkgo Biloba Leaf Extract	Body and hand products not spray	 0.002-0.1%
Ginkgo Biloba Leaf Extract	Moisturizing products not spray	 0.00038-0.1%
Ginkgo Biloba Leaf Extract	Night products not spray	 0.05%
Ginkgo Biloba Leaf Extract	Paste masks and mud packs	0.00002-0.00005%
Ginkgo Biloba Leaf Extract	Skin fresheners	0.0041%
Ginkgo Biloba Leaf Extract	Other skin care preparations	0.00002-0.08%
Ginkgo Biloba Leaf Extract	Suntan products not spray pump spray	 0.00002-0.1% 0.05%

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

Information collected in 2014

Table prepared August 4, 2014

Updated October 27, 2014: Ginkgo Biloba Leaf Extract: added baby lotions, oils and creams; skin cleansing product high concentration increased from 0.01% to 0.25%; face and neck products high concentration increased from 0.1% to 1%; moisturizing products high concentration increased from 0.02% to 0.1%; added suntan products pump spray

Updated March 20, 2018: Ginkgo Biloba Leaf Extract maximum use concentration in Face and neck products (not spray) decreased from 1% to 0.1%

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: April 2, 2018

SUBJECT: Ginkgo Biloba Leaf Extract

Anonymous. 2017. Clinical safety evaluation repeated insult patch test of a test article containing 0.0005% Ginkgo Biloba Leaf Extract.

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[redacted]

FINAL REPORT

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted] Test article contained 0.0005% Ginkgo Biloba Leaf Extract

Sponsor

[redacted]

Sponsor Representatives

[redacted]

Clinical Testing Facility

[redacted]

Sponsor Code: [redacted]
Panel No.:
Entry No.: [redacted]

Date of Final Report

7-6-17

[redacted]

[redacted] Panel No.: [redacted]
Entry No.:

SIGNATURE PAGE

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

[redacted] 6/16/2017
Date

[redacted] 6/30/17
Date

[redacted] 8/15/17
Date

[redacted]

QUALITY ASSURANCE STATEMENT

This study ([redacted] Panel No.: [redacted] Entry No.: [redacted]) was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in 21 CFR Part 50 (Protection of Human Subjects – Informed Consent) and the Standard Operating Procedures of [redacted]

For purposes of this clinical study:

_X_	Informed Consent was obtained.
____	Informed Consent was not obtained.
_X_	An IRB review was not required.
____	An IRB review was conducted and approval to conduct the proposed clinical research was granted.

To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the applicable study records and report. This report is considered a true and accurate reflection of the testing methods and source data.

[redacted]

3 July 2017
Date

[redacted]

[redacted] Panel No.:
Entry No.: [redacted]

TABLE OF CONTENTS

[redacted]

[redacted] Panel No.:
Entry No.: [redacted]

CLINICAL SAFETY EVALUATION

REPEATED INSULT PATCH TEST

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the irritation and/or sensitization potential of the test article after repeated application under occlusive patch test conditions to the skin of human subjects (non-exclusive panel).

2.0 SPONSOR

[redacted]

2.1 Sponsor Representatives

[redacted]

3.0 CLINICAL TESTING FACILITY

The study was conducted by:

[redacted]

4.0 CLINICAL INVESTIGATORS

[redacted]

5.0 STUDY DATES

Study initiation: April 26, 2017

Final evaluation: June 2, 2017

[redacted]

6.0 ETHICS

6.1 Ethical Conduct of the Study

This study was conducted in accordance with the intent and purpose of Good Clinical Practice regulations described in Title 21 of the U.S. Code of Federal Regulations (CFR), the Declaration of Helsinki and/or [redacted] Standard Operating Procedures.

6.2 Subject Information and Consent

This study was conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed Consent was obtained from each subject in the study and documented in writing before participation in the study. A copy of the Informed Consent was provided to each subject.

7.0 TEST MATERIAL

The test article used in this study was provided by:

[redacted]

It was received on March 10, 2017 and identified as follows:

[redacted] Entry No.	Test Article ID	Description
[redacted]	[redacted]	[redacted]

*The test article was volatilized at least 30 minutes, but less than 90 minutes, on the patch prior to application to the skin.

8.0 TEST SUBJECTS

At least 50 male and female subjects ranging in age from 18 to 79 years were to be empanelled for this test. Subject demographics are listed in Table 1.

The subjects chosen were to be dependable and able to read and understand instructions. The subjects were not to exhibit any physical or dermatologic condition that would have precluded application of the test article or determination of potential effects of the test article.

9.0 TEST PROCEDURE

The 9 Repeated Insult (occlusive) Patch Test (9-RIPT)[1] was conducted as follows:

9.1 Induction Phase

A sufficient amount of the test article (approximately 0.2 mL) was placed onto a Parke-Davis Readi-Bandage® occlusive patch (approximately 0.05 mL/cm^2 of test material), which was applied to the back of each subject between the scapulae and waist, adjacent to the spinal mid-line. This procedure was performed by a trained technician/examiner and repeated every Monday, Wednesday and Friday until 9 applications of the test article had been made.

The subjects were instructed to remove the patch 24 hours after application. Twenty-four hour rest periods followed the Tuesday and Thursday removals and 48-hour rest periods followed each Saturday removal. Subjects returned to the Testing Facility and the site was scored by a trained examiner just prior to the next patch application.

If a subject developed a positive reaction of a level 2 erythema or greater during the Induction phase or if, at the discretion of the Study Director, the skin response warranted a change in site, the patch was applied to a previously unpatched, adjacent site for the next application. If a level 2 reaction or greater occurred at the new site, no further applications were made. However, any reactive subjects were subsequently Challenge patch tested.

9.2 Challenge Phase

After a rest period of approximately 2 weeks (no applications of the test article), the Challenge patch was applied to a previously unpatched (virgin) test site. The site was scored 24 and 72 hours after application. All subjects were instructed to report any delayed skin reactivity that occurred after the final Challenge patch reading. When warranted, selected test subjects were called back to the Clinic for additional examinations and scoring to determine possible increases or decreases in Challenge patch reactivity.

Dermal responses for both the Induction and Challenge phases of the study were scored according to the following 6-point scale:

0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

All other observed dermal sequelae (eg, edema, dryness, hypo- or hyperpigmentation) were appropriately recorded on the data sheet and described as mild, moderate or severe.

[1] Marzulli FN, Maibach HI. (1976) Contact allergy: predictive testing in man. *Contact Dermatitis.* 2, 1-17.

[redacted]

9.0 TEST PROCEDURE (CONT'D)

9.3 Data Interpretation

Edema, vesicles, papules and/or erythema that persist or increase in intensity either during the Induction and/or Challenge phase may be indicative of allergic contact dermatitis. Allergic responses normally do not resolve or improve markedly at 72-96 hours.

Exceptions to typical skin reactions may occur. These may include, but not be limited to, symptoms of allergic contact sensitivity early in the Induction period to one or more test products. When this occurs in one subject, such a reaction usually suggests either an idiosyncratic response or that the subject had a pre-exposure/sensitization to the test material or component(s) of the test material or a cross-reactivity with a similar product/component. Data for such reactions will be included in the study report but will not be included in the final study analysis/conclusion of sensitization.

10.0 RESULTS AND DISCUSSION

(See Table 2 for Individual Scores)

A total of 55 subjects (6 males and 49 females ranging in age from 21 to 79 years) were empanelled for the test procedure. Fifty-two (52/55) subjects satisfactorily completed the test procedure on Test Article: [redacted] Two (2/55) subjects discontinued for personal reasons unrelated to the conduct of the study. One (1/55) subject (Subject No. 52) was discontinued due to violation of the protocol, the subject was concurrently testing at another facility. Discontinued subject data are shown up to the point of discontinuation, but are not used in the Conclusions section of this final report.

Induction Phase Summary

Test Article	Induction Scores (Number of Responses)						Evidence of Irritation
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

Challenge Phase Summary

Test Article	Challenge Scores (Number of Responses)						Evidence of Sensitization
	0.5	1	2	3	4	Other	
[redacted]	0	0	0	0	0	0	No

There was no skin reactivity observed at any time during the course of the study.

11.0 CONCLUSIONS

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in 52 subjects, Test Article: [redacted] was "Dermatologist-Tested" and was not associated with skin irritation or allergic contact dermatitis in human subjects.

[redacted]

[redacted] Panel No.: [redacted]
Entry No.:

TABLE 1

SUBJECT DEMOGRAPHICS

Test Article: [redacted]

Subject No.	Initials	Age	Sex	Race	Subject No.	Initials	Age	Sex	Race
1	PAC	58	F	CA	30	J-A	24	M	BA
2	ALC	28	F	HS	31	J-F	27	F	CA
3	DAZ	59	M	CA	32	LAM	62	F	CA
4	LMF	27	F	CA	33	KMB	56	F	BA
5	C-E	57	F	CA	34	AMS	71	F	CA
6	G-B	67	F	CA	35	D-W	62	F	CA
7	M-L	50	F	HS	36	VSK	23	F	CA
8	C-S	21	F	CA	37	MIM	44	F	CA
9	MDC	37	F	CA	38	E-M	38	F	HS
10	K-B	41	F	CA	39	V-G	49	F	CA
11	V-M	44	F	HS	40	H-E	65	M	CA
12	VLC	29	F	CA	41	FAS	54	F	CA
13	VKF	67	F	CA	42	CMA	29	F	HS
14	Y-G	51	F	HS	43	L-C	60	F	CA
15	RML	24	F	CA	44	RDG	64	F	CA
16	RMG	51	F	HS	45	N-S	59	M	HS
17	L-C	37	F	BH	46	CPA	46	F	HS
18	J-S	77	F	CA	47	SCC	21	F	HS
19	M-S	54	F	CA	48	CTK	53	F	CA
20	CMC	79	F	CA	49	D0B	46	F	CA
21	MGQ	22	F	HS	50	G-B	64	F	BA
22	JLJ	62	M	HS	51	A-G	31	F	HS
23	SEH	62	F	CA	52	AMJ	45	F	HS
24	A-L	78	F	CA	53	R-M	32	F	HS
25	BAM	79	F	CA	54	NAB	22	F	CA
26	A-D	31	F	HS	55	RMD	58	M	CA
27	DPG	46	F	CA					
28	BCG	70	F	CA					
29	J-G	71	F	CA					

BA = Black/African American
BH = Black Hispanic
CA = Caucasian
HS = Hispanic

Shaded area = discontinued subject

[redacted]

[redacted] Panel No.: [redacted]
Entry No.:

TABLE 2

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj. No.	Induction Evaluation Number									Challenge Virgin Site	
	1	2	3	4	5	6	7	8	9	24hr	72hr
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0
15	0	0	Discontinued								
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	Discontinued			
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

[redacted] Panel No.:
Entry No.: [redacted]

TABLE 2 (CONT'D)

INDIVIDUAL SCORES

REPEATED INSULT PATCH TEST - OCCLUSIVE

Test Article: [redacted]

Subj.	Induction Evaluation Number									Challenge Virgin Site	
No.	1	2	3	4	5	6	7	8	9	24hr	72hr
31	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	Discontinued	
53	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0

Scale:0 = No evidence of any effect
+ = Barely perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright red erythema with/without petechiae or papules)
4 = Severe (Deep red erythema with/without vesiculation or weeping)

[redacted]

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: April 2, 2018

SUBJECT: Concentration of Use by FDA Product Category: Ginkgo Biloba Leaf Cell Extract

Ginkgo Biloba Leaf Cell Extract was included in the February 2018 concentration of use survey. No uses of this ingredient were reported.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: February 23, 2018

SUBJECT: Draft Tentative Report: Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics (draft prepared for the March 5-6, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft tentative report, Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics.

Key Issues

Somewhere in the report it should state that CIR has previously reviewed the safety of *Camellia sinensis* (tea)-derived ingredients. Ingredients derived from *Camellia sinensis* leaves contain constituents similar to Ginkgo Biloba Meristem Cell (catechin, gallocatechin, epigallocatechin) and have been found safe when formulated to be non-sensitizing.

It should be clearly stated when the standardized GBE EGb 761 was studied. For example, the title of reference 47 indicates that extract EGb 761 was studied for reproductive and developmental toxicity in mice, but the description of this study in the DART section just says that "a standardized GBE was studied in mice."

Genotoxicity - Reference 51 (2015 review by Heinonen and Gaus) includes a number of published and unpublished genotoxicity studies of EGb 761 and also considered exposure levels when using dietary supplements. Based on their analysis they concluded: "The positive findings in some *in vitro* genotoxicity tests are linked to cytotoxic effects of the *G. biloba* extract and the use of very high concentrations compared to therapeutic use." Please include this conclusion in the CIR report. Since cosmetic use of Gingko Biloba Leaf Extract is lower than therapeutic use, genotoxicity should not be a concern.

Additional Considerations

Composition/Impurities - It should be made clear that ethanol/water was used to extract the Ginkgo Biloba Leaf Extract that is sold in butylene glycol (reference 6).

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Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: April 11, 2018

SUBJECT: Tentative Report: Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics (release date March 16, 2018)

The Council respectfully submits the following comments on the tentative report, Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics.

Composition/Impurities - It should be made clear that the composition information from references 6 and 15 came from companies supplying Ginkgo Biloba Leaf Extract to the cosmetics industry.

Short-Term, Oral, Ginkgo Biloba Meristem Cell - As the 13-week study was an oral study, "route of administration not described" should be changed to "method of oral administration not described".

Developmental and Reproductive Toxicity Studies - Three different dosing periods (28 days before mating, days 1-7 of gestation, days 10-18 of gestation) are described for reference 49. It is not clear if the effects reported occurred just in the group treated 28 days before mating or in all three treatment groups.

Genotoxicity, Summary - Although the conclusion from Heinonen and Gaus concerning genotoxicity has been added to the Summary, it should be presented first in the Genotoxicity section.

Other Clinical Reports - Please include more details about reference 62 such as: the GBE included in the formulations was a glycolic extract standardized by quercetin concentrations. There were actually two formulations, a sunscreen (TiO_2) containing formulation applied during the day and a formulation not containing sunscreen applied at night. The formulations were applied to the skin and forearms. If available, similar information should also be added for the formulation containing 0.3% GBE studied in reference 63.

Summary - In the description of the dermal penetration study of quercetin, it should be noted that quercetin was not found in the dermis or receptor fluid.

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As effects vary depending on when in relationship to gestation the animals are treated, the DART study descriptions in the Summary should also state when the animals were treated.

The genotoxicity conclusion from Heinonen and Gaus should not be presented in the middle of the description of the genotoxicity studies on the NTP studied extract. The current location of the conclusion from Heinonen and Gaus suggests that "the same GBE" might be EGb 761, not the extract studied by NTP.

As there was only one product containing 0.2% tested in an HRIPT, the following sentence should be revised. "No dermal sensitization was reported in HRIPTs of products containing 0.2% Ginkgo Biloba Extract."

Discussion - The extract used in the dietary cancer study is used as dietary supplement/herbal medicine. It should not be described as "similar to that used in dietary supplements".

Table 3 - If available, the extraction solvents used to prepare the extracts described in Table 3 should be stated. An additional footnote should be added to this table to indicate that constituents in extracts provided by suppliers of cosmetic ingredients are described in the Composition/Impurities section.

Reference 8 - Please correct the spelling of "Toxicoloty"

Reference 42 - Please correct the spelling of "epigallocetechin"

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

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

DATE: April 11, 2018

SUBJECT: Tentative Report: Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics (release date March 16, 2018)

We appreciate the opportunity to comment on the tentative report, Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics.

Ginkgo Biloba Leaf Extract is a widely used dietary supplement (typical dose of 240 mg/day) that has been extensively studied in numerous human studies. Based on a review of the toxicological and clinical data (75 studies; 7115 subjects), it has been concluded that Ginkgo Biloba Leaf Extract is well tolerated and safe for humans.[1]

A dermal penetration study[2], presented in the CIR report, is available for quercetin from a glycolic extract of ginkgo leaves. Quercitin, found in many plants, is often considered a constituent of concern by the CIR Expert Panel. This dermal penetration study showed that quercetin from a glycolic extract of ginkgo leaves entered the upper layers of the skin, but was below the limits of detection in the dermis and receptor fluid.

Composition information provided by suppliers of Ginkgo Biloba Leaf Extract sold to the cosmetics industry is presented in the Composition/Impurities section of the tentative report (references 6 and 15) and is presented in the attached table along with the composition of the standardized acetone/water extract EGb 761. Analyses of ginkgo leaf-derived preparations

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[1]Heinonen T, Gaus W. 2015. Cross matching observations on toxicological and clinical data for the assessment of tolerability and safety of *Ginkgo biloba* leaf extract. *Toxicology* 327: 95-115.

[2]dal Belo SE, Gaspar LR, Maia Campos PMBG, et al. 2009. Skin penetration of epigallocatechin-3-gallate and quercetin from green tea and *Ginkgo biloba* extracts vehiculated in cosmetic formulations. *Skin Pharmacol Physiol* 22: 299-304.

focuses on concentrations of flavonol glycosides and terpene lactones, components included in pharmacopeia specifications. Specifications also indicate low levels (≤5 ppm) of total alkylphenols (ginkgolic acids) which are present in ginkgo leaves at 0.5-4.82%[3]. The low levels of alkylphenols in the ingredients supplied to the cosmetics industry indicates that the extracts are standardized extracts. Therefore, the multiple studies that have been completed on the standardized extract EGb 761 support the safety of Ginkgo Biloba Leaf Extract as used in cosmetics.

In addition to the components used for standardization, preparations of ginkgo leaves also contain proanthocyanidins, carboxylic acids, flavanols and catechins as indicated in the table. The additional components reported in the standardized extract, EGb 761 shown in the attached table should be added to Table 3 of the CIR report.

In comparison to oral exposure from supplement use, potential exposure to Ginkgo Biloba Leaf Extract from cosmetic products is very low. The revised maximum concentration of use is 0.24% in other manicuring preparations, with a maximum of 0.2% reported for lipstick and 0.1% reported for body and hand products. These cosmetic use concentrations are supported by an HRIPT of a product containing 0.2% Ginkgo Biloba Leaf Extract, as well as a guinea pig study indicating a lack of sensitization of a leaf extract containing 24% flavone glycosides and about 1000 ppm ginkgolic acids[4].

Based on the low concentrations of use in cosmetic products; the long history of safe oral use by humans; safety data on standardized extracts; the limited ability of quercetin to become systemically available following dermal exposure; and negative sensitization data at levels of ginkgolic acids higher than found in the cosmetic ingredients, we consider that additional data are not needed to support the safety of extracts of *Ginkgo biloba* leaves as used in cosmetics.

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[3]van Beek TA, Montoro P. 2009. Chemical analysis and quality control of *Ginkgo biloba* leaves, extracts and phytopharmaceuticals. *Journal of Chromatography A* 1216: 2002-2032.

[4]Hausen BM. 1998. The sensitizing capacity of ginkgolic acids in guinea pigs. *Am J Contact Dermat* 9(3): 146-148.

Ginkgo Biloba Leaf Extract Composition

Compound class	Composition of EGb 761 (standardized acetone/water leaf extract)*	Composition of a Leaf Extract (powder)**	Composition of an ethanol/water leaf extract (solution) ***
Flavonol glycosides Quercetin Kaempferol Isohamnetin	24%	25.3%	0.51% 0.21%
Terpene trilactones Ginkgolide A Ginkgolide B Ginkgolide C Bilobalide	6%	6.4%	0.16% 0.04% 0.02% 0.02% 0.08%
Alkylphenols (Ginkgolic acids)	≤5 ppm	2.3 ppm	<0.1 ppm
Proanthocyanidins[#] Dimers of procyanidin and prodelphinidin classes	7%		
Carboxylic Acids[#] Non-phenolic e.g., ascorbic, D-glucaric, shikimic acid Phenolic e.g., protocatechuic, p-hydroxybenzoic, vanillic, caffeic, p-coumaric, ferulic, chlorogenic	13%		
Catechins[#]	2%		
Non-flavonol glycosides[#]	20%		
High molecular weight compounds[#]	4%		
Inorganic constituents[#]	5%		
Water, solvent[#]	3%		
Various[#]	3%		
Unknown[#]	13%		
Other components in ginkgo leaves[#]	Bioflavones 0 Polyprenols 0		

*As presented in: van Beek TA, Montoro P. 2009. Chemical analysis and quality control of *Ginkgo biloba* leaves, extracts and phytopharmaceuticals. *Journal of Chromatography A* 1216: 2002-2032.

**As provided by a cosmetic ingredient supplier (reference 15 of the CIR tentative report)

*** Diluted in 50% Butylene Glycol; as provided by a cosmetic ingredient supplier (reference 6 of the CIR tentative report).

[#]Not included in Table 3 of the CIR tentative report.