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

Status: Draft Final Report for Panel Review
Release Date: August 29, 2018
Panel Meeting Date: September 24-25, 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: August 29, 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 *ginkgo092018rep* in the pdf document).

In June 2018, the Panel reviewed data that had been received from Industry, including updated use concentrations. Based on the new data and the available dermal irritation and sensitization data, the Panel issued a Revised Tentative Report with the conclusion that the following 5 ingredients are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Ginkgo Biloba Leaf Extract	Ginkgo Biloba Leaf Powder
Ginkgo Biloba Leaf	Ginkgo Biloba Leaf Water
Ginkgo Biloba Leaf Cell Extract	

The Panel also determined that the data are insufficient to determine the safety of the following 5 ingredients:

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

The data needed to determine 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
- Ocular irritation data, if available

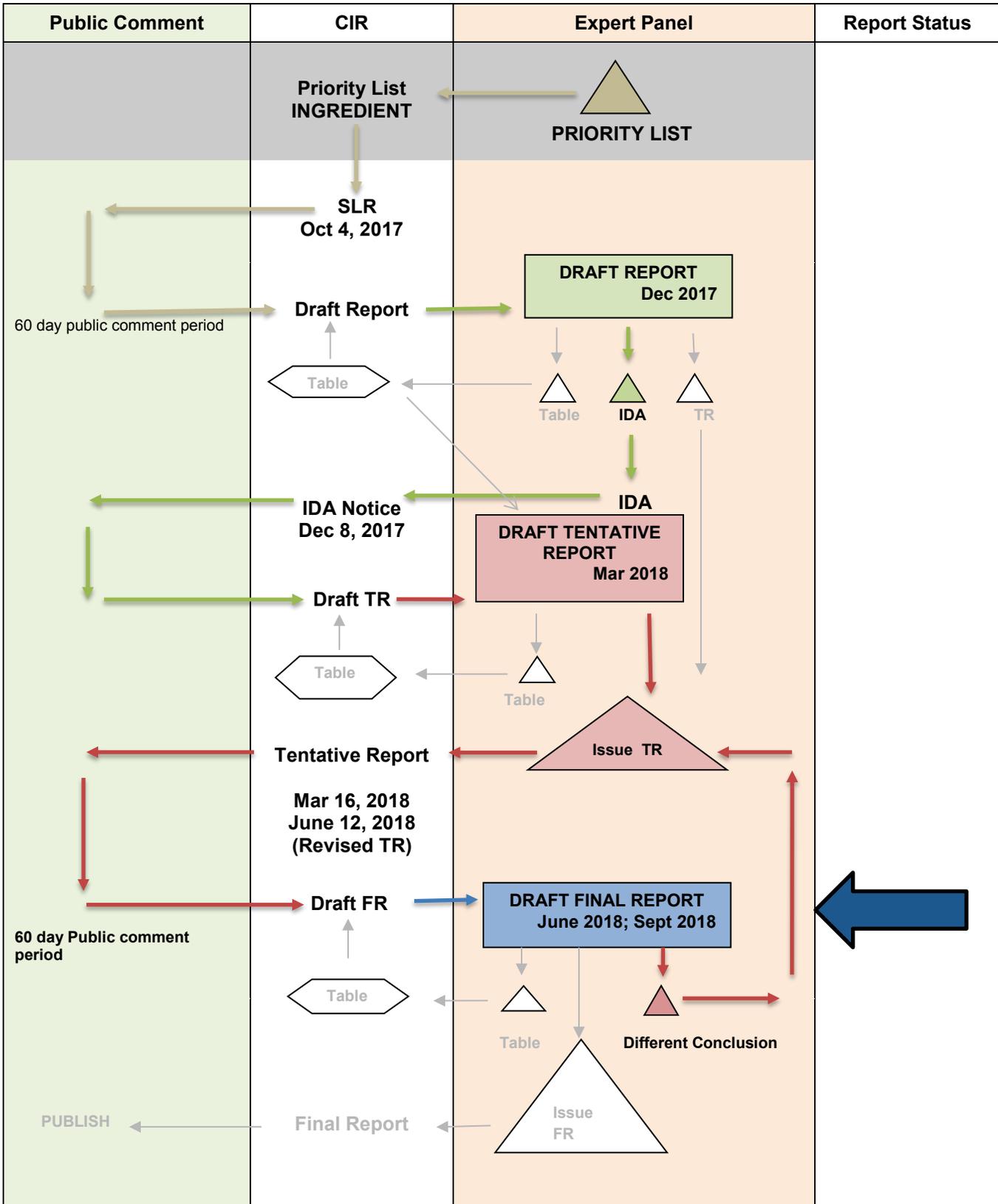
No new data has been received since the June Panel meeting. Comments provided by the Council prior to the June meeting and on the Revised Tentative Report have been addressed (*ginkgo092018pcpc1* and *ginkgo092018pcpc2*, respectively).

The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, the Panel should issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Ginkgo biloba-derived ingredients

MEETING Sept 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 carcinogenicity, 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.

June 2018 - The Panel issued a revised Tentative Report for public comment with the conclusion that the following 5 ingredients are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing:

Ginkgo Biloba Leaf Extract
Ginkgo Biloba Leaf
Ginkgo Biloba Leaf Cell Extract

Ginkgo Biloba Leaf Powder
Ginkgo Biloba Leaf Water

The Panel also determined that the data are insufficient to determine the safety of the following 5 ingredients:

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

The data needed to determine 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
- Ocular irritation data, if available

The Panel determined that the previous safety test data, methods of manufacturing, and composition and impurities data insufficiencies on Ginkgo Biloba Leaf Extract have been resolved, and reasonable inferences to 4 other leaf-derived ingredients can be made.

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one product formulation may each contribute to the final concentration of a single shared constituent. Therefore, when formulating products, manufacturers should avoid reaching concentrations of botanical constituents that may cause sensitization or other adverse effects.

<i>Ginkgo biloba</i>-Derived Ingredients Data Profile –September 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 terpenoids) 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 July 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/fcnavigation.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
June 4-5, 2018

Dr. Belsito's Team

DR. BELSITO: Okay. Ginkgo Biloba. At our March meeting we came up with an insufficient data announcement, there were five. Since the March meeting, we got HRIPT information, but not a concentration of use.

We received results of the concentration of use survey on the leaf cell extract, and updated concentrations on some of the other ingredients. But essentially, none of the requested materials. But we can eliminate the HRIPT at .2 percent, because the max, we're told now, is .1. What?

DR. SNYDER: It's .24 isn't it?

DR. BELSITO: No, I thought it was .1, no?

MS. BURNETT: But the ingredient that was at 1 percent is now being reported at .1 percent.

DR. BELSITO: Right.

MS. BURNETT: The highest concentration reported is .24 percent. And we have a HRIPT at .2.

DR. BELSITO: So, we have the sensitization covered?

MS. BURNETT: Pretty much.

DR. BELSITO: That was my point. Right?

DR. SNYDER: Yeah, but the maximum concentration of use is .24; it's not .1 as you stated.

DR. BERGFELD: 2.4, is that what you're saying?

DR. SNYDER: .24.

DR. BERGFELD: .24, yes.

DR. SNYDER: Originally, it was 1 percent, but that 1 percent went to .1, which now makes the highest concentration of use .24. And we previously already had a .2 HRIPT.

DR. BELSITO: Right.

DR. SNYDER: we got a new HRIPT at .0005 for the ingredient that previously was at 1 percent and went to .1 percent. So, it's a little confusing. So, the .2 should cover the .24.

DR. BELSITO: Yes.

DR. SNYDER: But we still don't have any method of manufacture and composition.

DR. EISENMANN: There is some in the paragraph, as written.

DR. SNYDER: We didn't get any new.

DR. EISENMANN: Correct, but I don't know if you saw the table, that we prepared, that compares the concentrations. This is in CIR SSC comments.

MS. BURNETT: PDF Page 77.

DR. LIEBLER: References 6 and 15?

DR. EISENMANN: Um-hum.

DR. LIEBLER: Yeah, I saw that in Alex's memo. References 6 and 15 referred to in Alex's memo.

DR. BELSITO: PDF what?

DR. LIEBLER: PDF end of document, 77.

MS. BURNETT: 76, 77. The memo from the Science and Support Committee.

DR. SNYDER: That has not been incorporated yet though, or it has?

DR. LIEBLER: It looks like a little bit of 6 has been, on PDF 35, at the end of the leaf extract description. It says, "The manufactures recorded that one ginkgo biloba leaf extract is produced through extraction with ethanol water solution, while another product is produced through extraction with an ethanol water solution before being evaporated and resolved in 50 percent butylene glycol." Which is probably adequate for our purposes. And then 15, I don't see reference to that in here; maybe I haven't gotten to it yet.

DR. EISENMANN: I think it's just in composition, not just method of manufacture.

DR. LIEBLER: So, we may have enough for the leaf. Do we have leaf extract? Love to know what's in 15.

DR. BELSITO: What's in what Dan?

DR. LIEBLER: Reference 15. Alex referred to that in her memo; and it's in our list, but I don't know what the content of that reference is, some report from industry.

DR. EISENMANN: This is where it's written up.

DR. BELSITO: Isn't that what's on the last page from PCPC? Isn't that Page 77?

DR. LIEBLER: Yeah, I believe so. That's a double asterisk.

DR. BELSITO: SpecChem?

DR. LIEBLER: Right. Okay, and then on page 36, about 2/3 of the way down the page, right before you get to ginkgo biloba meristem cell, go two paragraphs up, "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 percent ginkgo flavonol, 6.4 percent ginkgolides, et cetera. Less than 20ppm heavy metals." Reference 15 as cited right there.

So, this is composition, impurities on the leaf, and then the method of manufacture is Reference 6, on Page 35. Right above it again, a one sentence description, but it's probably about as much as we need.

DR. BELSITO: We don't have a 28-day dermal, but does that absorption study for quercetin, on whatever page that is, help you? It's PDF Page 37, dermal penetration of quercetin.

I mean, what else are we concerned about penetrating here? The sensitizer, but we now have that cleared with a HRIPT, right?

DR. LIEBLER: Right.

DR. BELSITO: So, do we need a 28-day dermal for this, for the leaf?

DR. LIEBLER: I don't think so. I think we're over the hump with the leaf extract, the leaf, the leaf cell extract. I don't know what leaf powder actually is.

Actually, we're over the hump with the leaf extract, that's what we have information on. Is it alcoholic extracts with no leaves? I don't know if that translate to the leaf, leaf powder, maybe leaf water.

DR. BELSITO: No, but if it's an alcohol extract, do we know what's in the water extract?

DR. SNYDER: I had a question on Page 77, on a table.

DR. BELSITO: Yes.

DR. SNYDER: The EGB 761, the one that was used in the NTP study, there was --

DR. EISENMANN: That was not used in NTP study.

DR. SNYDER: Oh, it was not?

DR. EISENMANN: So that's the standardized extract. That's traditionally sold. It was not used in the NTP study.

DR. SNYDER: Okay.

DR. EISENMANN: That was slightly different.

DR. SNYDER: So, the first two columns of the flavonol glycosides are around 24 to 25 percent and then it precipitously drops to .51.

DR. EISENMANN: That's a material that's diluted up for use in cosmetic. So, they make this powder and then they make a solution, so it's a weak extract.

DR. BELSITO: Yeah. See the triple asterisk below, diluted in 50 percent butylene glycol as provided by cosmetic ingredients supplier.

DR. SNYDER: Oh, okay.

DR. BELSITO: So hence, the drop.

DR. LIEBLER: So, is the leaf extract (powder) the same as a leaf powder?

DR. EISENMANN: It should not be. The leaf powder should be leaves --

DR. LIEBLER: That have been powdered.

DR. EISENMANN: -- crushed and powdered.

DR. LIEBLER: Yeah, okay.

DR. EISENMANN: Because a leaf extract that's a powder, should be named as an extract.

DR. LIEBLER: Right. Okay, I just try to --

DR. BELSITO: So, composition of leaf extract (powder) is the powder?

DR. EISENMANN: No.

DR. LIEBLER: Doesn't sound like it.

DR. EISENMANN: Leaf powder should be leaves you powdered, that you crushed.

MS. KOWCZ: And dry or whatever.

DR. EISENMANN: I haven't looked at the definition how exactly -- but that's how it should be named.

DR. BELSITO: So, we don't have composition on leaf powder?

DR. LIEBLER: Right.

DR. EISENMANN: Right.

DR. LIEBLER: And we don't have composition on leaf, but we do have it on leaf extract. I don't know what leaf cell extract is. I just don't know what that is. As long as that's not something taken out, like meristem, and grown ex vivo, and then you make an extract of that. If it's just from --

DR. BELSITO: What's our definition of leaf cell extract?

DR. EISENMANN: It is a culture.

DR. LIEBLER: It's a culture?

DR. EISENMANN: Yes.

DR. LIEBLER: Then that's a separate item.

DR. EISENMANN: It's the extract of a culture of the leaf cells.

DR. LIEBLER: Then we don't have that then, unless that's another name for the meristem. But if that's a different prep, then we don't have it.

MS. KOWCZ: Could that be the meristem though?

DR. EISENMANN: No, that's two different names.

DR. LIEBLER: I could justify using the leaf extract information, that we now have, to clear leaf extract, and leaf water; but not leaf, and not leaf powder, and not leaf cell extract.

DR. BELSITO: So, we're saying, leaf extract and leaf water, safe as used?

DR. LIEBLER: Right.

DR. BELSITO: And all of the other ginkgo ingredients, insufficient for everything we've listed before?

DR. LIEBLER: Yes. Yeah, because the terpenoids, the biflavones, the nut extract, the root extract, we don't have. And meristem, we already have it, so.

DR. BELSITO: Paul, Curt?

DR. KLAASSEN: Sounds fine.

DR. BERGFELD: But you have in the extracts, on your Page 77, that the terpenes, at least in that extract of the leaf, there are, whatever, four of them. Would that count at all? So, it might be in the leaf?

DR. LIEBLER: The terpene trilactones?

DR. BERGFELD: Yes.

DR. LIEBLER: Those are components here, but this ingredient sounds like it's a terpene prep from ginkgo somehow.

DR. BERGFELD: Okay.

DR. BELSITO: Right.

DR. EISENMANN: It says it consists of ginkgolide A, B, C, J and bilobalide.

DR. LIEBLER: Terpenoids?

DR. EISENMANN: Yes.

DR. SNYDER: On which page?

DR. EISENMANN: It's in the definition.

DR. LIEBLER: Table 1.

MS. FIUME: Page 47.

DR. LIEBLER: Thank you. Okay. Well, we know what that is then. I mean, if that's the defined mixture of purified terpenoids. If that's what that is, then we know what it is. So, we can't say it's undefined. Method of manufacture is probably pretty obvious. I don't know if there are any flavonoid impurities.

DR. BELSITO: But we don't have sensitization for that, which presumably will be a higher amount of these ginkgolides than what's in leaf water and leaf extract.

DR. LIEBLER: Yeah.

DR. EISENMANN: We already have concentration.

DR. BELSITO: We don't know what the impurities are, right?

DR. LIEBLER: I think that depending on how that is prepared, you can have more or less significant amount of impurities that are constituent of concerns. And without information, specifically, on the impurities from that, I don't think we give that a pass based on just knowing what are the nominal ingredients.

DR. BELSITO: Okay, so what I'm hearing is that we're saying the leaf extract and the leaf water are safe as used. And then the others are insufficient for the same reasons that we previously asked before.

DR. SNYDER: So, we only have three that are safe as used?

DR. BELSITO: No, two.

DR. SNYDER: Okay.

DR. BELSITO: Leaf extract and leaf water.

DR. LIEBLER: And we already had the meristem.

DR. BELSITO: No. We had composition, we didn't have safety. So, we're were asking before for method of manufacture, composition and impurities data for each, except ginkgo biloba meristem cell; 28-day dermal tox for each, dermal irritation and sensitization data at leave-on use concentration and ocular irritations. So, we have no new data for anything other than the leaf extract and the leaf water. Yes?

DR. LIEBLER: Yes.

DR. BELSITO: Okay.

MS. BURNETT: Just want to note that the conclusion for the two that you said are safe would be safe when formulated to be non-sensitizing, the botanical boilerplate.

DR. BELSITO: Non -- yes. Yeah.

DR. BERGFELD: Well, does not the conclusion have to be changed?

DR. BELSITO: Yeah.

DR. BERGFELD: And then that means this goes out again.

DR. BELSITO: Yes. Anything else on these? Okay.

Dr. Marks' Team

DR. MARKS: Ginkgo. Christina, you're up again. In March 2018, the panel issued a tentative report with the conclusion the data are insufficient to determine the safety of the ten ginkgo-derived ingredients. And in your memo, you list those; the method of manufacture, composition and impurities, 28-day dermal, irritation sensitization, ocular irritation.

Let me see here. We felt that we could, at the last meeting, instead of everything be determined as insufficient, that the five leaf ingredients, we had enough information to move forward with a formulate not to be sensitizing. And then there was discussion by the Belsito team, it seemed, in my review, that it really came down to method of manufacture.

Do we want to move forward with insufficient for the ten ingredients? Or do we want to, again, propose that we have safe for the five leaf ingredients, which we have. The new use concentration we have equals the safety from HRIPT. So, the leaf extract sensitization should not be an issue.

Team, Tom, Ron, Ron, is method of manufacture for the leaf extract and the other leaf ingredients of concern? And if not, should we move that an amended final report be issued with the conclusion that the five leaf ingredients are safe, as long as they're not sensitizing?

DR. SLAGA: We do have HRIPT data; so, would we want to take the non-sensitizing out?

DR. MARKS: Pardon?

DR. SLAGA: Do we still want to have that in the conclusion?

DR. MARKS: Oh, sensitization? I think the sensitization is always for additives; so other botanicals, that they would be put together. What we don't want to do is have an ingredient, in which if they're added to other botanicals. It's not specifically for the ginkgo leaf at this point.

DR. SLAGA: Only -- yeah. Okay.

MS. BURNETT: And also, you still have the nut and the root ingredient; but you don't have the data on them.

DR. MARKS: Right. That's why I limited it to the leaf. The five would be safe and the remainder would not be safe, because we don't have all the data for that. But that was essentially where our team was going the last time.

If anything, the only hold up I would have -- I have no hold up on sensitization now, because I think we can read across; the leaf extract would represent the other leaf ingredients. Presumably, everything in a leaf extract would be in the other leaf ingredients. To me it would be, is there any issue with method of manufacture.

DR. SHANK: Not for me. I would separate out the leaf extract ingredients as safe.

DR. MARKS: Mm-hmm.

DR. SHANK: so, that would change the conclusion. We got a response from the Science and Support Committee, from PCPC, which I think made a very strong case for the safety of the leaf extract ingredients.

DR. HILL: What about the powder? What I have written is, leaf powder might be okay, but we don't have concentration of use information -- unless I missed it. And we don't have method of manufacture, really, to tell us what it is.

DR. SLAGA: We don't have a concern for the method of manufacture.

DR. MARKS: No. That's why I bring it up again; because that was one of the thing when you read the minutes. And of course, the Belsito team was really concerned about the method of manufacture. We didn't raise that as an issue.

DR. HILL: My point was simply that there's a chance that something could be substantially more concentrated in powder, depending on how that powder is prepared and made, than it is in an extract. And we don't know. I mean, I doubt it, but we don't know.

DR. SLAGA: I would think it'd be higher in an extract.

DR. MARKS: Yeah. That was my idea. If it's a powder you're taking a leaf and just grinding it up and you get a powder.

DR. SLAGA: Yeah. And then you take that powder and extract it.

DR. MARKS: Extract it, yeah.

DR. HILL: I'm not sure. It is an extract that then is brought to dryness and lyophilized; and then you can get a powder with fairly high concentration of substances. So, if I knew -- if it's just grinding up the leaf, I agree with you, no problem.

MS. BURNETT: Can I ask, what's the difference -- we have ginkgo biloba leaf and ginkgo biloba leaf powder. What would the difference be between those two ingredients?

DR. HILL: What I just said. Suppose you did a leaf extract in supercritical fluid or cooked it up in ethanol for a long time, and then filtered that liquid off, and then concentrated it down and lyophilized at the end, then you have a powder. It will be a beautiful powder. And it will be very different than if we just ground up the leaf.

MS. BURNETT: Okay.

DR. HILL: In terms of concentration of substances.

DR. SLAGA: But what would you call the ground up leaf?

MS. BURNETT: The dictionary definition for leaf powder is, the powder obtained from the dried ground leaves.

DR. HILL: Obtained from is wide open.

MS. BURNETT: Okay.

DR. MARKS: Ron Hill, frankly I don't have a concern with that. To me, I think the leaf extract is adequate to represent everything.

DR. HILL: And I don't see -- is that leaf powder in use?

MS. BURNETT: There are five uses.

DR. HILL: Then why aren't we getting information as to how it's made?

DR. MARKS: Well, I think if we use the dictionary method of manufacture, it said you grind up the left and you get a powder. To me that's pretty straight forward.

DR. HILL: Then somebody could clarify that.

DR. MARKS: Well, I wouldn't hold it up for that. If we do not issue a final report, and that's where we're at -- our team -- and I will be moving tomorrow. I would move that we issue an amended tentative report with a safe for the five leaf ingredients.

That's the leaf extract, the leaf itself, the leaf cell extract, the leaf powder and the leaf water. And then the other ingredients would be insufficient for what was previously listed.

And, Ron Hill, again, I'll let you, Ron Shank or Tom -- Tom I get the sense from you, you're not concerned about the powder. We could use the extract as a read across.

DR. SLAGA: Right.

DR. HILL: I doubt that I am. It just bugs the snot out of me that we're missing that information. And yeah, if I take the dictionary definition at face value, I agree with you. But there are other ways you can make a powder from a leaf and that's my point.

DR. MARKS: So, Ron Shank, I see you're thinking.

DR. SHANK: Well, I'm looking at what the leaf powder is used in. One eye lotion, one hair straightener, one hair tonic or dressing, one cleansing agent and one body and hand product.

DR. HILL: Are ginkgo leaves green? They're green, aren't they?

DR. SHANK: Powder. I don't know.

MS. BURNETT: During the summer they're green.

DR. SHANK: They're fresh, yeah.

MS. BURNETT: In the fall they turn bright yellow.

DR. HILL: All right.

DR. MARKS: Oh, I like that.

MS. BURNETT: They're very pretty.

DR. HILL: And I've seen that. I've seen that. Okay. And so now what do we grind up and make powder? You would presume that you wouldn't want either bright yellow or green in your hand cream unless you're using it to color it.

DR. MARKS: We don't know. And there may not be enough to add much of a color. I think we're never -- with botanicals we're never going to be at 100 percent.

DR. HILL: We don't have a concentration of use. So, I agree with you about the color comment, if only we knew how much was there.

DR. ANSELL: We do have concentration of use.

DR. HILL: For leaf powder? I didn't find --

DR. SLAGA: No. It says NR.

MS. BURNETT: Not on leaf powder.

DR. HILL: Not on leaf powder.

DR. SHANK: In the tables it says NR.

DR. MARKS: So, team -- I hear your point, Ron Hill. Tomorrow should we -- I'll be moving. I'm willing to not move for final report with insufficient data, but to go back to our previous, the way the team lead -- I would move we issue an amended tentative final report, so we have another period of review.

And that the five leaf ingredients are safe when formulated not to be sensitizing; the other and insufficient. Does that sound good?

DR. SHANK: Yes. So, it's a split conclusion.

DR. MARKS: Yes. Yup.

DR. SHANK: Yes. I like this.

DR. MARKS: Safe and insufficient.

DR. SLAGA: Great.

DR. MARKS: Okay.

DR. ANSELL: Although, I don't think the insufficiencies are going to be address. If that's why you're recycling it, I don't think we need weight.

DR. MARKS: No. I'm thinking this is a different conclusion that was sent out. So, the reason we're doing it is because we're sending out a different conclusion.

DR. SHANK: We changed the conclusion.

DR. MARKS: Yeah. Not awaiting that.

DR. SHANK: Right. Because that's not going to go.

DR. MARKS: Yes.

MS. BURNETT: It would be revised tentative. The status coming out of the meeting would be a revised tentative report.

DR. SHANK: Right.

MS. BURNETT: Rather than a final.

DR. SHANK: And we think that the data --

DR. MARKS: Oh, revised rather than amended.

MS. BURNETT: Yeah, revised.

DR. MARKS: Okay. I think we've used it both ways, maybe, in the past. Revised is fine with me too. Just indicating that we -- okay, revised. Thanks for clarification on the terminology. Okay.

DR. HILL: I do have one question to ask, and it relates to part of their basis for insufficiency. And also, looking at the transcript of what they discussed last time in their group.

They wrote a need was 28-day dermal toxicity data. And then depending on the results of these, additional data and toxicological endpoints; and in that was included carcinogenicity. And they had a little discussion and I had the same question which is, if you did a 20-day dermal, would that tell you anything whatsoever about whether there was carcinogenicity, which I would think not.

MS. BURNETT: I think that's if there was a positive result coming from the 28 dermal, then they would want to see a carcinogenicity study performed.

DR. HILL: In other words, if they saw anything showing up. But my point is, if you didn't see anything in the 28-day dermal, that wouldn't tell you one way or another, anything, about potential for carcinogenicity.

DR. SLAGA: Well, it would give you some idea.

DR. HILL: Would it?

DR. SLAGA: Yeah.

DR. HILL: Why? How?

DR. SLAGA: Well, 28 days so it's set in motion. You know, if there's chronic inflammation, hyperplasia, proliferation. You know, that type of data which --

DR. HILL: Okay.

DR. SLAGA: If it was very strong then, you know, I would say it would be worthwhile to do a carcinogenicity. Especially if you had genotoxicity on top of it.

DR. HILL: Right which I mean, do we have genotox? We do, don't we? And I didn't think -- anyway, I was taking us off the map a little because I wanted, not in tomorrow's session, to ask that question of our toxicology guys. Because my comment was, you would need some sort of biomarker after 28 days to suggest that something was or was not likely to happen. So, we do have genotoxicity data.

And there were positive findings in some of the in vitro genotox tests. But then they said, associated with cytotoxic effects at high test concentrations, if I understood all of this correctly.

And there was a positive mutagenicity result in the L517AY cells. I think that's part of what raised the, "do we need more," on their side. That's all I have.

DR. MARKS: Okay. Any other comments? So tomorrow I'm going to move that a revised tentative final report be issued. That the five leaf extracts are safe when formulated to be not sensitizing. And for the five non-leaf ingredients, insufficient conclusion and the needs are listed below in the draft by Christina. Okay.

DR. SHANK: Well done, Christina.

MS. BURNETT: Thank you.

DR. MARKS: Thank you, Christina.

DR. HILL: Yes.

Full Panel Meeting

DR. MARKS: At the March meeting this year, the panel issued a tentative report with a conclusion that data are insufficient to determine the safety of the ten ginkgo-derived ingredients. Our team, after reviewing all the data, felt that we should issue a revised tentative final report, not move on to a final report with an insufficient conclusion, but a split conclusion.

We felt that five leaf ingredients are safe when formulated not to be sensitizing. And non-leaf ingredients are insufficient, and the needs were outlined in the memo from Christina with the bullet points.

We felt we had all the necessary data on a leaf extract, which could then be applied across the leaf ingredients, the leaf, the leaf cell extract, the leaf powder and the leaf water. And so, our team moves that we issue a revised tentative final report, with the conclusion of five leaf ingredients statement formulated not to be sensitizing, and a non-leaf ingredients insufficient data.

DR. BERGFELD: Is there a second or a comment?

DR. BELSITO: Not a second.

DR. BERGFELD: Okay, well that's a comment then.

DR. BELSITO: Okay. We thought that the leaf extract and the leaf water were safe as used, given the fact we've now gotten new information that the maximum concentration used is .1 percent. We clearly would like to point out that the leaf's cell extract is almost like the meristem extract, it's the cell that's taken and cultured. We felt we had no concept of what that consisted of in terms of composition.

And then I'll let Dan point out why he felt that the leaf and the leaf powder were not sufficiently characterized in the material we had.

DR. LIEBLER: Thanks Don. In our discussion yesterday, my point was that although the leaf extract -- we understand how that's prepared -- we really don't know what more is in the leaf, and we don't know what the leaf powder is. Don just explained the leaf cell extract is an also somewhat undefined material.

On the other hand, thinking over this a little bit more last night, I could see my way to bringing in the leaf ingredients, other than the cell extract. That's something that is really an unknown quantity. I don't know what happens when you take cells from these plants and then start growing them in dishes. You probably get nothing much actually.

But, anyway, I could see my way to okaying the leaf and the leaf powder; so, maybe we meet you two-thirds of the way.

DR. BERGFELD: Paul or Curt?

DR. SNYDER: No further comment.

DR. BERGFELD: Don?

DR. BELSITO: If Dan is happy with the leaf and the leaf powder, Don is happy.

DR. BERGFELD: So, where does that leave your motion?

DR. MARKS: Well it leaves -- unless our team -- do you want to make any comments? We obviously felt the extract had actually probably a concentrated amount of the ingredients found, not only in the botanical ingredients, but also in that cell extract.

And I think, you know, we're -- team, I have no problem in modifying our motion and eliminate the cell extract as you'd requested. I suspect it has nothing different than what the leaf extract has in it.

DR. BERGFELD: Ron Hill, you wanted to say something? I'm sorry.

DR. HILL: Ron Shank has something and then.

DR. SHANK: What are the uses and concentrations of use for the cell extract?

DR. BELSITO: It is not used. It start at the bottom, "not reported in current use."

DR. SHANK: Okay.

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

DR. HILL: I did. We talked about the leaf powder yesterday, because I questioned it. I think one thing that I realize quickly is -- and probably from before, but there's a lot of time between meetings -- is that everybody's assuming, per the dictionary definition, that this is just dried leaf that's grounded up and that's it.

And I think maybe there's a bit of lack of clarity, because there's another way one could get powder out a leaf, which is extract it, take down that extract to dryness, maybe lyophilize it, now you have a powder.

And so, I think that's where I was looking for the method and manufacture. And I feel like if it's out there in use, we can get clarification on that before this goes to press. Because I think everybody's making the assumption that it's just grinding up the leaves. And if that's the case, then I have no problem with that ingredient.

DR. SNYDER: On the other hand, the leaf cell extract's probably not much difference than the meristem. And so, I'm happy to cede further ground to the Marks team on one more ingredient; but I mean I think these are relatively close calls. But the fact is we don't really have MM, materials -- methods of manufacture, et cetera. But I think reasonable inference would support these; so, I'm okay with that. I think we're back to your motion, basically.

DR. BERGFELD: So, you're concurring with the motion that was placed that all the leaf --

DR. SNYDER: Well, I am, yeah. Yeah.

DR. BERGFELD: -- products are okay. Don't?

DR. BELSITO: I'm fine.

DR. BERGFELD: Okay. Are you going to second it?

DR. BELSITO: Second.

DR. BERGFELD: Thank you. Christina?

MS. BURNETT: Are there any further discussion points that you would like to add to the report that are not currently in there?

DR. MARKS: Not from me.

DR. BELSITO: I'm fine.

DR. BERGFELD: All right seeing none, going to call to question. And all those in favor of the conclusion as stated? Thank you. Unanimous.

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.

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. 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 5 *Ginkgo biloba* leaf-derived ingredients are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing; data are insufficient to determine the safety of the remaining 5 ingredients under the intended conditions of use in cosmetic formulations.

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 (U.S.) 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 Biloba Leaf Water
Ginkgo Biflavones	Ginkgo Biloba Meristem Cell
Ginkgo Biloba Leaf	Ginkgo Biloba Nut Extract
Ginkgo Biloba Leaf Cell Extract	Ginkgo Biloba Root Extract
Ginkgo Biloba Leaf Powder	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, the available toxicity data that corresponds to specific use of these ingredients as cosmetics are extremely limited. 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. These trees 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

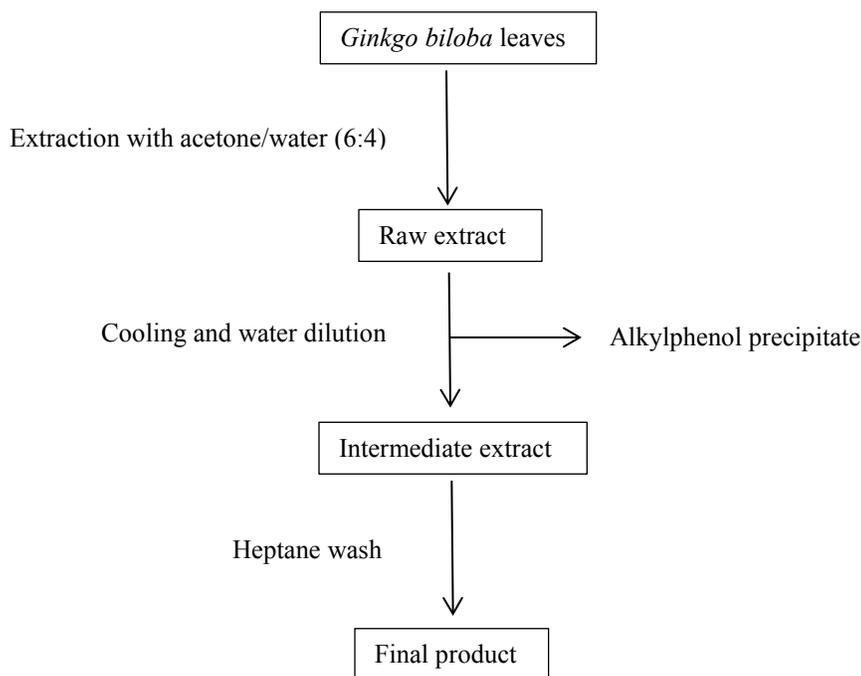
Product specifications for Ginkgo Biloba Leaf Extract (prepared in water) and Ginkgo Biloba Nut Extract (prepared in glycerin) reported by a supplier are described in Table 2.

Methods of Manufacturing

Ginkgo 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 taken from the published literature. It is not always clear whether any of these are similar to the cosmetic ingredient Ginkgo Biloba Leaf Extract. However, according to one supplier, their raw material is similar to GBE EGb 761[®].⁸

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.⁹

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)¹⁰

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*-methylmyricitins, 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. Ginkgoaceae).¹¹ 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).¹²

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.¹³ 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.¹⁴

Ginkgolic acid is a salicylic acid derivative with a C₁₅ side chain that is related to the pentadecylcatechols (i.e. urushiol) found in poison ivy.¹⁵ 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.⁹

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, 100 ppm free quercetin, 200 ppm free kaempferol, 200 ppm free isorhamnetin, and less than 20 ppm heavy metals.⁸

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 US 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, Ginkgo Biloba Leaf Powder and Ginkgo Biloba Nut Extract, are reported to be in use, with 27 or fewer uses reported in the VCRP. However, the results of concentration of use surveys on these 10 ingredients by the Council in 2014 and 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.²¹⁻²³ 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 $> 10 \mu\text{m}$, with propellant sprays yielding a greater fraction of droplets/particles below $10 \mu\text{m}$ compared with pump spray.²⁴⁻²⁷ 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.^{24,26} 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.²⁸⁻³⁰

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.³¹

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.^{2,3,32} 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.¹⁴ 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.³³⁻⁴¹

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.^{42,43} 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, 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.⁹

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.⁴⁴ The cosmetic formulation used in the study was an emulsion containing tri-laureth-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/cm²) 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 $0.17 \pm 0.002 \mu\text{g}/\text{cm}^2$ (24% of the applied dose) and $0.23 \pm 0.04 \mu\text{g}/\text{cm}^2$ (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.^{9,45} 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 [¹⁴C]-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 [¹⁴C]-CO₂ 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.⁴⁶ 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.⁴⁶

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Ginkgo Biloba Leaf Extract

The LD₅₀ of a standardized GBE (EGb 761[®]) administered orally to mice was reported to be 7730 mg/kg.⁴⁷

Ginkgo Biloba Meristem Cell

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).⁴⁸ 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.⁴⁸ 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.

Intravenous

Ginkgo Biloba Leaf Extract

The LD₅₀ after intravenous administration of a standardized GBE (EGb 761[®]) was 1100 mg/kg for both rats and mice.⁹

Short-Term Studies

Oral

Ginkgo Biloba Leaf Extract

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.⁴⁹ 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

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).⁴⁸ 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

Oral

Ginkgo Biloba Leaf Extract

The toxicity of a specific GBE was investigated in a 3-month mouse study performed by the NTP.⁹ 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.⁹

The NTP also performed a 3-month study of the same GBE used above in rats.⁹ 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.⁹

Ginkgo Biloba Meristem Cell

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).⁴⁸ 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

Ginkgo Biloba Leaf Extract

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.⁴⁷ 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

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.⁵⁰ 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.⁵⁰

Another study examined the dose response and pathologic effects of a standardized GBE (EGb 761[®]) in saline on cycling female Swiss albino mice.⁵¹ The test material was orally administered at doses of 0, 3.7, 7.4, or 14.8 mg/kg body weight/day for 28 days from the day of estrus phase (prior to mating), from day 1 to day 7 of gestation, or from day 10 to day 18 of gestation. A total of 200 cycling female mice were assigned for the experiments. There were 10 animals for each group used to study the effect of graded doses of GBE on anti-implantation and abortifacient activities and the remaining 120 animals were used to study the reproductive cycle (40 mice, 10 per group). Blood hormones of non-pregnant mice were

measured on day 28. Kidneys, liver, brain, placenta, spleen and ovaries were quickly removed and weighed from all animals that were killed. Post-mortem evaluations included preparing ovaries for histological examinations, and counting ovarian follicles. Maternal toxicity, estrous cycle, reproductive hormones, ovarian follicle counts, resorption index, implantation index, fetal viability and fetuses, and placenta mean weights were also evaluated.

No signs 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 any of the treatments, and there were no unscheduled deaths. Statistically significant decreases in body weight gains were observed in the 14.8 mg/kg/day dose group treated for 28 days when compared to the controls. In comparison to body weight, 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 treated 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. 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 in any of the different test 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. The highest dose tested was based on the equivalent to the suggested supplement dose level for humans of three 260 mg capsules/day⁵¹

The effects of an aqueous GBE (similar to EGb 761[®]) on embryo-fetal development were investigated in pregnant Wistar rats.⁵² 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.⁹

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.⁵³ 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.⁵⁴

Ginkgo 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.⁴⁸

Ginkgo Biloba Meristem Cell did not induce chromosomal aberrations in Chinese hamster lung cultured cells, with and without metabolic activation.⁴⁸ 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.⁹ 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 decrease 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 oil) for 90 days did not produce remarkable increases in *gpt* or *Spi* mutation frequencies in DNA extracted from the liver.⁴⁹ 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.⁴⁹

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.⁴⁸ 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

The carcinogenic potential of a GBE administered orally was studied by the NTP in male and female rats and mice.⁹ 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.⁹

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.⁵⁴ 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.⁵⁵ The animal data used to reach this determination were from the NTP studies that are described above that used a specific GBE. IARC also reviewed the findings of a randomized control study, 4 nested case-control epidemiological studies researching the potential effects of the use of GBE dietary supplements in elderly patients, and a population based case-control epidemiological study in 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.¹³ 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.⁵⁶ The pure ginkgolic acid was extracted from *Ginkgo biloba* fruit and the GBE was 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.⁵⁷⁻⁶⁰

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.⁶¹ 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.⁵⁹ 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% Ginkgo Biloba Leaf Extract, it was predicted that the test substance had no potential for eye irritation.⁵⁹ 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.^{3,15,62} 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.⁶³ 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.⁶⁴ 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 (no further information provided on adverse effect testing).⁶⁵ 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.⁶⁶ No further details regarding the GBE used or on adverse effect testing 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.⁵⁴ 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 use in herbal medicines or dietary supplements are numerous and are mainly based on oral administration. The available toxicity data that correspond to specific use of these ingredients in cosmetics are extremely limited. 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, Ginkgo Biloba Leaf Powder and Ginkgo Biloba Nut Extract, are reported to be in use, with 27 or fewer uses reported in the VCRP. However, the results of concentration of use surveys on these 10 ingredients conducted in 2014 and 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 medicines 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 ingredients 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) was 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 LD₅₀ of a standardized GBE (EGb 761[®]) administered orally to mice was reported to be 7730 mg/kg, and the LD₅₀ 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 of 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 in which mated female mice received standardized GBE (EGb 761[®]) on gestation days 6 through 15, the NOEL for dams and fetuses was greater than 1225 mg/kg/day. No maternal toxicity and no embryotoxic effects were observed. Another oral DART study investigated the effects of standardized GBE (EGb 761[®]) in female mice that received the test material during a 28 day period before mating, on gestation days 1 through 7, or on gestation days 10 through 18. The standardized GBE produced adverse effects at 14.8 mg/kg/day, including effects on the estrous cycle, fertility, reproductive performance, and hormone levels. The standardized GBE may also cause adverse effects on ovarian function as an antifertility agent. In an embryo-fetal development study, no adverse effects were observed in maternal or embryonic rats following dosing of an aqueous GBE similar to EGb 761[®] on gestation days 1 through 14, with doses up to 14 mg/kg/day.

The authors of a comparative review and analysis of published and unpublished data 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, as 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, or 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 or 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) based on data that included the NTP studies.

In a PLNA validation study, a GBE exposure yielded statistically significant lymphoproliferative reactions in the ipsilateral popliteal lymph node, which 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*.

The results of a phototoxicity and photosensitization study on a lip product containing 0.0072% Ginkgo Biloba Leaf Extract were negative.

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

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

This report assesses the safety of cosmetic ingredients 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 in cosmetics, which is a known dermal sensitizer. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

The Panel determined that the available safety test data, methods of manufacturing, and composition and impurities data on Ginkgo Biloba Leaf Extract are sufficient, and reasonable inferences to the safety of the 4 other leaf-derived ingredients can be made. The Panel considered the findings of the carcinogenicity studies performed by the 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 expected through cosmetic use. Additionally, the leaf extract used in dietary supplements did not produce increased incidences of cancer in a dietary study. This result, 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 determined that although a conclusion of safety could be made for five *Ginkgo biloba* leaf-derived ingredients, the data are insufficient to determine the safety of the remaining five ingredients: Ginkgo Biflavones, Ginkgo Biloba Meristem Cell, Ginkgo Biloba Nut Extract, Ginkgo Biloba Root Extract, and Ginkgo Leaf Terpenoids. 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 following *Ginkgo biloba*-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing:

Ginkgo Biloba Leaf Extract	Ginkgo Biloba Leaf Powder
Ginkgo Biloba Leaf*	Ginkgo Biloba Leaf Water*
Ginkgo Biloba Leaf Cell Extract*	

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

The Panel also concluded that the available data are insufficient to make a determination that the following *Ginkgo biloba*-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

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

***Not reported to be in current use.*

TABLES**Table 1.** Definitions 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 <i>Ginkgo biloba</i> .	skin-conditioning agent – misc.
Ginkgo Biflavones	Ginkgo biflavones is a mixture of biflavones derived from the leaves of <i>Ginkgo biloba</i> . It consists predominantly of sciadopitysin, bilobetin, ginkgetin, and isoginkgetin.	antioxidant
Ginkgo Biloba Leaf 90045-36-6	Ginkgo biloba leaf is the leaf of <i>Ginkgo biloba</i> .	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 <i>Ginkgo biloba</i> .	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 <i>Ginkgo biloba</i> .	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 <i>Ginkgo biloba</i> .	fragrance ingredient; skin-conditioning agent – misc.
Ginkgo Biloba Meristem Cell	Ginkgo biloba meristem cell are the cultured meristem cells isolated from <i>Ginkgo biloba</i> .	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 <i>Ginkgo biloba</i> .	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 <i>Ginkgo biloba</i> .	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 <i>Ginkgo biloba</i> 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 Extract¹⁶

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 (opg)	> 100	> 100
Odor	Characteristic	Characteristic
pH @ 25 °C	4.8 (range 4.0 - 6.5)	4.7 (range 4.0 - 6.5)
Refractive Index @ 25° C	1.3332 (range 1.3295-1.3395)	1.3982 (range 1.3920-1.5000)
Solubility	Soluble in any proportion in water	Soluble in any proportion in water
Specific Gravity @ 25° C	1.00 (range 0.99-1.02)	1.12 (range 1.05-1.15)

opg = organisms per gram

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

Class	Identified	Standardized Extract (EGb 761®) Specification [‡]	Standardized and Non-Standardized GBEs ^{*14,67-69}	NTP Study Extract ⁹
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 ingredients²⁰⁻²²

	# 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	0.00002-0.24	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	⁶⁰
0.0085% in a cream	48	HRIPT, tested neat under occlusive patch	No dermal irritation or sensitization	⁵⁹
0.0072% in a lip product	109	HRIPT, tested neat under occlusive patch	No dermal irritation or sensitization	⁵⁹
0.1% in a leave-on product	201	HRIPT, 4 cm ² semi-occlusive patches; dose density = 0.05 mg/cm ²	No sensitization	⁵⁸
0.2% in a lotion	208	HRIPT, 0.2 ml applied with a 2 cm ² Webril pad and semi-occluded	No sensitization	⁵⁷

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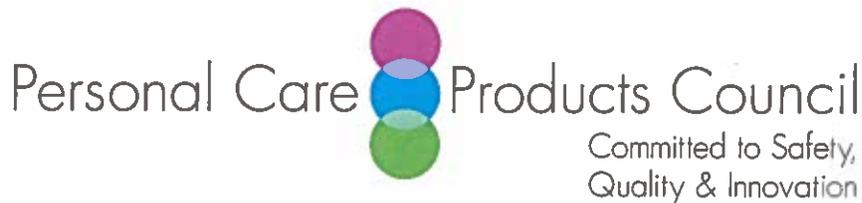
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2018 FDA VCRP RAW DATA

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



Memorandum

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

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: May 30, 2018

SUBJECT: Draft Final Report: Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics (draft prepared for the June 4-5, 2018 CIR Expert Panel meeting)

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

Key Issues

Cosmetic Use, Summary, Reference 21 - It is not appropriate to indicate that the Council's concentration of use survey was completed "in 2018". The survey of 9 ingredients was completed in 2014. The survey of Ginkgo Biloba Leaf Cell Extract was completed in 2018. Also in 2018, the company reporting use of 1% Ginkgo Biloba Leaf Extract in the 2014 survey indicated that this concentration was a mistake and it should have been 0.1%.

Composition/Impurities, Table 3 - Rather than being "major constituents", the components shown in Table 3 are the components traditionally used to standardize Ginkgo Biloba Leaf Extract. The title of the table and the text of the Composition/Impurities section should be revised.

Additional Considerations

Introduction, Summary - It is incorrect to state that "there are no publically available toxicity data that corresponds to specific use of these ingredients as cosmetics." The Other Clinical Reports section includes two studies on cosmetic formulations containing Ginkgo Biloba Leaf Extract (0.3% and 1.5%), although the results are limited, no adverse effects were reported in these studies.

Composition/Impurities - In the certificate of analysis of a Ginkgo Biloba Leaf Extract sold as a cosmetic ingredient (reference 15), the specifications for free quercetin, free kaempferol and free isorhamnetin are given as "in 1g (dry product)". Therefore the actual

measurements for free quercetin, free kaempferol and free isorhamnetin (not currently in the report) should be stated as 0.1 mg/g, 0.2 mg/g and 0.2 mg/g (they could also be stated as 100, 200 and 200 ppm), respectively.

Cosmetic Use, Summary - In the text, please state the other two ingredients with reported uses.

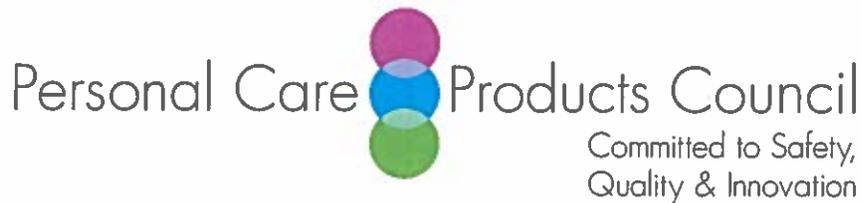
DART Studies, Summary - the study in Swiss mice included three different treatment periods (28 days before mating; days 1-7 of gestation; days 10-18 of gestation). The effects observed at each treatment period are not clear. What maternal toxicity was observed in this study? What fetal toxicity was observed in this study?

Carcinogenicity - The sentence concerning the epidemiology studies reviewed by IARC is not accurate. There was only one randomized controlled trial reviewed by IARC. There were 4 nested case-control studies from the VITAL cohort and one population based case-control study concerning ovarian cancer. The studies reviewed by IARC were not consistent in showing associations between various cancers and oral use of ginkgo leaf extracts.

Summary - The first paragraph of the Summary needs to be revised. The first sentence describes the reported functions of *Ginkgo biloba*-derived ingredients in cosmetic products. The second sentence indicates that investigations “for these uses are numerous and are mainly based on oral administration of supplements.” In the second sentence “these uses” appears to be referring to the cosmetic functions mentioned in the first sentence.

The Summary should also state that the IARC conclusion was based on the NTP study.

Discussion - The Discussion should also note that the rats and mice in the NTP study were treated with the leaf extract in corn oil.



Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: July 12, 2018

SUBJECT: Revised Tentative Report: Safety Assessment of *Ginkgo biloba*-Derived Ingredients as Used in Cosmetics (posted June 12, 2018)

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

Key Issues

In the Abstract, it would be helpful to state that all of the ingredients with conclusions of safe when formulated to be non-sensitizing are derived from the leaves of *Ginkgo biloba*.
Composition/Impurities; Table 3 - Rather than being "major constituents", the components shown in Table 3 are the components traditionally used to standardize Ginkgo Biloba Leaf Extract. The title of the table and the text of the Composition/Impurities section should be revised.

Discussion - The maximum reported use concentration and the highest concentration tested in an HRIPT should be mentioned in the Discussion.

Conclusion - Asterisks still need to be added to the insufficient data ingredients with no uses.

Additional Considerations

Composition/Impurities - As one supplier (reference 15) provided information indicating that their cosmetic ingredient was similar to EGb 761, the following sentence should be deleted: "It is not clear whether any of these are similar to the cosmetic ingredient Ginkgo Biloba Leaf Extract."

Summary - In the first paragraph of the Summary, please revise "use of these ingredients as cosmetics" to "use of these ingredients in cosmetics".

In the paragraph summarizing the DART studies, please delete the word "abortifacient" in the following as it does not make sense: "produced adverse effects on the estrous cycle, fertility, abortifacient, reproductive performance..."